1 Increased deaths from fungal infections during the COVID-19 pandemic — National Vital

2 Statistics System, United States, January 2020–December 2021

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1 ABSTRACT:

Background: COVID-19-associated fungal infections cause severe illness, but comprehensive data on 2 3 disease burden are lacking. We analyzed US National Vital Statistics System (NVSS) data to characterize disease burden, temporal trends, and demographic characteristics of persons dying from 4 fungal infections during the COVID-19 pandemic. 5 6 Methods: Using NVSS's January 2018–December 2021 Multiple Cause of Death Database, we 7 examined numbers and age-adjusted rates (per 100,000 population) of fungal deaths by fungal pathogen, COVID-19 association, demographic characteristics, and year. 8 **Results:** Numbers and age-adjusted rates of fungal deaths increased from 2019 (n = 4,833, rate 1.2, 95% 9 confidence interval [CI] = 1.2-1.3) to 2021 (n = 7,199, rate: 1.8, 95% CI = 1.8-1.8); of 13,121 fungal 10 deaths during 2020-2021, 2,868 (21.9%) were COVID-19-associated. Compared with non-COVID-19-11 associated fungal deaths (n = 10,253), COVID-19-associated fungal deaths more frequently involved 12 *Candida* (n = 776 [27.1%] versus n = 2,432 [23.7%]) and *Aspergillus* (n = 668 [23.3%] versus n = 1,486 13 [14.5%]) and less frequently involved other specific fungal pathogens. Fungal death rates were generally 14 highest in non-White and non-Asian populations. Death rates from Aspergillus infections were 15 approximately two times higher in the Pacific US census division compared with most other divisions. 16 **Conclusions:** Fungal deaths increased during 2020–2021 compared with previous years, primarily 17 driven by COVID-19-associated fungal deaths, particularly those involving Aspergillus and Candida. 18 Our findings may inform efforts to prevent, identify, and treat severe fungal infections in COVID-19 19 patients, especially in certain racial/ethnic groups and geographic areas. 20 **Key words:** death certificates; invasive fungal infections; COVID-19; aspergillosis; candidiasis 21

1 BACKGROUND

2	Fungal infections cost the US healthcare system >\$7.2 billion each year and cause substantial
3	morbidity and mortality [1, 2]. The most common pathogenic fungi include certain yeasts (e.g.,
4	Candida, Cryptococcus), yeast-like fungi (Pneumocystis), molds (e.g., Aspergillus, Mucorales spp.), and
5	dimorphic fungi (e.g., Histoplasma, Coccidioides). The clinical spectrum of fungal diseases ranges from
6	superficial mucocutaneous lesions to severe, life-threatening infections. Severe fungal infections
7	typically affect persons with immunocompromising conditions such as solid organ and stem cell
8	transplantation, cancer, receipt of immunosuppressive medications, advanced HIV disease, and critical
9	illness [3-6]. Other increasingly recognized risk factors include uncontrolled diabetes, chronic lower
10	respiratory tract diseases, influenza, and more recently, COVID-19 [2, 6].
11	Since the first US case was detected during January 2020 [7], more than 880,000 US residents
12	have died from COVID-19 (as of March 9, 2022) [8]. COVID-19 might increase the risk for severe
13	fungal infections because of COVID-19-related immune system dysfunction, structural lung damage,
14	and treatments (e.g., corticosteroids, immunomodulatory drugs) that impair host defenses against fungal
15	pathogens [6]. The development of severe fungal infections in COVID-19 patients can lead to poor
16	outcomes, including death [6, 9-13].

In the United States, public health surveillance for most types of fungal infections is lacking. Data on the landscape of fungal infections during the COVID-19 pandemic era could help guide the prioritization of public health resources related to disease prevention, diagnosis, and treatment. Vital statistics data, made publicly available through the US National Vital Statistics System (NVSS), can provide comprehensive assessments of mortality burden and disease trends during public health emergencies [14]. We analyzed NVSS data to characterize fungal disease burden, temporal trends, and demographic characteristics of persons who died from fungal infections during January 2020–

24 December 2021.

1 METHODS

We analyzed NVSS's Provisional Multiple Cause of Death datafiles. These files include final 2 mortality data for residents of the 50 US states and the District of Columbia during 2018-2020 and 3 provisional mortality data for 2021. We accessed data on February 17, 2022, using CDC's Wide-ranging 4 Online Data for Epidemiologic Research (CDC-WONDER) (https://wonder.cdc.gov/mcd-icd10-5 provisional.html), a free, web-based platform. NVSS last updated the data analyzed for this report on 6 7 February 6, 2022. The mortality data are based on death certificates, which are completed according to instructions provided by the National Center for Health Statistics [15]. Death certificates include a single 8 underlying cause of death, up to 20 additional multiple causes of death, and demographic data. Causes 9 of death are coded according to the International Classification of Diseases, Tenth Revision (ICD-10) 10 [15]. We identified deaths involving fungal pathogens ("fungal deaths") using the following ICD-10 11 codes: B44 (Aspergillus); B37 (Candida); B38 (Coccidioides); B45 (Cryptococcus); B39 (Histoplasma); 12 B46 (Mucorales spp.); B59 (Pneumocystis); B35-B36, B40-B43, or B47-B48 (other specified fungal 13 14 pathogens); and unspecified fungal pathogens (B49). We used ICD-10 code U07.1 to identify deaths involving COVID-19 ("COVID-19 deaths"). The underlying cause of death is the condition that started 15 the chain of events leading to a person's death. All diagnoses listed on a death certificate must be part of 16 17 the causal pathway of events and conditions leading to death or be a significant condition that contributed to the death [15]; therefore, we defined death from a particular condition as the condition's 18 inclusion on the death certificate, regardless of whether the condition was a contributing or underlying 19 cause. 20

We calculated age-adjusted death rates using the year 2000 standard US population [16]. For fungal deaths occurring during January 2018–December 2021, we examined the numbers, percentages, and age-adjusted rates by fungal pathogen, COVID-19 association (i.e., whether COVID-19 contributed to death [2020–2021 only]), and year. To visualize trends in fungal deaths during the COVID-19

1 pandemic, we examined the monthly number of fungal deaths by COVID-19 association alongside the

2 monthly total number of COVID-19 deaths.

3	For fungal deaths occurring during January 2020–December 2021, we stratified data by COVID-
4	19 association and examined numbers, percentages, and age-adjusted rates of death by sex,
5	race/ethnicity, US census division of residence (https://www.census.gov/programs-surveys/economic-
6	census/guidance-geographies/levels.html), and type of fungal disease; we examined crude death rates
7	across 10-year age groups and urban-rural 2013 classifications of residence
8	(https://www.cdc.gov/nchs/data_access/urban_rural.htm). Crude death rates were shown for urban-rural
9	classification because age-stratified death rates by urban-rural status were not available on CDC-
10	WONDER. Death rates based on counts of less than twenty were not calculated. We categorized
11	race/ethnicity as Hispanic or Latino (Hispanic), non-Hispanic White (White), non-Hispanic Black
12	(Black), non-Hispanic Asian (Asian), non-Hispanic American Indian or Alaska Native (AI/AN), non-
13	Hispanic Native Hawaiian or other Pacific Islander (NHPI), non-Hispanic multiracial, and unknown. We
14	analyzed data using the six single race categories because these were the only categories for which race-
15	specific population estimates for rate denominators were available on the CDC-WONDER platform.

16 **RESULTS**

During 2018–2021, 22,700 fungal deaths occurred (Table 1). The number and age-adjusted rates 17 of fungal death per 100,000 population were similar in 2018 (n = 4,746) and 2019 (n = 4,833) (rate 18 during both years: 1.2, 95% confidence interval [CI] = 1.2-1.3) and increased in 2020 (n = 5,922, rate: 19 1.5, 95% CI = 1.5–1.5) and 2021 (n = 7,199, rate: 1.8, 95% CI = 1.8–1.8). Of the 13,121 fungal deaths 20 that occurred during 2020–2021, 2,868 (21.9%) were COVID-19-associated. For these 2,868 deaths, 21 COVID-19 was the most frequent underlying cause of death (n = 2,596, 90.5%). COVID-19–associated 22 23 fungal deaths (n = 2,868) comprised 0.3% of the total number of COVID-19 deaths (n = 840,817) during 24 2020-2021.

1	For all 2020–2021 fungal deaths ($n = 13,121$), the most commonly documented fungal pathogens
2	were <i>Candida</i> (n = 3,208, 24.4%) and <i>Aspergillus</i> (n = 2,154, 16.4%); for 4,673 (35.6%) fungal deaths,
3	the fungal pathogen was unspecified. Compared with non-COVID-19-associated fungal deaths (n =
4	10,253), COVID-19–associated fungal deaths ($n = 2,868$) more frequently involved <i>Candida</i> ($n = 776$
5	[27.1%] versus n = 2,432 $[23.7%]$) and <i>Aspergillus</i> (n = 668 $[23.3%]$ versus n = 1,486 $[14.5%]$) and less
6	frequently involved other specific fungal pathogens. During 2018–2021, the age-adjusted rate of death
7	involving Mucorales spp. was <0.1 per 100,000 population each year; however, the number of fungal
8	deaths involving Mucorales spp. increased from 134 in 2019 to 232 (47 COVID-19-associated, 185
9	non-COVID-19–associated) in 2021.
10	During 2018–2019, the average number of fungal deaths per month was 399 (median = 402 ,
11	range = 351–492) (Figure 1). During the first US peak in COVID-19 deaths (April 2020), 423 fungal
12	deaths occurred (47 COVID-19-associated, 376 non-COVID-19-associated). The monthly number of
13	fungal deaths subsequently peaked during January 2021 (690 fungal deaths; 282 COVID-19 associated,
14	408 non-COVID-19-associated) and October 2021 (718 fungal deaths; 269 COVID-19-associated, 449
15	non-COVID-19-associated), coinciding with peaks in COVID-19 death counts.
16	Among the 13,121 persons who died from fungal infections during 2020–2021, the majority
17	were aged ≥ 65 years (n =7,102, 54.1%) and male (n = 7,828, 59.7%) (Table 2). For COVID-19–
18	associated fungal deaths, age-adjusted death rates per 100,000 population were higher for persons who
19	were AI/AN (1.3, 95% CI = 1.0–1.7), Hispanic (0.7, 95% CI = 0.7–0.8), and Black (0.6, 95% CI = 0.5–
20	0.6), compared with White (0.2, 95% CI = $0.2-0.3$) and Asian (0.3, 95% CI = $0.3-0.4$) persons.
21	Likewise, for non-COVID-19-associated fungal deaths, age-adjusted death rates were higher for persons
22	who were AI/AN (3.0, 95% CI = 2.5–3.5), NHPI (2.4, 95% CI = 1.6–3.5), Black (1.9, 95% CI = 1.8–
23	2.0), and Hispanic (1.5, 95% CI = 1.5–1.6) compared with White (1.1, 95% CI 1.1–1.2) and Asian (1.2,
24	95% CI = $1.1-1.3$) persons. Crude fungal death rates per 100.000 population were higher among

residents of non-metropolitan areas (2.4, 95% CI 2.3–2.5) compared with residents of metropolitan areas
 (1.9, 95% CI = 1.9–2.0), a finding consistent across COVID-19–associated and non-COVID-19–
 associated fungal deaths.

Regarding geographic distribution, the observed age-adjusted rate of fungal deaths per 100,000 4 population were higher in the Mountain (2.1, 95% CI = 2.0-2.2) and Pacific (2.0, 95% CI = 1.9-2.1) US 5 census divisions, and lower in the New England division (1.3, 95% CI = 1.1-1.4) (Figure 2). For 6 COVID-19-associated fungal deaths, the observed rates were higher in the Mountain (0.5, 95% CI = 7 0.4–0.6) and West South Central (0.5, 95% CI = 0.4-0.5) divisions and lower in the New England (0.2, 8 95% CI = 0.2-0.3) division. The contribution of specific fungal pathogens to overall fungal death rates 9 varied across US census divisions (Figure 3). Observed death rates from Coccidioides infections were 10 higher in the Mountain (0.5, 95% CI = 0.5-0.6) and Pacific divisions (0.2, 95% CI = 0.2-0.3) and were 11 <0.1 deaths per 100,000 population in all other US census divisions. Observed death rates from 12 Aspergillus infections were approximately twice as high in the Pacific division (0.4, 95% CI = 0.4-0.5) 13 14 compared with most other divisions.

15 **DISCUSSION**

Our analysis of US death certificate data found that >13,000 persons died from fungal infections during 2020–2021, representing an increase in the numbers and age-adjusted rates of death from fungal infections compared with previous years. This increase was primarily driven by COVID-19–associated fungal deaths, particularly those involving *Aspergillus* and *Candida*, and highlights the importance of considering fungal infections in patients with COVID-19. We also found striking racial/ethnic disparities and geographic differences in rates of death from fungal infections.

In our analysis, fungal death counts rose in tandem with COVID-19 surges during January and
October 2021 but not during the first COVID-19 surge in April 2020. Recent analyses of testing
practices have documented a precipitous decrease in testing for pathogens other than SARS-CoV-2 (the

virus that causes COVID-19) during April 2020, a finding that authors have attributed to strained 1 healthcare resources during the early COVID-19 pandemic [17, 18]. We suspect that the absence of a 2 peak in fungal deaths during April 2020 might reflect a lack of disease detection and reporting rather 3 than a truly low number of COVID-19-associated fungal deaths. Conversely, the peaks in fungal deaths 4 that occurred during January and October 2021 might reflect increased clinician awareness and testing 5 6 for COVID-19-associated fungal infections, and possibly, the increased use of corticosteroids and tocilizumab (both known risk factors for invasive mold infections and candidiasis) [6] to treat patients 7 8 with severe COVID-19.

Our finding that *Candida* and *Aspergillus* were the most commonly identified fungal pathogens 9 causing death is consistent with previous literature describing fungal disease epidemiology both before 10 and during the COVID-19 pandemic [6, 9, 12, 19]. In our analysis, a higher percentage of COVID-19-11 associated fungal deaths involved Candida and Aspergillus compared with non-COVID-19-associated 12 fungal deaths, a finding that aligns with reports identifying COVID-19 as a risk factor for invasive 13 aspergillosis and candidiasis [6, 12]. Although US data on the incidence of COVID-19-associated 14 fungal infections are sparse, a multicenter study from Europe found that >10% of critically ill COVID-15 19 patients might develop invasive aspergillosis, with mortality rates exceeding 40% [12]. Limited 16 reports also suggest that the incidence of invasive candidiasis might have increased during the COVID-17 19 pandemic [6, 20]. In contrast, research has not identified a clear link between the COVID-19 18 pandemic and the incidence of other types of fungal infections in the United States, although US cases 19 of COVID-19-associated fungal infections with Pneumocystis, Cryptococcus, endemic fungi (i.e., 20 Coccidioides, Histoplasma), and Mucorales spp. have all been reported [6, 10, 21-23]. 21

Although we identified an increase in the number of deaths from Mucorales spp. during 2020– 2021 compared with previous years, yearly rates of death for this pathogen remained low throughout the 24 study period (<0.1 per 100,000 population). This finding is consistent with reports highlighting the rarity 1 of mucormycosis in the United States [4, 24, 25]. Nonetheless, previous reports suggest that

mucormycosis can cause severe illness, disfiguration, and death in COVID-19 patients, including among
those who lack severe immunocompromising conditions [10, 13].

Compared with the White and Asian populations, other groups had higher rates of fungal death, 4 particularly when examining fungal deaths associated with COVID-19. This finding is consistent with 5 previous literature describing the disproportionate burdens of both COVID-19 and fungal diseases on 6 certain communities of color [26]. Racial/ethnic disparities in the rates of infection and mortality from 7 COVID-19 are well documented and may stem from inequities in the social determinants of health; for 8 example, persons from certain racial/ethnic groups might be more likely to live in crowded settings, hold 9 jobs requiring in-person work, or have limited healthcare access [27, 28]. The impact of these inequities 10 might extend to fungal diseases, many of which are environmentally acquired and associated with 11 certain occupational exposures [29-31]. Other factors linked to inequities in the social determinants of 12 health, particularly differences in underlying conditions that increase fungal disease risk (e.g., diabetes) 13 and pre-COVID-19 health status, likely contributed to the observed racial/ethnic disparities in fungal 14 burden. 15

Fungal death rates varied widely among US census divisions, a finding largely accounted for by 16 17 differences in rates of death from *Coccidioides* and *Aspergillus* infections. *Coccidioides* is primarily endemic to the southwestern United States; that this pathogen contributed so markedly to the fungal 18 19 death rates in the Mountain and Pacific divisions underscores the threat it poses to public health in the region [32]. To our knowledge, the finding that death rates from *Aspergillus* were twice as high in the 20 Pacific division compared with other divisions has not previously been documented, although research 21 22 suggests that airborne Aspergillus spore counts and rates of invasive aspergillosis might vary depending on factors such as temperature, precipitation, geography, and season [33]. The geographic distribution of 23 aspergillosis has not been well described, in part because aspergillosis is only reportable in one US state 24

1 [34]. Greater public health surveillance for fungal infections, involving geographically and

2 demographically diverse populations, might provide critical information to guide the prevention,

3 diagnosis, and treatment of fungal diseases.

Because US census divisions have differing racial/ethnic compositions and because fungal death 4 rates varied substantially by both US census division and race/ethnicity, we assessed potential 5 6 confounding or interactions between race/ethnicity and census division by examining division-stratified racial/ethnic fungal death rates and race/ethnicity-stratified division fungal death rates. A complete 7 analysis of these stratified death rates was not possible because of NVSS privacy restrictions on small 8 data cells involving geographically stratified data. However, we found that racial/ethnic disparities 9 generally persisted within each US census division and that rates of fungal deaths generally differed by 10 race/ethnicity when stratified by census division (data not shown). Further research may help to describe 11 the intersection of demographic and geographic factors associated with severe fungal diseases. 12

Our findings have several notable limitations. First, provisional mortality data from 2021 are 13 14 incomplete and subject to change, particularly during recent months, as delayed reports might later increase death counts. Our use of broad single race categories limited the level of detail with which we 15 could assess racial/ethnic disparities, particularly among multiracial persons. Another limitation was that 16 we could not assess underlying medical conditions among patients with COVID-19-associated fungal 17 deaths; this is because the CDC-WONDER platform does not allow for the tabulation of more than two 18 19 sets of conditions in combination. Further, data based on ICD-10 codes for fungal infections, particularly those for mold infections such as invasive aspergillosis, are subject to imprecision in 20 reporting and underreporting [35]. In our analysis, more than one-third of deaths involved an unspecified 21 22 fungal pathogen, limiting our ability to precisely describe each fungal pathogen's contribution to overall fungal mortality. Also, our analysis likely underestimates the impact of fungal diseases during the 23 24 COVID-19 pandemic. Current fungal diagnostic tests generally lack sensitivity and might not be widely

available or utilized if healthcare providers do not suspect a fungal infection [36, 37]. Deaths from
invasive mold infections including aspergillosis might be particularly undercounted because this
diagnosis is frequently missed. Studies of autopsies, a procedure performed for <5% of COVID-19
decedents during 2020–2021 [8], have identified mold infections as one of the most commonly missed
diseases among ICU and hematologic malignancy patients [38, 39]. Finally, in focusing only on deaths
from fungal infections, our analysis did not address the considerable long-term morbidity faced by
certain survivors of severe fungal infection [40].

8 Despite its limitations, our analysis demonstrates the substantial burden of fungal infections in 9 the United States and highlights an increase in fungal deaths during the first two years of COVID-19 10 pandemic. These data might help increase clinician awareness and support public health planning, with 11 the ultimate goals of decreasing morbidity and mortality from fungal infections. Detailed public health 12 surveillance for fungal infections, involving geographically and demographically diverse patient 13 populations, might help better characterize disease epidemiology and guide ongoing efforts to prevent 14 fungal infections among disproportionately affected populations.

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16 NOTES

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- consistent with applicable federal law and CDC policy (e.g., 45 C.F.R. part 46, 21 C.F.R. part 56; 42

23 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq).

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References:
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3	1.	Benedict K, Jackson BR, Chiller T, Beer KD. Estimation of Direct Healthcare Costs of Fungal
4		Diseases in the United States. Clinical infectious diseases : an official publication of the
5		Infectious Diseases Society of America 2019; 68(11): 1791-7.
6	2.	Rayens E, Norris KA, Cordero JF. Mortality Trends in Risk Conditions and Invasive Mycotic
7		Disease in the United States, 1999–2018. Clinical Infectious Diseases 2021; 74(2): 309-18.
8	3.	Neofytos D, Treadway S, Ostrander D, et al. Epidemiology, outcomes, and mortality predictors
9		of invasive mold infections among transplant recipients: a 10-year, single-center experience.
10		Transplant infectious disease : an official journal of the Transplantation Society 2013; 15(3):
11		233-42.
12	4.	Ibrahim AS, Spellberg B, Walsh TJ, Kontoyiannis DP. Pathogenesis of mucormycosis. Clinical
13		infectious diseases : an official publication of the Infectious Diseases Society of America 2012;
14		54 Suppl 1(Suppl 1): S16-22.
15	5.	Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of
16		Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clinical Infectious
17		Diseases 2015 ; 62(4): e1-e50.
18	б.	Baddley JW, Thompson GR, III, Chen SC-A, et al. Coronavirus Disease 2019–Associated
19		Invasive Fungal Infection. Open forum infectious diseases 2021; 8(12).
20	7.	Holshue ML, DeBolt C, Lindquist S, et al. First Case of 2019 Novel Coronavirus in the United
21		States. The New England journal of medicine 2020; 382(10): 929-36.
22	8.	Centers for Disease Control and Prevention, National Center for Health Statistics. Provisional
23		Multiple Cause of Death on CDC WONDER Online Database, released 2021. Data are from the
24		final Multiple Cause of Death Files, 2018-2020, and from provisional data for years 2020-2021,
25		as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics

1		Cooperative Program. Accessed at <u>http://wonder.cdc.gov/mcd-icd10-provisional.html</u> on Mar 9,
2		2022 7:39:36 AM.
3	9.	Seagle EE, Jackson BR, Lockhart SR, et al. The Landscape of Candidemia During the
4		Coronavirus Disease 2019 (COVID-19) Pandemic. Clinical Infectious Diseases 2021.
5	10.	Dulski TM, DeLong M, Garner K, et al. Notes from the Field: COVID-19-Associated
6		Mucormycosis - Arkansas, July-September 2021. MMWR Morbidity and mortality weekly
7		report 2021 ; 70(50): 1750-1.
8	11.	Narayanan S, Chua JV, Baddley JW. COVID-19 associated Mucormycosis (CAM): risk factors
9		and mechanisms of disease. Clinical Infectious Diseases 2021.
10	12.	Janssen NAF, Nyga R, Vanderbeke L, et al. Multinational Observational Cohort Study of
11		COVID-19-Associated Pulmonary Aspergillosis(1). Emerging infectious diseases 2021; 27(11):
12		2892-8.
13	13.	Mejia-Chew C, O'Halloran JA, Olsen MA, et al. Effect of infectious disease consultation on
14		mortality and treatment of patients with candida bloodstream infections: a retrospective, cohort
15		study. The Lancet Infectious Diseases 2019; 19(12): 1336-44.
16	14.	Ahmad FB, Anderson RN. The Leading Causes of Death in the US for 2020. JAMA 2021;
17		325(18): 1829-30.
18	15.	Centers for Disease Control and Prevention. Instructions for Classifying the Multiple Causes of
19		Death, 2021. Nastional Vital Statistics System. Hyattsville, MD: US Department of Health and
20		Human Services, CDC, National Center for Health Statistics; 2021;
21	X	https://www.cdc.gov/nchs/nvss/manuals/2a-sectioni-2021.htm Accessed: May 14, 2022.
22	16.	Klein RJ, Schoenborn CA. Age adjustment using the 2000 projected U.S. population. Healthy
23		People 2010 Stat Notes 2001 ; (20): 1-10.
24	17.	Pinto CN, Niles JK, Kaufman HW, et al. Impact of the COVID-19 Pandemic on Chlamydia and
25		Gonorrhea Screening in the U.S. Am J Prev Med 2021; 61(3): 386-93.

1	18.	Kaufman HW, Bull-Otterson L, Meyer WA, 3rd, et al. Decreases in Hepatitis C Testing and
2		Treatment During the COVID-19 Pandemic. Am J Prev Med 2021; 61(3): 369-76.
3	19.	Rayens E, Norris KA. Prevalence and Healthcare Burden of Fungal Infections in the United
4		States, 2018. Open forum infectious diseases 2022 ; 9(1).
5	20.	Nucci M, Barreiros G, Guimarães LF, Deriquehem VAS, Castiñeiras AC, Nouér SA. Increased
6		incidence of candidemia in a tertiary care hospital with the COVID-19 pandemic. Mycoses 2021;
7		64(2): 152-6.
8	21.	Shah AS, Heidari A, Civelli VF, et al. The Coincidence of 2 Epidemics, Coccidioidomycosis and
9		SARS-CoV-2: A Case Report. J Investig Med High Impact Case Rep 2020; 8:
10		2324709620930540.
11	22.	Menon AA, Berg DD, Brea EJ, et al. A Case of COVID-19 and Pneumocystis jirovecii
12		Coinfection. American journal of respiratory and critical care medicine 2020 ; 202(1): 136-8.
13	23.	Heller HM, Gonzalez RG, Edlow BL, Ard KL, Gogakos T. Case 40-2020: A 24-Year-Old Man
14		with Headache and Covid-19. The New England journal of medicine 2020 ; 383(26): 2572-80.
15	24.	Hoenigl M, Seidel D, Carvalho A, et al. The emergence of COVID-19 associated mucormycosis:
16		a review of cases from 18 countries. Lancet Microbe 2022.
17	25.	Pal R, Singh B, Bhadada SK, et al. COVID-19-associated mucormycosis: An updated systematic
18		review of literature. Mycoses 2021.
19	26.	Gold JAW, Rossen LM, Ahmad FB, et al. Race, Ethnicity, and Age Trends in Persons Who Died
20		from COVID-19 — United States, May–August 2020. MMWR Morbidity and mortality weekly
21	Y	report 2020 ; 69(42): 1517-21.
22	27.	Webb Hooper M, Nápoles AM, Pérez-Stable EJ. COVID-19 and Racial/Ethnic Disparities.
23		JAMA 2020 ; 323(24): 2466-7.

1	28.	Bui DP, McCaffrey K, Friedrichs M, et al. Racial and Ethnic Disparities Among COVID-19
2		Cases in Workplace Outbreaks by Industry Sector — Utah, March 6–June 5, 2020. MMWR
3		Morbidity and mortality weekly report 2020 ; 69(33): 1133-8.
4	29.	de Perio MA, Benedict K, Williams SL, et al. Occupational Histoplasmosis: Epidemiology and
5		Prevention Measures. Journal of fungi (Basel, Switzerland) 2021; 7(7).
6	30.	Das R, McNary J, Fitzsimmons K, et al. Occupational coccidioidomycosis in California:
7		outbreak investigation, respirator recommendations, and surveillance findings. J Occup Environ
8		Med 2012 ; 54(5): 564-71.
9	31.	Choptiany M, Wiebe L, Limerick B, et al. Risk factors for acquisition of endemic blastomycosis.
10		Can J Infect Dis Med Microbiol 2009; 20(4): 117-21.
11	32.	Lockhart SR, Toda M, Benedict K, Caceres DH, Litvintseva AP. Endemic and Other Dimorphic
12		Mycoses in The Americas. Journal of fungi (Basel, Switzerland) 2021; 7(2).
13	33.	Panackal AA, Li H, Kontoyiannis DP, et al. Geoclimatic Influences on Invasive Aspergillosis
14		after Hematopoietic Stem Cell Transplantation. Clinical Infectious Diseases 2010; 50(12): 1588-
15		97.
16	34.	Centers for Disease Control and Prevention. Reportable Fungal Diseases by State. Atlanta, GA:
17		US Department of Health and Human Services, CDC. https://www.cdc.gov/fungal/fungal-
18		disease-reporting-table.html Accessed: January 28, 2022.
19	35.	Gold JAW, Revis A, Thomas S, et al. Clinical Characteristics, Healthcare Utilization, and
20		Outcomes among Patients in a Pilot Surveillance System for Invasive Mold Disease—Georgia,
21	Ķ	United States, 2017–2019. Open forum infectious diseases 2022.
22	36.	Clancy CJ, Nguyen MH. Finding the "missing 50%" of invasive candidiasis: how nonculture
23		diagnostics will improve understanding of disease spectrum and transform patient care. Clinical
24		infectious diseases : an official publication of the Infectious Diseases Society of America 2013;
25		56(9): 1284-92.

- I 37. Lass-Flörl C. Current Challenges in the Diagnosis of Fungal Infections. Methods Mol Biol 2017;
 I508: 3-15.
- 3 38. Tejerina EE, Abril E, Padilla R, et al. Invasive aspergillosis in critically ill patients: An autopsy
 study. Mycoses 2019; 62(8): 673-9.
- 5 39. Lewis RE, Cahyame-Zuniga L, Leventakos K, et al. Epidemiology and sites of involvement of
 6 invasive fungal infections in patients with haematological malignancies: a 20-year autopsy study.
 7 Mycoses 2013; 56(6): 638-45.
- 8 40. Thompson GR, 3rd. Pulmonary coccidioidomycosis. Semin Respir Crit Care Med **2011**; 32(6):
- 9 754-63.
- 10

1 **TABLES**

Table 1. Deaths from fungal infections and COVID-19 — National Vital Statistics System Multiple Cause of Death Database, United States, 2018–2021^a

						202	20			20	21	
Fundad	2018		20	19	COVID-19-					COVID-19-		
Fungai					All associa			ciated		All	asso	ciated
pathogen	No.	Rate,	No.	Rate,	No.	Rate,	No.	Rate,	No.	Rate,	No.	Rate,
	(%)	95% CI	(%)	95% CI	(%)	95% CI	(%)	95% CI	(%)	95% CI	(%)	95% CI
	795	0.2,	723	0.2,	918	0.2,	170	0.0,	1236	0.3,	498	0.1,
Aspergillus	(16.8)	0.2–0.2	(15.0)	0.2–0.2	(15.5)	0.2–0.2	(18.9)	0.0–0.0	(17.2)	0.3–0.3	(25.3)	0.1–0.1
	1,010	0.3,	1,171	0.3,	1,439	0.3,	281	0.1,	1,769	0.4,	495	0.1,
Candida	(21.3)	0.2–0.3	(24.2)	0.3–0.3	(24.3)	0.3–0.4	(31.2)	0.1–0.1	(24.6)	0.4–0.4	(25.2)	0.1–0.1
	253	0.1,	192	0.0,	319	0.1,	33	0.0,	359	0.1,	71	0.0,
Coccidioides	(5.3)	0.1–0.1	(4.0)	0.0–0.1	(5.4)	0.1–0.1	(3.7)	0.0–0.0	(5.0)	0.1–0.1	(3.6)	0.0–0.0
	290	0.1,	334	0.1,	341	0,1,	24	0.0,	342	0.1,	49	0.0,
Cryptococcus	(6.1)	0.1–0.1	(6.9)	0.1–0.1	(5.8)	0.1–0.1	(2.7)	0.0–0.0	(4.8)	0.1–0.1	(2.5)	0.0–0.0
	146	0.0,	133	0.0,	130	0.0,	6		199	0.0,	21	0.0,
Histoplasma	(3.1)	0.0–0.0	(2.8)	0.0–0.0	(2.2)	0.0–0.0	(0.7)	_	(2.8)	0.0–0.1	(1.1)	0.0–0.0
Mucorales	151	0.0,	134	0.0,	169	0.0,	17		232	0.0,	47	0.0,
spp.	(3.2)	0.0–0.0	(2.8)	0.0–0.0	(2.9)	0.0–0.0	(1.9)	_	(3.2)	0.0–0.0	(2.4)	0.0–0.0
	371	0.1,	436	0.1,	381	0.1,	13		449	0.1,	48	0.0,
Pneumocystis	(7.8)	0.1–0.1	(9.0)	0.1–0.1	(6.4)	0.1–0.1	(1.4)	_	(6.2)	0.1–0.1	(2.4)	0.0–0.0
Other	116	0.0,	118	0.0,	131	0.0,	3		131	0.0,	9	
specified pathogens	(2.4)	0.0–0.0	(2.4)	0.0–0.0	(2.2)	0.0–0.0	(0.3)	—	(1.8)	0.0–0.0	(0.5)	—
	1,649	0.4,	1,623	0.4,	2,135	0.5,	362	0.1,	2,538	0.7,	746	0.2,
Unspecified	(34.7)	0.4–0.5	(33.6)	0.4–0.4	(36.1)	0.5–0.6	(40.2)	0.1–0.1	(35.3)	0.6–0.7	(37.9)	0.2–0.2
All	4,746	1.2,	4,833	1.2,	5,922	1.5,	901	0.2,	7,199	1.8,	1,967	0.5,
		1.2–1.3		1.2–1.3		1.5–1.5		0.2–0.2		1.8–1.8		0.5–0.5

Abbreviation: ICD-10 = International Classification of Diseases, Tenth Revision; CI = confidence interval

^aData for 2021 are provisional and were last updated February 6, 2022. Death certificates could list more than one fungal ICD-10-CM code; this occurred on <1% of death certificates listing a fungal pathogen. Fungal deaths were defined as deaths where a fungal infection was listed as a contributing or underlying cause of death. COVID-19–associated deaths were defined as deaths where COVID-19 was listed as a contributing or underlying cause of death. The method for calculating the 95% confidence intervals is available online (https://wonder.cdc.gov/wonder/help/mcdprovisional.html#Confidence-Intervals). Age-adjusted death rates were calculated by the direct method using the 2000 U.S. standard population (https://wonder.cdc.gov/wonder/help/mcd-provisional.html#2000%20Standard%20Population). Rates are not shown for groups where the death count was less than 20 (indicated by the symbol "—"). Rates were rounded to one decimal point; therefore, rates of "0.0" might not represent true zeros. Table 2. Demographic characteristics of persons who died from fungal infections and COVID-19 — National Vital Statistics System Multiple Cause of Death Database,^a United States, 2020–2021

Characteristic	AI	I fungal de	aths	C	OVID-19–asso	ciated ^b	Non-COVID-19-associated			
	No.	%	rate (95% CI) $^{\circ}$	No.	%	rate (95% CI) $^\circ$	No.	%	rate (95% CI) $^\circ$	
Overall	13,121	100.0	1.6 (1.6–1.7)	2,868	100.0	0.4 (0.4–0.4)	10,253	100.0	1.3 (1.3–1.3)	
Age group, yrs							\mathcal{R}			
<1	70	0.5	0.9 (0.7–1.2)	1	0.0	- 0	69	0.7	0.9 (0.7–1.2)	
1–4	39	0.3	0.1 (0.1–0.2)	1	0.0	E	38	0.4	0.1 (0.1–0.2)	
5–14	97	0.7	0.1 (0.1–0.1)	7	0.2	C	90	0.9	0.1 (0.1–0.1)	
15–24	193	1.5	0.2 (0.2–0.3)	20	0.7	0.0 (0.0–0.0)	173	1.7	0.2 (0.2–0.2)	
25–34	464	3.5	0.5 (0.5–0.5)	58	2.0	0.1 (0.0–0.1)	406	4.0	0.4 (0.4–0.5)	
35–44	766	5.8	0.9 (0.8–1.0)	135	4.7	0.2 (0.1–0.2)	631	6.2	0.7 (0.7–0.8)	
45–54	1,476	11.2	1.8 (1.7–1.9)	364	12.7	0.5 (0.4–0.5)	1,112	10.8	1.4 (1.3–1.5)	
55–64	2,914	22.2	3.4 (3.3–3.6)	764	26.6	0.9 (0.8–1.0)	2,150	21.0	2.5 (2.4–2.6)	
65–74	3,742	28.5	5.7 (5.6–5.9)	851	29.7	1.3 (1.2–1.4)	2,891	28.2	4.4 (4.3–4.6)	
75–84	2,454	18.7	7.5 (7.2–7.8)	529	18.4	1.6 (1.5–1.7)	1,925	18.8	5.9 (5.6–6.1)	
≥85	906	6.9	6.8 (6.4–7.2)	138	4.8	1.0 (0.9–1.2)	768	7.5	5.8 (5.4–6.2)	
Male sex	7,828	59.7	2.1 (2.1–2.2)	1,800	62.8	0.5 (0.4–0.5)	6,028	58.8	1.6 (1.6–1.7)	
Race/ethnicity								0.0		
White, NH	7,837	59.7	1.4 (1.4–1.4)	1,440	50.2	0.2 (0.2–0.3)	6,397	62.4	1.1 (1.1–1.2)	
Hispanic or Latino	2,195	16.7	2.3 (2.2–2.4)	719	25.1	0.7 (0.7–0.8)	1,476	14.4	1.5 (1.5–1.6)	
Black, NH	2,088	15.9	2.5 (2.3–2.6)	469	16.4	0.6 (0.5–0.6)	1,619	15.8	1.9 (1.8–2.0)	
Asian, NH	621	4.7	1.5 (1.4–1.6)	132	4.6	0.3 (0.3–0.4)	489	4.8	1.2 (1.1–1.3)	
American Indian or Alaska Native, NH	215	1.6	4.3 (3.7–4.9)	67	2.3	1.3 (1.0–1.7)	148	1.4	3.0 (2.5–3.5)	

Native Hawaiian or									
other Pacific	43	0.3	3.8 (2.7–5.1)	17	_		26	0.3	2.4 (1.6–3.5)
Islander, NH									
Multiracial, NH	85	0.6	1.0 (0.8–1.2)	17	—	_	68	0.7	0.8 (0.6–1.0)
Unknown	37	—	_	7	_	_	30	Ċ	—
Urban-rural 2013									
classification of							\checkmark	-	
residence [°]									
Metropolitan	10,948	83.4	1.9 (1.9–2.0)	2,351	82.0	0.4 (0.4–0.4)	8,597	83.8	1.5 (1.5–1.5)
Large central metro	4,186	31.9	2.1 (2.0–2.1)	933	32.5	0.5 (0.4–0.5)	3,253	31.7	1.6 (1.6–1.7)
Large fringe metro	2,764	21.1	1.7 (1.6–1.7)	567	19.8	0.3 (0.3–0.4)	2,197	21.4	1.3 (1.3–1.4)
Medium metro	2,772	21.1	2.0 (1.9–2.1)	553	19.3	0.4 (0.4–0.4)	2,219	21.6	1.6 (1.5–1.7)
Small metro	1,226	9.3	2.0 (1.9–2.2)	298	10.4	0.5 (0.4–0.6)	928	9.1	1.5 (1.4–1.6)
Non-metropolitan	2,173	16.6	2.4 (2.3–2.5)	517	18.0	0.6 (0.5–0.6)	1,656	16.2	1.8 (1.7–1.9)
Micropolitan	1,211	9.2	2.2 (2.1–2.3)	287	10.0	0.5 (0.5–0.6)	924	9.0	1.7 (1.6–1.8)
Non-core	962	7.3	2.6 (2.4–2.7)	230	8.0	0.6(0.5–0.7)	732	7.1	2.0 (1.8–2.1)

Abbreviation: NH = non-Hispanic/non-Latino

^aData for 2021 are provisional and were last updated February 6, 2022. COVID-19–associated fungal deaths (n = 2,868) comprised 0.3% of the total number of COVID-19 deaths (n = 840,817) during 2020–2021.

^bFor these 2,868 deaths, COVID-19 was the most frequent underlying cause of death (n = 2,596, 90.5%)

^cAge-adjusted rates are shown for sex and race/ethnicity; crude rates are shown for age groups and urban-rural 2013 classification of residence. Rates are not shown for conditions where the death count was less than 20, and rates were not available for persons with "unknown" race/ethnicity. These suppressed rates are indicated by the symbol "—". The method for calculating the 95% confidence intervals is available online: https://wonder.cdc.gov/wonder/help/mcd-provisional.html#Confidence-Intervals. Age-adjusted death rates were calculated using the 2000 U.S. standard population (https://wonder.cdc.gov/wonder/help/mcd-provisional.html#2000%20Standard%20Population).

°https://www.cdc.gov/nchs/data_access/urban_rural.htm

1 FIGURE LEGENDS

- 2 Figure 1. Monthly number of deaths from fungal infections and COVID-19 National Vital Statistics
- 3 System, United States, 2018–2021^a
- ^aData for 2021 are provisional and were last updated February 6, 2022.
- 5 Figure 2. Age-adjusted rates of death (per 100,000 population) for all fungal deaths (A) and COVID-
- 6 19–associated fungal deaths (B) by US census division of residence,^a National Vital Statistics System —
- 7 United States, 2020–2021^b
- ^aThe United States Census Bureau defines nine census divisions: New England (CT, MA, ME, NH, RI,
- 9 and VT), Middle Atlantic (NJ, NY, and PA), East North Central (IL, IN, MI, OH, and WI), West North
- 10 Central (IA, KS, MN, MO, ND, NE, and SD), South Atlantic (DC, DE, FL, GA, MD, NC, SC, VA, and
- 11 WV), East South Central (AL, KY, MS, and TN), West South Central (AR, LA, OK, and TX), Mountain
- 12 (AZ, CO, ID, MT, NM, NV, UT, and WY), and Pacific (AK, CA, HI, OR, and WA) divisions.
- ^bData for 2021 are provisional and were last updated February 6, 2022. Error bars represent 95%
 confidence intervals.
- Figure 3. Age-adjusted rates of death from fungal infections, by US census division of residence^a —
 National Vital Statistics System, United States, 2020–2021^b
- ^aThe United States Census Bureau defines nine census divisions: New England (CT, MA, ME, NH, RI,
- and VT), Middle Atlantic (NJ, NY, and PA), East North Central (IL, IN, MI, OH, and WI), West North
- 19 Central (IA, KS, MN, MO, ND, NE, and SD), South Atlantic (DC, DE, FL, GA, MD, NC, SC, VA, and
- 20 WV), East South Central (AL, KY, MS, and TN), West South Central (AR, LA, OK, and TX), Mountain
- 21 (AZ, CO, ID, MT, NM, NV, UT, and WY), and Pacific (AK, CA, HI, OR, WA) divisions.
- ^bData for 2021 are provisional and were last updated February 6, 2022. Rates are not shown for
- conditions where the death count was less than 20.





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