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MAJOR ARTICLE

Mortality Trends in Risk Conditions and Invasive Mycotic Disease in the United States, 1999–2018

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Background. Invasive fungal infections in the United States are chronically underdiagnosed and a lack of coordinated surveillance makes the true burden of disease difficult to determine. The purpose of this analysis was to capture mortality-associated burden of risk conditions and fungal infections.

Methods. We analyzed data from the National Vital Statistics System from 1999 through 2018 to estimate the mortality attributed to risk conditions and related fungal disease.

Results. The number of risk conditions associated with fungal disease is steadily rising in the United States, with 1 047 422 diagnoses at time of death in 2018. While fungal disease decreased substantially from 1999 to 2010, primarily due to the control of human immunodeficiency virus (HIV) infection, the number of deaths with fungal diagnosis has increased in the non-HIV cohort, with significant increases in patients with diabetes, cancer, immunosuppressive disorders, or sepsis.

Conclusions. The landscape of individuals at risk for serious fungal diseases is changing, with a continued decline in HIV-associated incidence but increased diagnoses in patients with cancer, sepsis, immunosuppressive disorders, and influenza. Additionally, there is an overall increase in the number of fungal infections in recent years, indicating a failure to control fungal disease mortality in these new immunocompromised cohorts. Improvement in the prevention and management of fungal diseases is needed to control morbidity and mortality in the rising number of immunocompromised and at-risk patients in the United States.

Keywords. mycoses; fungal disease; mortality analysis; United States.

Serious and invasive fungal infections generally occur in conjunction with other health issues that have resulted in mild to severe immunocompromised states. In the early 1980s, increased attention regarding the clinical importance of invasive fungal infections (IFIs) was a sequela of the eruption of the human immunodeficiency virus (HIV)/AIDS epidemic. The opportunistic fungal pathogen, *Pneumocystis jirovecii*, the causative agent of *Pneumocystis* pneumonia (PCP), was identified as an early AIDS-defining illness and the leading cause of morbidity and mortality in these patients for many years [1]. The advent of antiretroviral therapy substantially increased control of HIV, and thus PCP, as well as morbidity and mortality associated with other related opportunistic fungal pathogens.

Recently, there has been a shift in the populations most frequently associated with IFIs away from those who are HIV positive to patients with drug-induced immunosuppression. These include solid-organ and stem cell transplant recipients [2], patients with cancer [3], patients receiving immunomodulators for autoimmune disease and inflammatory diseases [4–6], as well a small cohort of patients with newly diagnosed HIV and those with poor viral control. Fungal infections are also found in patients with less severe comorbidities, including diabetes [7, 8], asthma [9], cystic fibrosis [10, 11], tuberculosis [12], influenza [13, 14], and most recently, coronavirus disease 2019 (COVID-19) [15, 16]. While these immunocompromised cohorts are primarily affected by opportunistic pathogens like *Candida*, *Aspergillus*, and *Pneumocystis*, endemic mycoses, such as *Coccidioides*, *Histoplasma*, and *Blastomycoses*, can cause disease in both immunocompetent and immunocompromised hosts, with a state of impaired immunity resulting in more severe disease [17, 18].

Despite increasing appreciation of the role of fungal disease in immunocompromised patients, active improvement in diagnostic and therapeutic options has only recently gained momentum [19]. The development of new antifungal drugs has primarily focused on the azole and echinocandin classes, with reformulations as a priority, while some vaccine candidates work their way towards clinical trials [20]. However, in the clinical setting, poor patient outcomes continue to be exacerbated by delayed diagnosis and treatment due to the nonspecific symptoms of invasive fungal disease, such as fever, fatigue, cough, and difficulty breathing. Furthermore, a lack

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of standard diagnosis and treatment guidelines means there is still a high degree of variability in the prognosis of infected individuals [21]. Even with prophylactic strategies with standard antifungals, breakthrough infections occur, and these regimens fail to provide long-term protection once discontinued. There are additional concerns regarding drug–drug interactions and the potential for the development of antifungal drug resistance with extended use for prophylaxis and treatment [22–24].

In addition to mortality concerns, IFIs in the United States resulted in at least $7.2 billion in healthcare costs in 2017, demonstrating a considerable economic burden [25]. The true healthcare cost is likely much higher due to extensive underdiagnosis and a lack of public health surveillance [26], resulting in a continued inability to fully assess the burden of fungal disease in the United States. A more comprehensive understanding of the extent of IFIs in the immunocompromised population, as well as IFI-associated mortality, is needed to highlight the importance of fungal disease management. We used data from the National Vital Statistics System to identify the trends in risk conditions and fungal disease in people who died in the United States from 1999 through 2018.

METHODS

The National Vital Statistics System's multiple-cause-of-death mortality files for 1999–2018 (including all ages) were used for this analysis. *International Classification of Diseases, 10th Revision* (ICD–10), codes (Table 1) were used to identify high-risk patients, coinfections, and fungal disease in any of the 20 "entity axis" data fields for multiple causes of death. In this analysis, deaths "from" a particular fungal disease include any mention of fungal disease on the death certificate, regardless of whether it was identified as the primary cause of death, as all listed diagnoses must have contributed to death. The total number of infections were used for all fungal analyses in order to more equally assess all fungal pathogens. Total counts were assessed longitudinally in Figures 1 and 2 for risk conditions and fungal infections, respectively. For the remaining analyses, only mortality records that contained at least 1 fungal infection and at least 1 risk condition were utilized.

Age-adjusted rates were calculated using the direct method and the 2000 US standard population. All statistical analysis was performed with SAS version 9.4 (SAS Institute, Inc, Cary, NC). Figures were created using GraphPad Prism (GraphPad Software, La Jolla, CA). To test recent trends in the number of fungal diagnoses in each high-risk cohort, linear regression evaluated the relationship between year, ranging from 2009 to 2018, and number of fungal infections. Risk ratio analysis, with corresponsing 95% confidence internals (CI), was conducted to determine if a single fungal pathogen was more likely associated with a given risk condition over all other fungal pathogens, using the most recent data from 2018.

RESULTS

Of the 2.8 million people who died in the United States in 2018, 429 447 (15.1%) had 1 049 267 diagnoses associated with elevated risk of IFIs. There has been a steady rise in the absolute number of immunosuppressed conditions diagnosed at time of death, most notably over the past 10 years (Figure 1). The greatest decrease in immunosuppressed populations during this time was a steady decline in the incidence of HIV infections. Deaths related to cancer also declined, while the total number of diagnoses for pneumonia, diabetes, and sepsis all rose appreciably.

While the total number of diagnoses of fungal infections in all deaths declined steadily from 1999 through 2010 (Figure 2A), the total number of infections plateaued in 2010 and has since started to rise. Figure 2B depicts the total number of fungal infections in all mortality unrelated to an HIV diagnosis, demonstrating that the decrease in cases was primarily attributable to HIV infections, and the number of infections in other at-risk groups has risen from 2013 through 2018. In 2018, 5601 fungal infections were diagnosed in 3186 (0.112%) of the 2.8 million people who died in the United States. These results demonstrate that patients were often diagnosed with more than 1 fungal infection at time of death (average: 1.76; range: 1–4). Of the 3186 deaths, 40.9% (1304) had fungal infections listed as the primary cause of death. Additionally, 5016 (89.6%) of the diagnosed fungal infections depicted in Figure 2A were associated with a risk condition listed in Figure 1. The fungal pathogens least accounted for by these risk conditions were primarily endemic, with only 72.8% of *Coccidioides*, 82.5% of *Histoplasma*, and 76.1% other (including *Blastomycoses*), while opportunistic pathogens *Candida and Pneumocystis* each had 99.4% of their diagnoses accounted for by association with these risk conditions.

Rates of Fungal Infections by Associated Condition

Figure 3A highlights the rate of fungal infections within each at-risk cohort, with the rate calculated as the number of infections within that at-risk cohort over the total number of at-risk individuals within that cohort per year. Patients with HIV are still diagnosed at the greatest rate at time of death, but a subset of transplant recipients (noted for specific transplant complications) and patients with tuberculosis or underlying immunosuppressive disorders have additionally elevated rates of fungal disease diagnosis. The rates of fungal diagnosis in these cohorts have been relatively stable for the past decade, indicating that there has not been significant improvement in diagnostics or therapeutic options/strategies in patients who died. Figure 3B depicts the absolute number of diagnosed fungal infections in each at-risk cohort. Initially, patients with HIV were the group with the highest number of diagnosed fungal infections, but rates in this group have steadily declined since 2004; however, the number of cases diagnosed in this cohort has been stable

Table 1. Number of Risk Conditions and Fungal Cases Diagnosed at Time of Death in 2018, United States

	ICD-10 Code	Cases Diagnosed by Time of Death
Risk condition		
Asthma	J45-J46	12 349
Autoimmune conditions	G35, G70, K90, L93, M05, M35	13 012
Celiac disease	K90	792
Lupus	L93	1210
Rheumatoid arthritis	M05	198
Polymyalgia rheumatica	M35	2030
Multiple sclerosis	G35	6380
Myasthenia gravis	G70	2479
Cancer	C00-C97	327 046
Breast	C50	52 674
Colon, rectum, anus	C18–21	61 384
Leukemia	C91–C95	28 895
Lung, trachea, bronchus	C33–C34	153 331
Non-Hodgkin's lymphoma	C82–C85	25 746
Ovary, uterus, cervix	C53–56	32 249
Pancreas	C25	47 320
Stomach	C16	12 055
Urinary	C64–C68	39 000
Other	C00–C15, C17, C22–C24, C26–C32, C37–C49, C51–C52, C57–C60, C62–C63, C69–C81, C88, C90, C96–C97	269 618
Cystic fibrosis	E84	501
Diabetes mellitus	E10–E14	276 528
HIV	B20–B24	7456
Immunosuppressive disorders	D80–D89	4325
Influenza	J09–J11	14 481
Pneumonia	J12–J18	182 950
Sepsis	A40–A41	207 739
Transplant complications	T86	1845
Tuberculosis	A16–A19	1035
Fungal disease		
Aspergillus	B44	807
Invasive	B44.0, B44.1, B44.7	456
Noninvasive	B44.2, B44.8	9
Candida	B37	1031
Invasive	B37.1, B37.5, B37.6, B37.7	595
Noninvasive	B37.0, B37.2, B37.3, B37.4, B37.8	237
Coccidioides	B38	268
Cryptococcus	B45	392
Histoplasma	B39	167
Mucor	B46	151
Pneumocystis	B59	554
Other	B35, B36, B40, B41, B42, B43, B47, B48	460
Unspecified mycoses	B49	1771

Abbreviations: HIV, human immunodeficiency virus; ICD-10, *International Classification of Diseases, 10th Revision.*

since 2011. Since 2010, the highest frequency of fungal diagnoses has been in individuals with sepsis, with a steady rise in that cohort, as well as patients with cancer. Supplementary Figure 1 highlights cohorts with lower rates (<1000 per associated condition diagnosis) and total numbers (<100 per associated condition diagnosis) of fungal infections, including patients with asthma, influenza, or autoimmune conditions. It is more difficult to highlight trends in these cohorts, given the smaller sample size; however, the total number of fungal infections in patients with influenza has increased within the past decade.

Trends in Fungal Diagnoses by Associated Condition

Trends in fungal disease by underlying condition are displayed in Figure 4, including linear regression results. Focusing within the past decade (2009–2018), the number of fungal infections

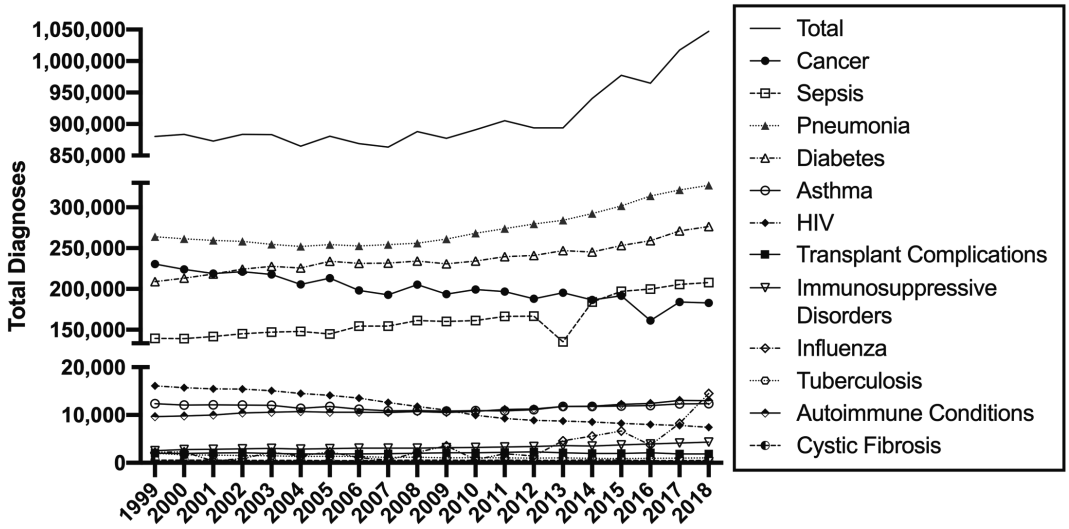

Figure 1. Burden of immunosuppressive diseases and conditions. Total number of diagnoses of associated risk conditions and diseases at time of death over time. Abbreviation: HIV, human immunodeficiency virus.

is significantly increasing in the non-HIV cohorts. In patients with cancer, total fungal diagnoses increased by 149% (Figure 4A) ($P = .0004$), with additional significant increases in patients with diabetes (Figure 4B) ($P = .0318$), immunosuppressive disorders (Figure 4E) ($P = .0355$), or sepsis (Figure 4F) ($P = .0008$). The steady decrease in the HIV-positive cohort has continued over the decade and this is the only risk group with a significant regression that has a negative coefficient (Figure 4C) ($P = .0005$). There is a steady upward trend in patients with influenza, although the significance of this trend was tempered by the spike in cases during the 2009 influenza pandemic (Figure 4D) ($P = .0702$). Risk conditions with a net fungal case count of less than 10 were categorized as not demonstrating a clinically significant change in trend (Supplementary Figure 2). These included patients with asthma ($P = .7880$), autoimmune diseases ($P = .3839$), cystic fibrosis ($P = .3845$), pneumonia ($P = .7611$), transplant complications ($P = .0515$), and tuberculosis ($P = .2686$).

Pathogen Diversity by Associated Condition

Within the cancer, transplant, and autoimmune disease cohorts, clinical diversity in these underlying conditions translates to a wide variety of fungal diagnoses and related complications, including death. Patients with leukemia and non-Hodgkin's lymphoma were predominantly affected by unspecified fungal infections, followed by *Aspergillus*, at much higher rates compared with the larger cancer cohort (Figure 5A). Within the HIV-positive cohort, *Pneumocystis* and *Cryptococcus* were the primary diagnoses in this group (Figure 5B). Transplant analysis was limited to patients with reported complications at time of death, as opposed to all transplant recipients. However, *Aspergillus* was a major contributor in patients with complications related to bone marrow transplant (Figure 5C). There were no transplant complications in the mortality reports for heart/lung, liver, or stem cell transplant recipients. Patients with autoimmune conditions, which may include those receiving immunomodulating therapies, had a diverse prevalence of fungal diagnoses with *Candida,* primarily diagnosed in patients with celiac disease, while those with rheumatoid arthritis were more likely to be diagnosed with *Pneumocystis* and those with lupus were most likely to be diagnosed with an unspecified fungal infection (Figure 5D).

As noted in Figure 5, some risk conditions are predominantly associated with a single fungal pathogen and these associations should be taken into consideration when diagnosing infections in these cohorts. In Figure 6, longitudinal analysis of the rate of fungal diagnoses by risk condition further highlights these relationships, with risk ratio (RR) analysis conducted for the 2018 data. Notably, unspecified mycoses were diagnosed at the highest rate in patients with cancer, diabetes, and sepsis. However, secondary to unspecified mycoses, the prevalence of *Aspergillus* and *Candida* has remained elevated in patients with diabetes compared with other fungal diagnoses, with a combined risk of diagnosis of 1.33 (confidence interval [CI]: 1.2–1.4; $P < .0001$). Cancer and sepsis were both defined by *Candida* infections as well (RR [CI]: 1.57 [1.4–1.8], $P < .0001$; 2.2 [2.0–2.4], $P < .0001$). Individuals with transplant complications were significantly more likely to be diagnosed with *Aspergillus* than any other fungal pathogen (RR: 2.34; CI: 1.7–2.9; $P < .0001$). Influenza and *Aspergillus* diagnoses have been more closely associated in recent years with an RR of 1.96 (Supplementary Figure 3) (CI: 1.4–2.5; $P = .0004$). Finally, HIV diagnosis continues to be most closely associated with *Pneumocystis* (RR: 4.93; CI: 4.3–5.6; $P < .0001$). Pathogen-specific screening in

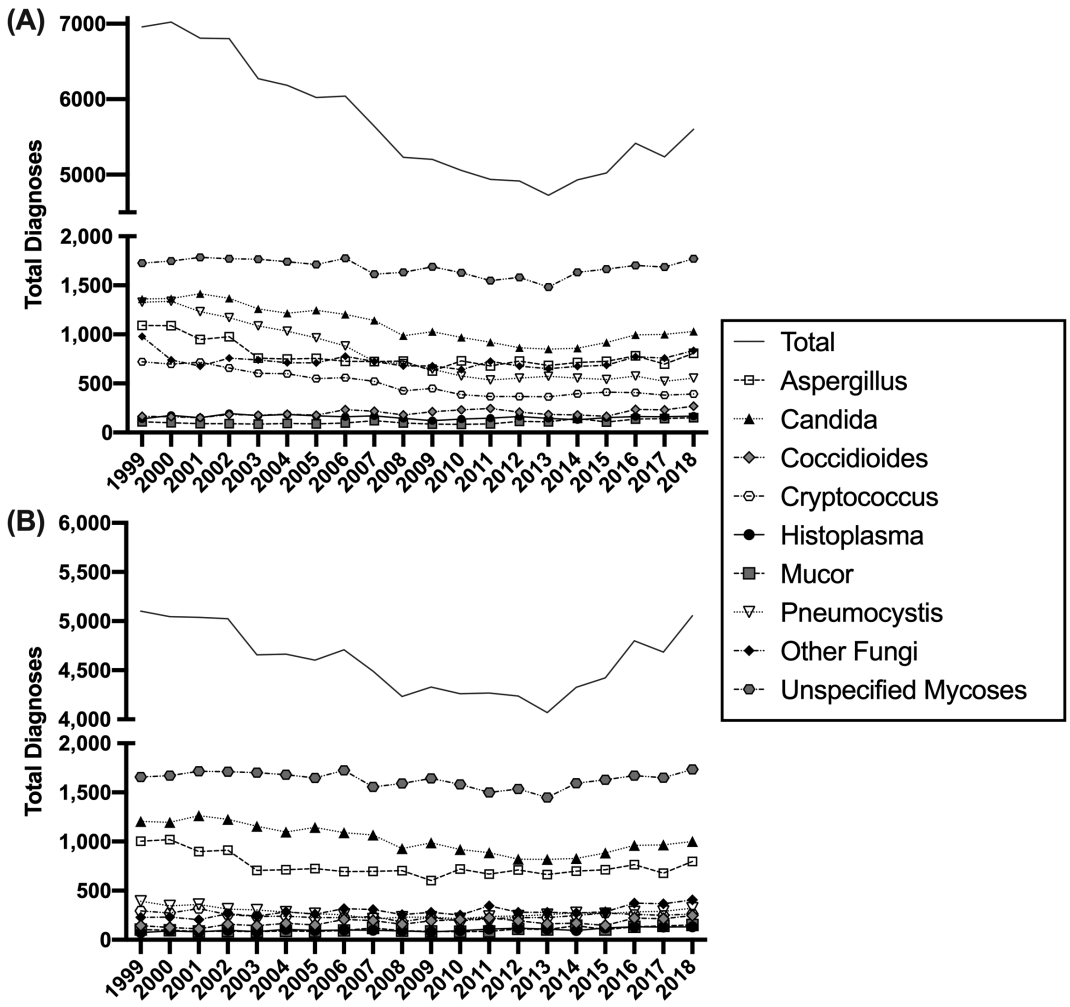

Figure 2. Burden of fungal disease. Total number of diagnosed fungal infections by type in (*A*) all recorded deaths and (*B*) in persons without an HIV diagnosis, over time. Abbreviation: HIV, human immunodeficiency virus.

these cohorts may increase the odds of a more accurate and rapid diagnosis. No significant association with a single pathogen was found in patients with asthma, autoimmune diseases, cystic fibrosis, immunosuppressive disorders, pneumonia, or tuberculosis (Supplementary Figure 3)

DISCUSSION

This analysis provides the first update on the burden of risk conditions and fungal disease at time of death in the United States since 2001 [27]. Our findings demonstrate that the landscape of the immunosuppressed population and those at risk for fungal infections in the United States is changing. With the advent of improved HIV prevention and treatment, as well as the increase in other high-risk populations, the incidence of serious fungal infections and mortality has shifted. Following the trends observed by McNeil et al [27], fungal infections substantially decreased in the early 2000s with HIV control and public health intervention. However, after stabilizing around 2009, the number of deaths with fungal diagnosis has increased, primarily in the cohort without HIV, with significant upward trends in patients with cancer, diabetes, influenza, immunosuppressive disorders, or sepsis. These results reflect the transformation of those affected by fungal disease, both in an expanding recognition of at-risk groups as well as the increase in lifespans and the size of these at-risk patient populations. With improvements in transplant surgeries and management regimens (Organ Procurement and Transplantation Network data as of 8 January 2019), immunomodulators, and cancer treatments [28], this translates to larger patient populations undergoing immunosuppressive treatments moving forward.

In 2018, the patients impacted by fungal disease at the highest rate at time of death were those with HIV, transplant complications, immunosuppressive disorders, or tuberculosis, while patients with cancer, sepsis, HIV, or pneumonia were diagnosed with the highest total numbers. We observed that the relationships between immunosuppression and

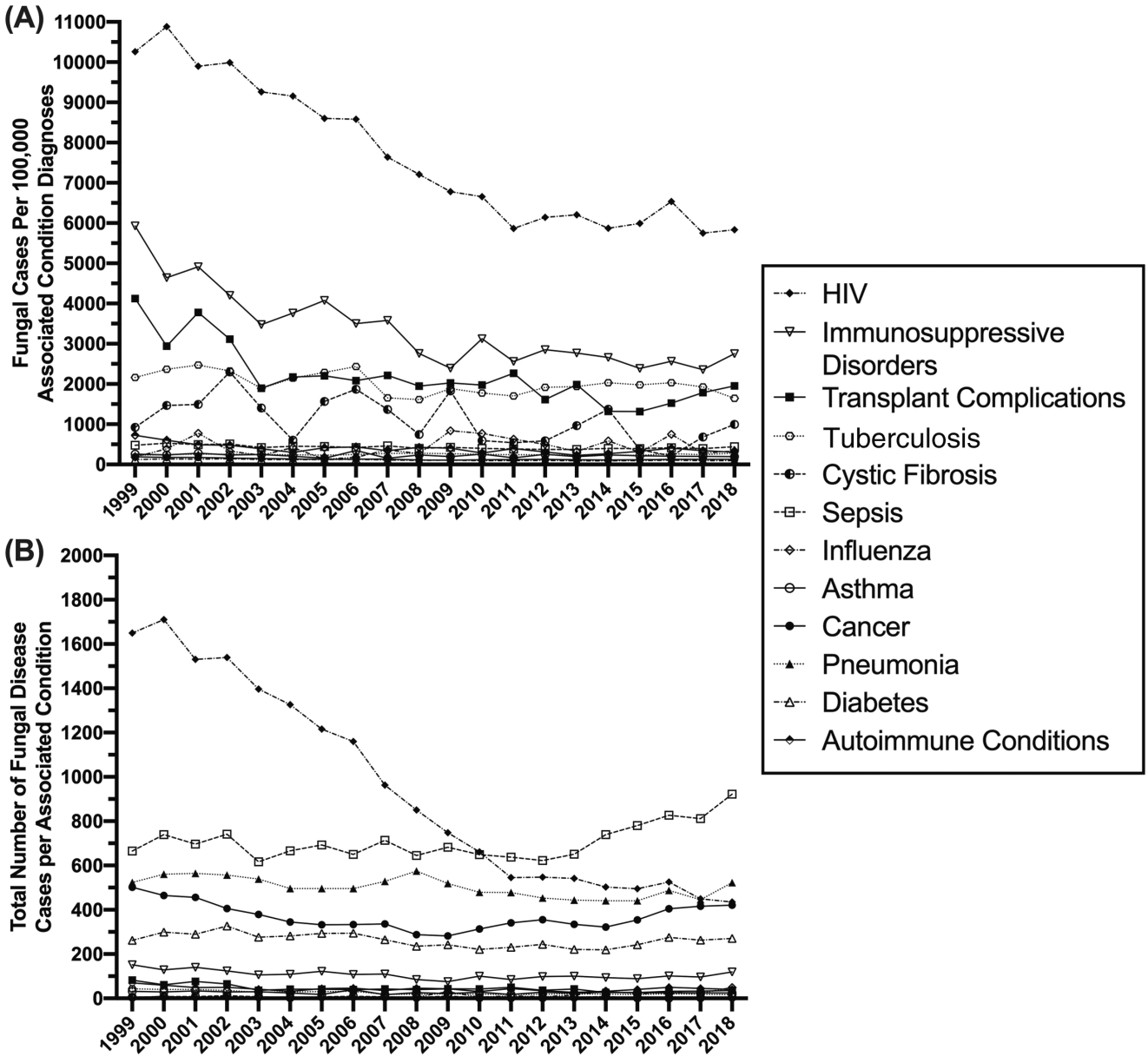

Figure 3. Fungal disease diagnosis by underlying condition. A) Age adjusted rate and B) total number of diagnosed fungal infections by underlying at-risk condition at time of death. Abbreviation: HIV, human immunodeficiency virus.

frequency of specific fungal diagnosis is consistent with previous findings regarding *Aspergillus* infections and asthma complications [9], *Candida* and *Aspergillus* infections associated with diabetes mellitus [7, 8], and *Pneumocystis* in persons with HIV. Interestingly, transplant complications reported at time of death appear to be most closely associated with *Aspergillus* infections, as studies in the US-based Transplant-Associated Infection Surveillance Network (TRANSNET) found *Candida* to be the predominant pathogen associated with solid-organ transplantation [2] and *Aspergillus* in bone marrow transplantation [29]. The majority of transplant complications reported here were in patients who had received a bone marrow transplant, so these results broadly reflect the TRANSNET findings. While pathogen-specific screening may increase speed and accuracy of diagnosis, and thus improve morbidity and mortality in IFIs, there is emerging evidence of other fungal infections associated with chronic diseases, such as *Pneumocystis* in asthma [30, 31] and chronic obstructive pulmonary disease [32] and *Mucor* in transplant recipients [33]. Additionally, the high rate of unspecified mycoses reporting highlights clinical gaps in specific fungal diagnostics, which is especially notable in patients with cancer or sepsis.

The findings observed in this dataset echo a field that is constantly expanding the known clinical implications of fungal

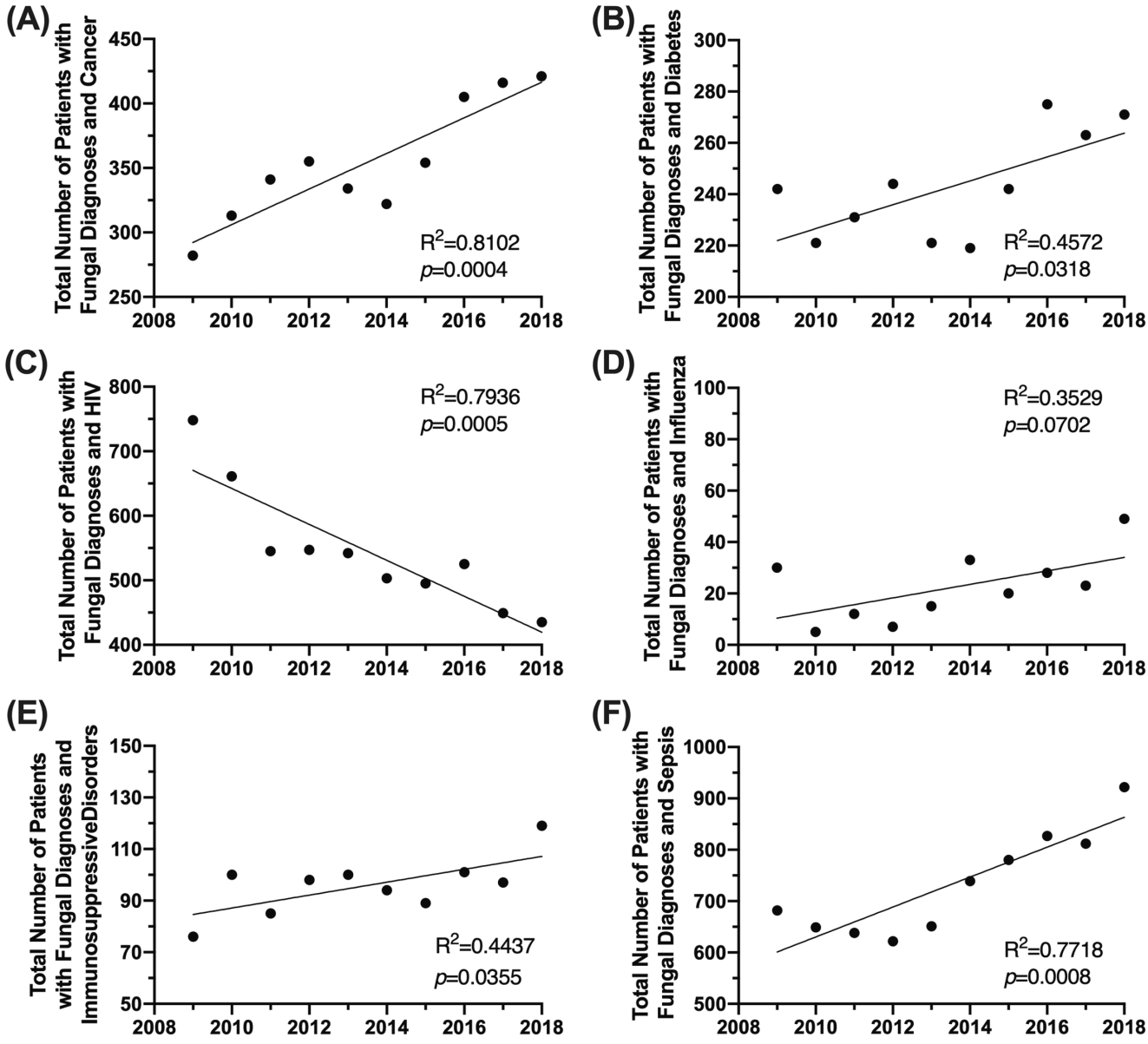

Figure 4. Trends in fungal disease diagnosis by underlying condition. Linear regression of the total number of fungal disease diagnoses reported from 2009 to 2018 in patients with (*A*) cancer, (*B*) diabetes, (*C*) HIV, (*D*) influenza, (*E*) immunosuppressive disorders, and (*F*) sepsis. Abbreviation: HIV, human immunodeficiency virus.

disease. Here, we found that an emerging relationship of *Aspergillus* with influenza, likely due to clinical observations of *Aspergillus* superinfections in the 2009/2010 influenza pandemic [34, 35]. However, the connection between *Aspergillus* and viral coinfections has recently extended to include severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and COVID-19–associated pulmonary aspergillosis. While COVID-19–related mortality could not be assessed in this dataset, given that it predates the pandemic, patients with COVID-19 who are mechanically ventilated have high rates of *Aspergillus* coinfection (10–33%) [16, 36]. Furthermore, additional underlying immunosuppression has been found to correlate with increased risk of invasive mold infections (including aspergillosis) in patients with COVID-19 in intensive care, with solid-organ transplant recipients having 4.66 times the odds and patients on long-term corticosteroids having 8.55 times the odds of invasive aspergillosis compared with those without underlying immunosuppression [37].

The analysis conducted in the National Vital Statistics System dataset had a number of limitations. There was a high rate of unspecified fungal infections, especially within *Aspergillus* (31.2%) and *Candida* (19.3%), limiting a clear assessment of invasive disease. Furthermore, unspecified mycoses made up one-third (33.7%) of the fungal infections reported in 2018, somewhat limiting pathogen-specific analysis. Patient conditions and history unrelated to their death are not listed as

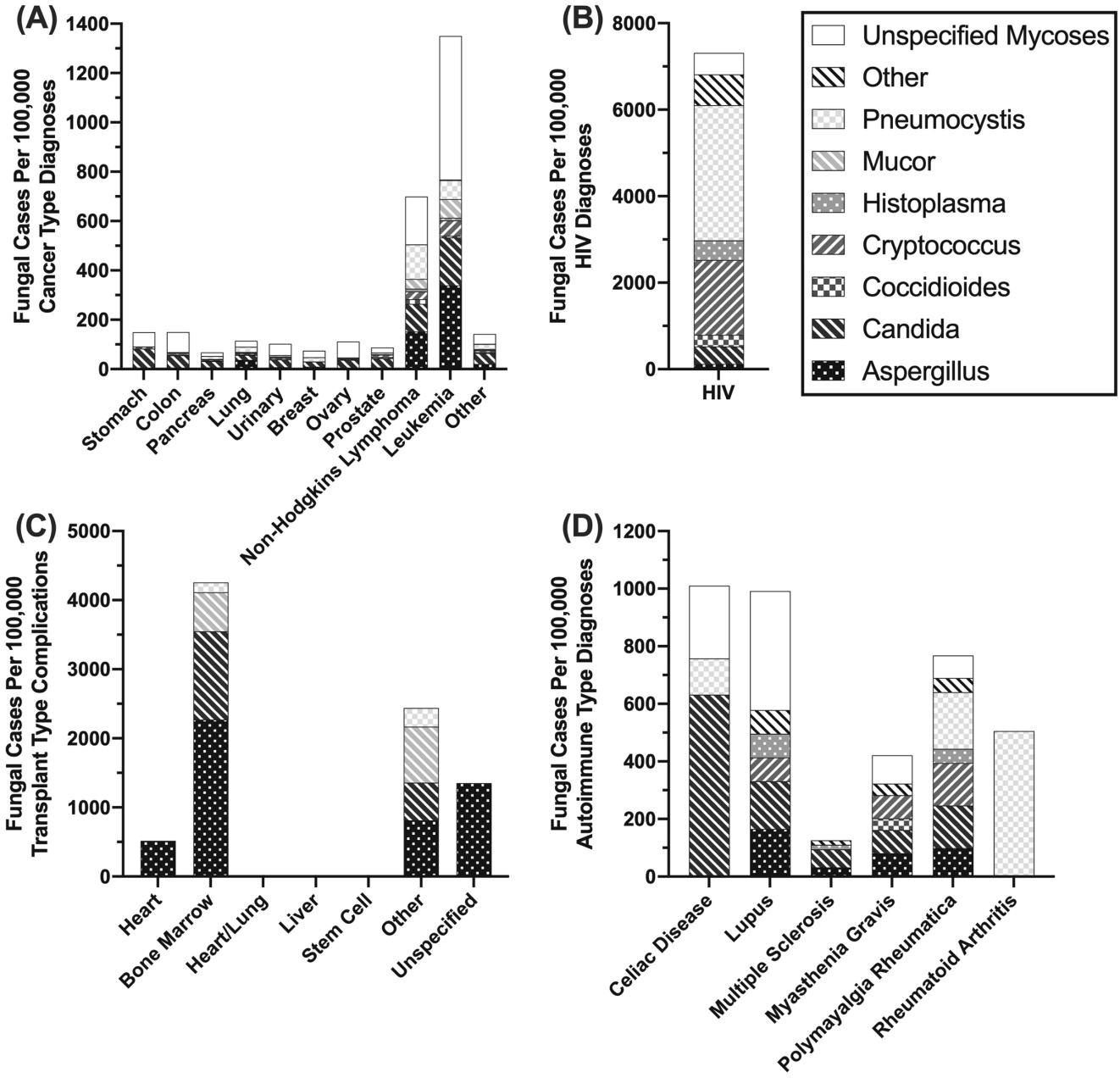

Figure 5. Burden of fungal infections in diverse risk condition types, 2018. Rate of fungal infections in patients with (*A*) cancer, (*B*) HIV, (*C*) transplant complications, or (*D*) autoimmune disease, by type. Abbreviation: HIV, human immunodeficiency virus.

part of this dataset. For example, the ICD-10 code related to transplants was specific to transplant complications while the broader code for history of organ transplantation was not included. This primarily limited the analysis of transplant cohorts as some common transplant types, including stem cell, were not included in any patient mortality report, indicating that a transplant complication was not identified by the physician as a comorbidity contributing to patient death. Further analysis of the morbidity of fungal disease in high-risk groups in the hospitalization setting will also be informative in evaluating the impact of these pathogens.

While this analysis focused on a rise in fungal infections as a result of the increasing size of at-risk populations, these are a number of reasons for fungal disease to be of major clinical concern. From agriculturally linked azole resistance in *Aspergillus* species [38] to multidrug-resistant *Candida auris* in healthcare settings [39], fungal pathogens are matching and outcompeting our current standard of care. With nonspecific clinical symptoms and a lack of pathogen-specific diagnostic options or standardized diagnostic procedures, fungal infections are chronically underdiagnosed. In this dataset, patients were often diagnosed with more than 1 fungal condition related

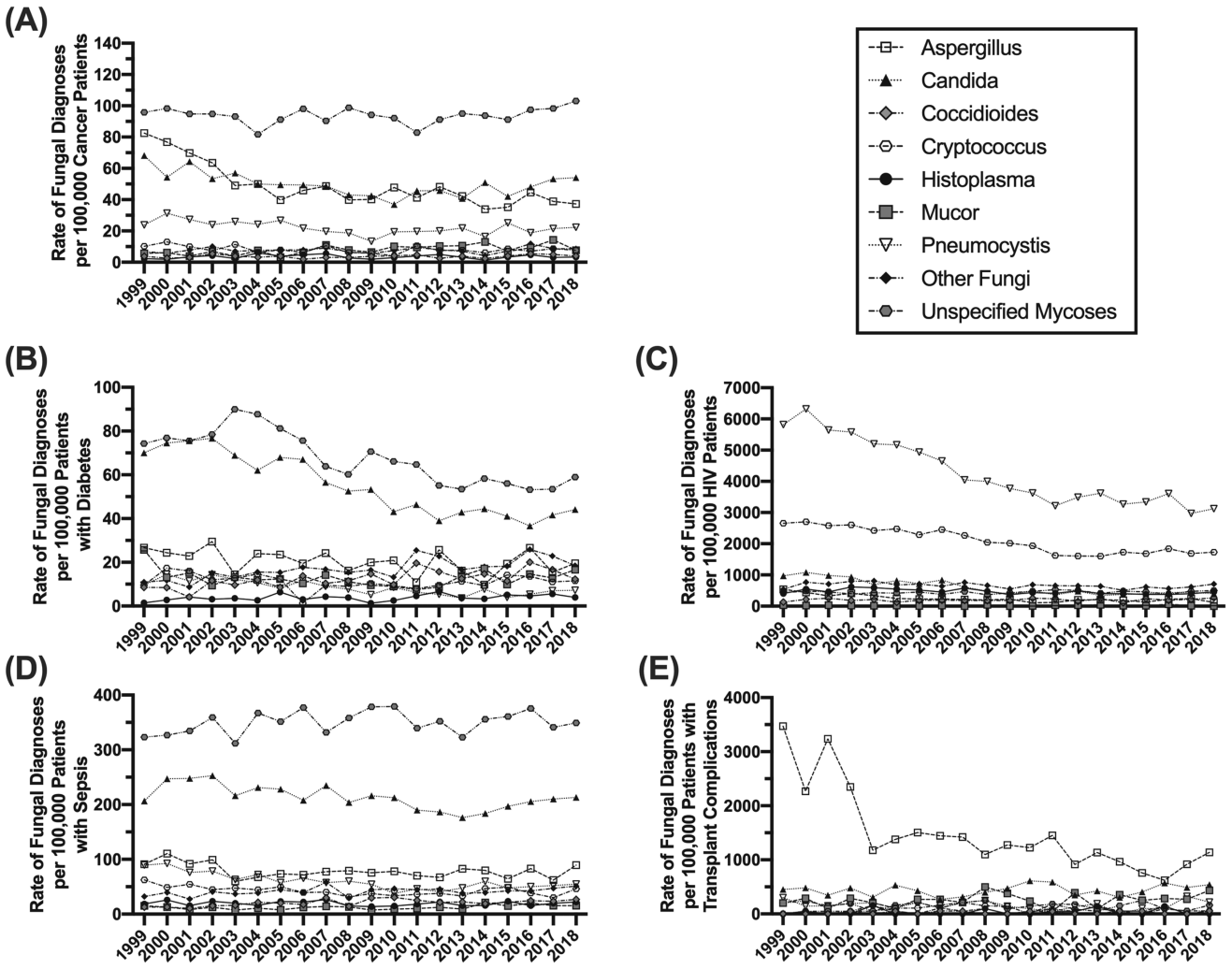

Figure 6. Fungal disease type by associated condition. Rate of fungal diagnoses by type in patients with (*A*) cancer, (*B*) diabetes mellitus, (*C*) HIV, (*D*) sepsis, or (*E*) transplant complications. Abbreviation: HIV, human immunodeficiency virus.

to mortality, if they were diagnosed with any at all. Additionally, endemic mycoses, including *Coccidioides* and *Histoplasma*, make up a smaller proportion of fungal infections compared with opportunistic pathogens. As noted in the Results section, infections caused by endemic pathogens were less likely to be reported than opportunistic pathogens in association with high-risk conditions, fitting with the literature that documents endemic mucosal infections in immunocompetent hosts [18]. While these infections are less frequent, these mycoses are increasingly reported in areas where they were not previously considered endemic. It has been proposed that these changes are associated with human migration, agricultural practices, deforestation, and climate change [40].

Invasive fungal infections present a growing risk in the United States. The number of immunocompromised and at-risk patients is increasing, observed through reported deaths annually. There has been a demonstrated increasing trend in fungal infections, especially within non-HIV cohorts. A lack of advancement in diagnostics, standardized prophylactic regimens, and therapeutics has likely contributed to the increased number of fungal disease deaths in the past decade. These results continue to highlight a critical need for improvement in fungal disease surveillance, prevention, and management.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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