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Enhanced Surveillance for Histoplasmosis—9 States, 2018–2019

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Background. Histoplasmosis is often described as the most common endemic mycosis in the United States, but much remains unknown about its epidemiology among the general population.

Methods. We conducted enhanced surveillance in 9 states during 2018–2019 by identifying cases through routine surveillance and interviewing 301 patients about their clinical features and exposures.

Results. Before being tested for histoplasmosis, 60% saw a health care provider ≥3 times, and 53% received antibacterial medication. The median time from seeking health care to diagnosis (range) was 23 (0–269) days. Forty-nine percent were hospitalized, and 69% said that histoplasmosis interfered with their daily activities (median [range], 56 [2–3960] days). Possible exposures included handling plants (48%) and bird or bat droppings (24%); 22% reported no specific exposures. Only 15% had heard of histoplasmosis before their illness.

Conclusions. Histoplasmosis can be severe and prolonged. Additional educational efforts to increase public and provider awareness and reduce delays in diagnosis are needed.

Keywords. epidemiology; histoplasmosis; United States.

Histoplasmosis is a fungal infection caused by inhalation of the environmental fungi *Histoplasma* spp. Depending on host immune status and exposure intensity, a range of manifestations can occur after a 3–17-day incubation period, including asymptomatic, acute or chronic pulmonary, or life-threatening disseminated infections [1]. Focal infections, including long-term pulmonary nodules, can also occur. In the United States, histoplasmosis appears to be most common in central and eastern states [2], but *Histoplasma* can exist in microfoci both within and outside these regions, particularly in association with organic matter enriched with bird or bat droppings [3, 4]. Therefore, its geographic range is likely much wider than is often appreciated but is difficult to determine due to limited public health surveillance and infrequent environmental sampling [4–6]. Occupational exposures are frequently implicated in histoplasmosis outbreaks [7].

In the United States, histoplasmosis is not nationally notifiable but is reportable in 12 states, where surveillance detects <1000 total cases per year [6]. In June 2016, the Council of State and Territorial Epidemiologists (CSTE) passed a position statement to create a standardized histoplasmosis case definition, a first step toward more consistent and comprehensive surveillance methodology. Before this change, states used slightly different case definitions. A multistate analysis of cases reported to public health during 2011–2014 also revealed variation in data elements collected by each state; most did not routinely collect data about possible exposures, underlying medical conditions, symptoms, or antifungal treatment [6]. This type of information is typically only available from outbreak investigations [7] or clinical studies of high-risk patients, such as those with HIV/AIDS, solid organ or stem cell transplant recipients, or those taking immunomodulating medications [8–11]. Effects of histoplasmosis on patients (eg, diagnostic delays, symptom duration, and impaired productivity) and awareness about histoplasmosis are also not well known.

We conducted enhanced surveillance in 9 states to better describe the epidemiology of histoplasmosis in the general population, help understand its true public health burden, inform

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routine surveillance practices, and guide future awareness efforts and prevention strategies.

METHODS

During July 1, 2018–June 30, 2019, surveillance in 9 states (Arkansas, Indiana, Kentucky, Louisiana, Michigan, Minnesota, Nebraska, Pennsylvania, and Wisconsin) identified histoplasmosis cases according to the CSTE case definition [12]. The CSTE clinical criteria require compatible symptoms, abnormal chest imaging, or evidence of disseminated disease. Confirmatory laboratory criteria include culture, histopathology, molecular detection, detection of H band by immunodiffusion antibody test or detection of M band after a previous lack of M band, or a ≥4-fold rise in antibody titer. Nonconfirmatory laboratory criteria include cytopathology or a single positive antibody or antigen enzyme immunoassay (EIA) test. Confirmed cases must meet both clinical and confirmatory laboratory criteria. Probable cases can either (1) meet clinical and nonconfirmatory laboratory criteria, (2) meet confirmatory laboratory criteria but have no available clinical information, or (3) meet clinical criteria and have epidemiologic linkage to a confirmed case without meeting laboratory criteria.

State or local health department personnel contacted patients to participate in a voluntary telephone interview. Personnel in Kentucky, Louisiana, Michigan, Nebraska, Pennsylvania, and Wisconsin attempted to contact every patient. Some health departments with large case counts undertook sampling strategies and attempted to contact a subset of patients: in Arkansas, those reported during July–November 2018; in Indiana, a geographically representative sample; and in Minnesota, all patients with confirmed cases and every other patient with a probable case. A parent or guardian was interviewed for patients <18 years old, and a relative or health care provider could complete the interview if the patient was incapacitated or deceased. Using a standardized questionnaire, interviewers asked about symptoms, underlying medical conditions, health care–seeking behaviors, diagnosis, treatment, outcomes, exposures, and knowledge about histoplasmosis. Investigators also collected information from electronic surveillance databases and medical records about laboratory tests for histoplasmosis, testing indication(s), and provider diagnoses.

We performed descriptive analysis and examined differences between confirmed and probable cases among interviewed patients. We analyzed categorical variables by using χ^2 or Fisher exact tests, used *t* tests and Wilcoxon rank-sum tests to compare continuous variables, and calculated odds ratios and 95% CIs.

We used the National Institute for Occupational Safety and Health's Industry & Occupation Computerized Coding System (NIOCCS) to translate free-text industry and occupation data into standardized codes. These codes were grouped into 20 industry and 22 occupation categories based on the simple recodes designed by the Centers for Disease Control and Prevention's (CDC's) National Center for Health Statistics for classifying industry and occupation in the National Health Interview Survey [13]. Industry- and occupation-specific histoplasmosis incidence rates (IRR) and Poisson-based 95% CIs were calculated using denominator data from the 2018 American Community Survey 1-year Public Use Microdata Sample file [14]. To assess the potential association of industry and occupation with the incidence of histoplasmosis, we calculated incidence rate ratios and Poisson-based 95% CIs using the industry and occupation categories with the largest populations (health care and social assistance industries and office and administrative support occupations, respectively) as the referent categories.

Patient Consent Statement

CDC Human Subjects Review determined this project to be nonresearch public health surveillance.

RESULTS

Features of Interviewed and Noninterviewed Patients

Surveillance detected 590 persons with histoplasmosis; 189 cases were confirmed, 308 were probable, and 93 (all noninterviewed) in Indiana met the CSTE case definition but insufficient information was available to further classify them. Of the probable cases, 294 met clinical and nonconfirmatory laboratory criteria, 6 met confirmatory laboratory criteria but had no available clinical information, and 8 had no available laboratory information but were epidemiologically linked to a confirmed case. In total, 301 (51%) patients were interviewed, a median (range) of 47 (0–408) days after being reported to public health departments. Among 289 noninterviewed patients, interviews were either not attempted or were not completed due to unknown reasons in 146 (51%), loss to follow-up in 88 (31%), refusal in 34 (12%), and death in 21 (7%). Interviewed and noninterviewed patients were similar in age and sex, but noninterviewed patients were more likely to have probable cases (68% vs 58%; odds ratio [OR], 1.5; 95% CI, 1.0–2.2) or to have died (8% vs 1%; OR, 6.1; 95% CI, 2.1–18.0).

Demographics and Underlying Medical Conditions

Among 301 interviewed patients, most were male (63%) and White (92%), and the median age (range) was 52 (0.3–88) years (Table 1); 32 (11%) were aged <18 years. Patients with confirmed cases were more likely to be immunosuppressed than those with probable cases (41% vs 26%; OR, 2.0; 95% CI, 1.2–3.2). Autoimmune disease was the most common underlying condition (19%); among those patients, the specific illnesses most frequently reported were rheumatoid arthritis (40%) and inflammatory bowel disease (10%). Other common underlying conditions included chronic obstructive pulmonary disease

Table 1. Demographic Features, Underlying Medical Conditions, Symptoms, and Health Care Use Among Histoplasmosis Patients Reported From 9 States, by Case Status, 2018–2019

Characteristic	Total, No. (%)	Confirmed, No. (%)	Probable, No. (%)	*P* Value
Total	301 (100)	126 (41.9)	175 (58.1)	
Sex, n = 299				.123
Male	189 (63.2)	86 (68.3)	103 (59.5)	
Female	110 (36.8)	40 (31.8)	70 (40.5)	
Median age (range), n = 299, y	52.2 (0.3–87.7)	55.6 (0.3–84.5)	50.4 (5.2–87.7)	.088
Race, n = 289				
White	266 (92.0)	111 (89.5)	155 (93.9)	.169[a]
Black/African American	8 (2.8)	4 (3.2)	4 (2.4)	
Asian	5 (1.7)	4 (3.2)	1 (0.6)	
American Indian or Alaska Native	2 (0.7)	0 (0.0)	2 (1.2)	
Other	8 (2.8)	5 (4.0)	3 (1.8)	
Hispanic or Latino, n = 286	8 (2.8)	5 (4.0)	3 (1.9)	.268
Health insurance coverage, n = 266	250 (94.0)	105 (90.5)	145 (96.7)	.037
Some college education or higher, n = 240	130 (54.2)	51 (48.6)	79 (58.5)	.125
Yearly household income >$50 000, n = 220	113 (51.4)	47 (49.0)	66 (53.2)	.530
Smoking, n = 294				.394
Currently	46 (15.7)	16 (13.0)	30 (17.5)	
In the past	98 (33.3)	39 (31.7)	59 (34.5)	
None	150 (51.0)	68 (55.3)	82 (48.0)	
Underlying medical conditions				
Autoimmune disease	57 (18.9)	25 (19.8)	32 (18.3)	.734
COPD or emphysema	45 (15.0)	14 (11.1)	31 (17.7)	.113
Asthma requiring an inhaler	41 (13.6)	13 (10.3)	28 (16.0)	.156
Heart disease	41 (13.6)	14 (11.1)	27 (15.4)	.281
Cancer	38 (12.6)	19 (15.1)	19 (10.9)	.277
Diabetes	32 (10.6)	17 (13.5)	15 (8.6)	.172
Kidney disease	25 (8.3)	14 (7.9)	11 (6.3)	.135
Transplant	19 (6.3)	17 (11.1)	2 (1.1)	<.001
Other lung disease	17 (5.7)	10 (7.9)	7 (4.0)	.144
Liver disease	13 (4.3)	10 (7.9)	3 (1.7)	.009
HIV/AIDS	8 (2.7)	6 (4.8)	2 (1.1)	.054
Pregnancy	2 (0.7)	1 (0.8)	1 (0.6)	1.000
No underlying medical conditions reported	96 (31.9)	33 (26.2)	63 (33.0)	.072
Immunosuppressed[b]	98 (32.6)	52 (41.3)	46 (26.3)	.006
Immunosuppressive medications, n = 281	90 (32.0)	45 (37.8)	45 (27.8)	.075
History of histoplasmosis, n = 266	6 (2.3)	1 (0.8)	5 (3.4)	.227
Symptoms	262 (87.0)	117 (92.9)	145 (82.9)	.011
Cough	193 (64.1)	82 (65.1)	111 (63.4)	.768
Fatigue	177 (58.8)	82 (65.1)	95 (54.3)	.061
Shortness of breath	165 (54.8)	76 (60.3)	89 (50.9)	.104
Fever	164 (54.5)	76 (60.3)	88 (50.3)	.085
Chills	138 (45.9)	70 (55.6)	68 (38.9)	.004
Night sweats	135 (44.9)	65 (51.6)	70 (40.0)	.046
Headache	114 (37.9)	58 (46.0)	56 (32.0)	.013
Weight loss without trying	104 (34.6)	61 (48.4)	43 (24.6)	<.001
Chest pain	103 (34.2)	40 (31.8)	63 (36.0)	.443
Muscle pain	91 (30.2)	41 (32.5)	50 (28.6)	.460
Joint pain	72 (23.9)	35 (278)	37 (21.1)	.183
Wheezing	72 (23.9)	26 (20.6)	46 (26.3)	.257
Sore throat	43 (14.3)	20 (15.9)	23 (13.1)	.504
Rash	36 (12.0)	17 (13.5)	19 (10.9)	.487
Stiff neck	33 (11.0)	15 (11.9)	18 (10.3)	.657
Coughing up blood	22 (7.3)	10 (7.9)	12 (6.9)	.723
Other symptoms	70 (23.3)	35 (27.8)	35 (20.0)	.115
Type of facility where patient first sought care, n = 248				.455
Primary care	106 (42.7)	45 (40.9)	61 (44.2)	

Table 1. Continued

Characteristic	Total, No. (%)	Confirmed, No. (%)	Probable, No. (%)	*P* Value
Emergency department	78 (31.5)	39 (35.5)	39 (28.3)	
Urgent care	40 (16.1)	14 (12.7)	26 (18.8)	
Specialist	16 (6.5)	9 (8.2)	7 (5.1)	
Other	8 (3.2)	3 (2.7)	5 (3.6)	
Diagnosed with something else before histoplasmosis, n = 266	150 (56.4)	70 (59.3)	80 (54.1)	.389
Pneumonia	60 (42.3)	29 (42.7)	31 (41.9)	
Other noninfectious condition besides cancer	21 (14.8)	7 (10.3)	14 (18.9)	
Another type of infection or infectious syndrome[c]	37 (26.1)	19 (27.9)	18 (24.3)	
Cancer	16 (11.3)	10 (14.7)	6 (8.1)	
A different fungal infection	4 (2.8)	1 (1.5)	3 (4.1)	
Tuberculosis	4 (2.8)	2 (2.9)	2 (2.7)	
Number of visits before being tested for histoplasmosis, n = 168				.260
1	27 (16.1)	9 (11.8)	18 (19.6)	
2	41 (24.4)	17 (22.4)	24 (26.1)	
≥3	100 (59.5)	50 (65.8)	50 (54.4)	
Type of doctor who first tested for histoplasmosis, n = 242				.107
Pulmonologist	110 (45.4)	38 (36.9)	72 (51.8)	
Infectious disease	75 (31.0)	37 (35.9)	38 (27.3)	
Primary care	26 (10.7)	11 (10.7)	15 (10.8)	
Emergency department	6 (2.5)	2 (1.9)	4 (2.9)	
Other	25 (10.3)	15 (14.6)	10 (7.2)	
Site of infection, n = 250[d]				
Lungs	227 (90.8)	102 (88.7)	125 (92.6)	.288
Disseminated	28 (11.2)	17 (14.8)	11 (8.2)	.097
Lymph nodes	20 (8.0)	10 (8.7)	10 (7.4)	.708
Other[e]	39 (15.6)	24 (20.9)	15 (11.1)	.034
Prescribed antifungal medication, n = 269	162 (60.2)	88 (74.6)	74 (49.0)	<.001
Itraconazole	135 (50.2)	73 (61.9)	62 (41.1)	<.001
Amphotericin B	34 (12.6)	23 (19.5)	11 (7.3)	.003
Fluconazole	16 (6.0)	9 (7.6)	7 (4.6)	.303
Voriconazole	6 (2.2)	3 (2.5)	3 (2.0)	.759
Posaconazole	5 (1.9)	4 (3.4)	1 (0.7)	.100
Recovered at interview	214 (71.1)	81 (64.3)	133 (76.0)	.027
Median symptom duration among patients recovered at interview (range), n = 103, d	42 (2–3960)	60 (2–270)	30 (6–3960)	.352

Abbreviation: COPD, chronic obstructive pulmonary disease.

[a]White vs non-White.

[b]HIV/AIDS, solid organ or bone marrow transplant, or immunosuppressive medication use.

[c]Besides a fungal infection, pneumonia, or tuberculosis.

[d]Based on patient report. Patients can have >1 site of infection.

[e]Includes bones or joints (n = 8), abdomen (n = 23), or other sites (n = 11).

(COPD; 15%), asthma (14%), and heart disease (14%); 3% had HIV/AIDS. Thirty-two percent reported no underlying conditions. Two percent reported a history of histoplasmosis.

Symptoms, Health Care Use, and Diagnosis

Most (87%) patients had symptoms compatible with histoplasmosis, most commonly cough (64%), fatigue (59%), shortness of breath (55%), and fever (55%) (Table 1). Males were more likely to report symptoms than females (91% vs 80%; OR, 2.5; 95% CI, 1.3–5.0). Patients first sought health care a median (range; interquartile range [IQR]) of 6 (0–505; 2–13) days after symptom onset. Most sought care first at a primary care office (43%) or an emergency department (32%). Before being tested for histoplasmosis, 60% of patients visited a health care provider ≥3 times, 56% reported receiving a diagnosis of another illness, and 53% were prescribed antibacterial medication. Most patients were first tested for histoplasmosis by a pulmonologist (45%) or an infectious disease specialist (31%). The median time between seeking health care and diagnosis (range; IQR) was 23 (0–269; 10–43) days. Abnormal imaging results (58%) and compatible symptoms (55%) were the most common reasons for testing; providers considered histoplasmosis an incidental finding in 11%. Patients with abnormal imaging results listed as a reason for testing had a longer mean time (47 vs 29 days; $P = .02$) between health care seeking and diagnosis than those without. Positive laboratory tests included complement fixation (54%), immunodiffusion (46%), antigen EIA (35%), and culture (23%) (Table 2). Immunosuppressed patients were more likely than

Table 2. Positive Laboratory Tests for Histoplasmosis Among Patients Reported From 9 States, 2018–2019

Type of Test	Number of Patients (%), n = 293
Antibody serology	
Complement fixation	159 (54.3)
Median highest complement fixation titer (range), n = 152	1:64 (1:8–1:2048)
Complement fixation only	51 (17.4)
Immunodiffusion H band	48 (16.4)
Immunodiffusion H band only	2 (0.7)
Immunodiffusion M band	130 (44.4)
Immunodiffusion M band only	24 (8.2)
Immunodiffusion H or M band	136 (46.4)
Immunodiffusion H or M band only	29 (9.9)
Antigen testing	
Enzyme immunoassay	103 (35.2)
Median highest value (range), n = 75, ng/mL	4.03 (0.50–26.20)
Enzyme immunoassay only	36 (12.3)
Other diagnostic methods	
Culture	67 (22.9)
Culture only	19 (6.5)
Molecular evidence	12 (4.1)
Histopathology	21 (7.2)
Histopathology only	1 (0.3)
Cytopathology/smear	14 (4.8)
Cytopathology/smear only	1 (0.3)
Type of Specimen	Number of Specimens (%)
Culture, n = 72	
Bronchial specimen	23
Blood	12
Lymph node	10
Bone marrow	9
Sputum	5
Lung tissue	3
Other	11
Histopathology, n = 21	
Lung tissue	11
Bone marrow	3
Lymph node	3
Bronchial specimen	1
Other	3

nonimmunosuppressed patients to have positive EIA (58% vs 24%; OR, 4.5; 95% CI, 2.7–7.5) culture (39% vs 15%; OR, 3.5; 95% CI, 2.0–6.1) or histopathology tests (12% vs 5%; OR, 2.4; 95% CI, 1.0–5.9). Providers diagnosed 96% (n = 213) of patients with histoplasmosis; of those, 39% were acute pulmonary infections, 17% were disseminated, 6% were chronic pulmonary, 7% were other types of infections, and no type was specified in 30%.

Treatment and Outcomes

Patients with confirmed cases were more likely to be hospitalized than those with probable cases (62% vs 40%; OR, 2.4; 95% CI, 1.5–3.8). A higher proportion of males were hospitalized (54% vs 42% female; OR, 1.6; 95% CI, 1.0–2.6). Confirmed case status was associated with receiving antifungal medication (75% vs 49% of patients with probable cases; OR, 3.1; 95% CI, 1.8–5.1). Among the 162 patients prescribed antifungal medication, 83% received itraconazole and 21% received amphotericin B. Seventy-one percent of patients were no longer symptomatic at the time of the interview; of those, the median symptom duration (range; IQR) was 42 (2–3960; 16–90) days. Histoplasmosis interfered with 69% of patients' usual daily activities for a median (range) of 56 (2–3960) days. Among 178 (65%) who had a job or were in school, 69% missed work or school (median [range], 10 [1–300] days). Four (1%) interviewed patients died.

Exposures, Occupation, and Outbreaks

Forty-nine percent of patients lived in a rural area, and 24% traveled out of state in the month before symptom onset or testing positive (if asymptomatic) (Figure 1; Supplementary Figure 1). Common exposures included gardening, landscaping, or other handling of plants or trees (48%); digging soil (37%); construction, demolition, or renovation (28%); and handling bird or bat droppings (24%) (Supplementary Figure 2). Twenty-two percent did not recall any specific exposures. By immune status, patients were equally likely to report any exposures, but immunosuppressed patients reported fewer exposures than nonimmunosuppressed patients (mean, 2.5 vs 3.2; $P = .02$). Of the 178 (65%) patients who had a job or were in school, 129 had occupation information and 110 had industry information that could be converted into standardized codes. Those in construction and extraction occupations (n = 16; IRR, 4.8; 95% CI [2.1–11.2]) and in agriculture, forestry, fishing, and hunting industries (n = 8; IRR, 9.5 95% CI [3.7–24.5]) were at highest risk (Table 3). We identified 7 outbreaks involving 28 patients total (range, 2–16 patients per outbreak) (Supplementary Table 1).

Knowledge of Histoplasmosis

Most (88%) patients knew about their positive histoplasmosis laboratory test results before the interview. Fifteen percent had heard of histoplasmosis before being diagnosed; of those, most first heard about it from a family member or friend (47%) or from working in the medical field (28%). Patients who knew about histoplasmosis before diagnosis were more likely to ask for a histoplasmosis test than those who did not know about it (26% vs 5%; OR, 6.4; 95% CI, 2.4–16.9).

DISCUSSION

These enhanced surveillance data contribute to an increased understanding of the patient burden of histoplasmosis. Consistent with descriptions of the disease in other populations, histoplasmosis was associated with a wide range of illness. Many patients experienced substantial illness, and diagnostic delays and misdiagnoses were common. Exposures to specific sources

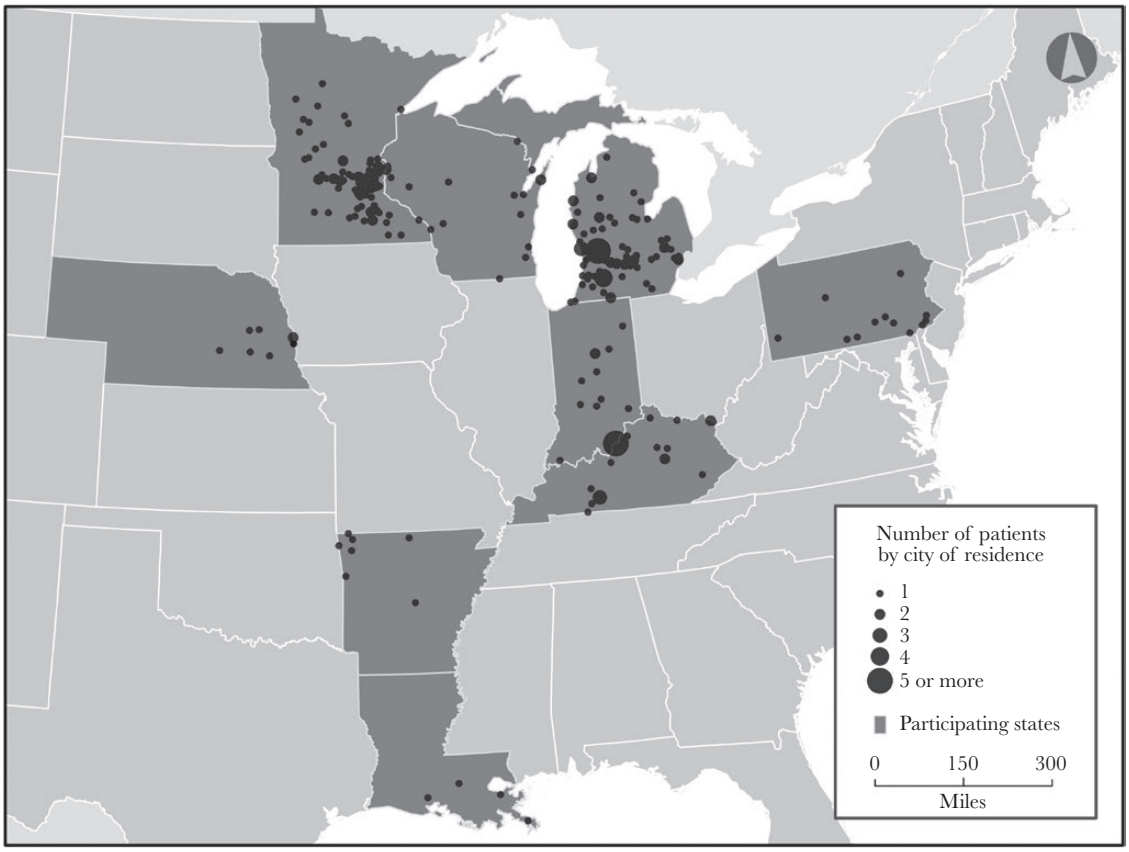

Figure 1. Locations of residence among interviewed histoplasmosis patients reported from 9 states, 2018–2019.

frequently implicated in past histoplasmosis outbreaks were less common among these patients, and prior knowledge of histoplasmosis was low, indicating the need for greater awareness among both the public and providers, even in the absence of classic exposures.

More severe disease occurred in patients with confirmed cases based on presence and number of symptoms, hospitalization, antifungal treatment, and impacts on daily activities. Severity appeared to reflect both immune status and exposure intensity, a well-known association [3]. The prolonged symptom duration in this analysis (~6 weeks) was identical to that of coccidioidomycosis [15, 16], a similar fungal disease that receives far more attention from medical and public health communities. The trend toward greater morbidity among males is similar to other studies [6, 17–19], though the reasons are unclear and are not clearly explained by differences in exposures. Altogether, our findings confirm that histoplasmosis can be a severe illness with considerable effects on patients' quality of life, particularly for immunosuppressed persons.

Many patients experienced apparent diagnostic delays, consistent with previous reports [19]. A common sequence involved initial consultation at a primary care provider, urgent care, or emergency department followed by multiple health care visits spanning >3 weeks and diagnosis at a specialist (pulmonary more frequently than infectious disease), suggesting missed opportunities for earlier diagnosis. The nonspecific symptoms of acute histoplasmosis, such as cough, shortness of breath, and fever, are similar to those of other pneumonia etiologies. Not surprisingly, more than half of patients received an antibacterial medication before diagnosis, possibly for empiric treatment for suspected bacterial infections, supported by the finding that >40% of patients reported receiving a diagnosis of pneumonia before histoplasmosis. Although some patients may have had bacterial coinfections, many of the reported antibacterial medications likely reflect treatment, which is concerning given its contribution to antimicrobial resistance. Greater testing for histoplasmosis could contribute to antibacterial stewardship. Furthermore, histoplasmosis is often indistinguishable on chest imaging from other causes of pneumonia, lung cancer, and other illnesses [20, 21]. Longer time to diagnosis among patients who had abnormal imaging listed as a reason for histoplasmosis testing reflects the challenging nature of obtaining a histoplasmosis diagnosis and might also point to incidental diagnoses, a frequently described phenomenon [19]. Notably, >10% of patients reported receiving a diagnosis of cancer before histoplasmosis was identified. Diagnosis of histoplasmosis can be challenging even when specifically considered, evidenced in part by the diversity of test types we observed. These results

Table 3. Histoplasmosis Cases, Rates per 1 000 000 Employed Persons and Incident Rate Ratios By Simple Occupation and Industry Recode Categories, 9 States, 2018–2019

NHIS Simple Occupation Recode Category	Number of Cases	Rate (95% CI)	Incidence Rate Ratio (95% CI)
Management	23	9.2 (6.1–14.0)	3.5 (1.6–7.8)
Business and financial operations	2	1.5 (0.4–5.9)	0.6 (0.1–2.6)
Computer and mathematical	2	2.9 (0.7–11.0)	1.1 (0.2–5.1)
Architecture and engineering	2	3.7 (0.9–15.0)	1.4 (0.3–6.6)
Life, physical, and social science	1	4.3 (0.6–30.0)	1.6 (0.2–13.0)
Community and social services	2	4.1 (1.0–16.0)	1.6 (0.3–7.4)
Legal	0		
Education, training, and library	4	2.6 (1.0–7.1)	1.0 (0.3–3.3)
Arts, design, entertainment, sports, and media	1	2.3 (0.3–16.0)	0.9 (0.1–7.0)
Health care and technical	9	5.0 (2.6–9.7)	1.9 (0.7–5.0)
Health care support	2	2.1 (0.5–8.6)	0.8 (0.2–3.8)
Protective service	0		
Food preparation and serving	6	4.0 (1.8–9.0)	1.5 (0.5–4.4)
Building and grounds cleaning and maintenance	6	6.4 (2.9–14.0)	2.4 (0.8–7.0)
Personal care and service	7	10.0 (4.8–21.0)	3.8 (1.4–10.6)
Sales and related	9	3.5 (1.8–6.7)	1.3 (0.5–3.5)
Office and administrative support	8	2.6 (1.3–5.3)	Ref
Farming, fishing, and forestry	2	11.0 (2.8–45.0)	4.3 (0.9–20.3)
Construction and extraction	16	13.0 (7.7–21.0)	4.8 (2.1–11.2)
Installation, maintenance, and repair	4	4.8 (1.8–13.0)	1.8 (0.5–6.0)
Production	13	6.1 (3.5–11.0)	2.3 (1.0–5.6)
Transportation and material moving	10	4.6 (2.5–8.5)	1.7 (0.7–4.4)
Total	129	4.9 (4.1–5.8)	
NHIS Simple Industry Recode Category	Number of Cases	Rate (95% CI)	Incidence Rate Ratio (95% CI)
Agriculture, forestry, fishing, and hunting	8	21.0 (10.0–42.0)	9.5 (3.6–24.5)
Mining	0		
Utilities	0		
Construction	17	10.5 (6.5–17.0)	4.7 (2.1–10.6)
Manufacturing	16	4.1 (2.5–6.7)	1.8 (0.8–4.2)
Wholesale trade	3	4.5 (1.5–14.0)	2.0 (0.6–7.6)
Retail trade	10	3.4 (1.8–6.3)	1.5 (0.6–3.7)
Transportation and warehousing	10	8.5 (4.6–16.0)	3.8 (1.6–9.4)
Information	0		
Finance and insurance	3	2.5 (0.8–7.9)	1.1 (0.3–4.2)
Real estate and rental and leasing	0		
Professional, scientific, and technical services	4	2.7 (1.0–7.1)	1.2 (0.4–3.9)
Management of companies and enterprises	0		
Administrative and support and waste management and remediation services	4	4.2 (1.6–11.0)	1.9 (0.6–6.2)
Education services	7	2.9 (1.4–6.1)	1.3 (0.5–3.5)
Health care and social assistance	9	2.2 (1.2–4.3)	Ref
Arts, entertainment, and recreation	3	5.9 (1.9–18.0)	2.7 (0.7–9.9)
Accommodation and food services	5	2.8 (1.1–6.6)	1.2 (0.4–3.7)
Other services (except public administration)	7	5.7 (2.7–12.0)	2.6 (1.0–6.9)
Public administration	4	3.8 (1.4–10.0)	1.7 (0.5–5.6)
Total	110	4.2 (3.4–5.0)	

Abbreviation: NHIS, National Health Interview Survey.

underscore the need for increased health care provider education, particularly primary care professionals, about the importance of considering histoplasmosis early in the course of a compatible respiratory illness or in the context of abnormal chest imaging results.

Previously, limited data about potential exposure sources have been available for non-outbreak-associated histoplasmosis [6]. Overall, specific exposures were less commonly described than in outbreaks [7], with nearly a quarter of patients reporting none of the exposures we asked about. Specifically, only a quarter reported handling bird or bat droppings, a classic feature present in 77% of histoplasmosis outbreaks [7]. Our finding is similar to past surveillance data showing that 8%–29% of patients reported contact with bird or bat droppings [6] and to a study of HIV-infected

patients in which 18% of those with HIV and histoplasmosis had such exposures, compared with 9% of histoplasmosis-uninfected controls [8]. Gardening or other handling of plants or trees was frequent, in nearly half of patients, though gardening is also a popular hobby in general. Unfortunately, how other exposure frequencies among histoplasmosis patients compare with the overall US population is not well known. Together, these results suggest that patients (particularly those who are immunosuppressed) with non-outbreak-associated histoplasmosis may have small exposures that were unnoticed, not easy to remember, or not recent. Clinicians should be aware that histoplasmosis is not always associated with clear environmental disruption or bird or bat droppings, and absence of these exposures should not exclude histoplasmosis as a possible cause of illness.

Although nearly a quarter of patients traveled in the month before symptom onset, the similarities between residence locations and potential exposure locations suggests that most exposures were not travel-associated and may have occurred near the home. Nearly half of patients lived in rural areas, compared with only 19% of the general population [22]; historical evidence from large-scale skin testing studies performed in the 1950s and 1960s also supports greater exposures in rural settings, with 29% of people who resided on farms having a positive skin test reaction compared with 11% of metropolitan area residents [23]. Therefore, rural communities may be an important population for targeted histoplasmosis-related education and prevention efforts.

This study underscores the importance of histoplasmosis as a work-related illness, particularly for construction and agricultural work. Increased histoplasmosis risk for workers in specific occupations and industries has not previously been quantified, and although we cannot confirm that these patients were exposed in the workplace, the high-risk occupations and industries in this analysis are consistent with outdoor work that may involve environmental disruption in settings known to be associated with histoplasmosis [7]. We also observed high histoplasmosis rates among management occupations, but this is likely because the NIOCCS classifies some farming occupations as management. National Institute for Occupational Safety and Health guidance describes ways for workers and employers to reduce potential exposures to *Histoplasma*, including preventing birds or bats from roosting indoors, controlling dust during environmental disruption, properly disposing of contaminated material posting warning signs, wearing personal protective equipment, and education about histoplasmosis [24].

Histoplasmosis outbreak investigations can provide key insights into high-risk settings and activities [7]. This study helped detect several outbreaks and confirms that outbreak-associated cases represented a small fraction (5%) of overall cases, though some outbreaks may have gone undetected because we did not interview every reported patient. Histoplasmosis outbreaks often involve intense exposures after environmental disruption, high attack rates, and severe illnesses, as was true among the group of campers exposed to bat droppings in Louisiana [25].

Public awareness about histoplasmosis has not been well described. Here, awareness was very low (15%), and many patients who knew about histoplasmosis before their diagnosis worked in the medical field. For comparison, although coccidioidomycosis is more geographically concentrated than histoplasmosis, coccidioidomycosis awareness among the general population is extremely high (97%) in Arizona and modest (51%) among coccidioidomycosis patients in areas where the disease is not highly endemic [15, 26]. Public health messaging about histoplasmosis should not only convey risks associated with activities such as handling large amounts of bird or bat droppings, but also emphasize that a specific exposure source is not always evident.

Consistent with other data sources including hospital discharges [17], health insurance claims [19], and medical chart reviews [10], autoimmune diseases were frequent in this study. Histoplasmosis is a well-known complication among people taking tumor necrosis factor (TNF) inhibitor therapy, causing considerable morbidity [11]. That one-third of patients reported immunosuppression and another third reported no underlying conditions indicates that health care providers should remain alert to histoplasmosis regardless of immune status. COPD is an established risk factor for cavitary histoplasmosis [27] and was present in 15% of patients with reported cases vs 6% in the general population [28]. In contrast, asthma has not been associated with histoplasmosis, but prevalence among reported cases (14%) was also higher than the general population (8%) [29]. Presence of underlying lung disease may make it more likely for patients to present to care with a respiratory infection and be tested for histoplasmosis, particularly since pulmonologists comprised the largest share of diagnosing providers.

The CSTE case definition appears to primarily capture acute histoplasmosis as intended, supported by the high proportions of patients who were given a provider diagnosis of histoplasmosis and were symptomatic, the low proportion who self-reported a previous history of histoplasmosis, the relatively short time between symptom onset and care-seeking (6 days), and frequent initial care-seeking at an urgent care center or emergency department. In the context of the wide spectrum of illness associated with histoplasmosis, our findings are likely biased toward more severe cases, as is typical for public health surveillance and is apparent from the high proportions of patients who were hospitalized and had positive cultures. Patients with severe cases may have also been more willing to participate in an interview, although the higher death rate among noninterviewed cases suggests that this bias may cut both ways. Other unmeasured differences between interviewed and noninterviewed patients may have also biased our results. Overall, many more histoplasmosis cases almost certainly go undiagnosed or are not reported to public health.

Our study's main limitation is potential recall bias, a particular concern with self-reported underlying medical conditions

and dates of illness onset and care-seeking. For example, we could have underestimated delays to care-seeking and diagnosis if patients with particularly long delays could not recall exact dates. However, interviews yield information that other data sources cannot on topics such as exposures and effects on daily activities. Lastly, the extent to which geography influences our results is unknown; 65% of the interviewed cases were residents of Michigan or Minnesota, where health department personnel conducted extensive patient follow-up. These states are not traditionally considered highly endemic for histoplasmosis, although multiple lines of evidence suggest that these areas have changed since the first comprehensive mapping was performed in the 1950s [2, 5, 6]. In 2020, the CDC updated the map of the estimated areas with histoplasmosis to reflect cases occurring to the north of the previously described areas [30].

These enhanced surveillance data help fill critical gaps in our understanding of histoplasmosis, particularly in terms of severity, patient burden, exposures, and knowledge about the disease. Greater access to and use of rapid histoplasmosis-specific diagnostic tests could help reduce delays in diagnosis and avoid unnecessary antibacterial treatment and invasive testing. Expanded, strengthened public health surveillance for histoplasmosis and educational efforts to increase awareness among health care providers and the public are needed.

Supplementary Data

Supplementary materials are available at *Open Forum 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.

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References

1. Wheat LJ, Freifeld AG, Kleiman MB, et al; Infectious Diseases Society of America. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis **2007**; 45:807–25.
2. Manos NE, Ferebee SH, Kerschbaum WF. Geographic variation in the prevalence of histoplasmin sensitivity. Dis Chest **1956**; 29:649–68.
3. Cano MV, Hajjeh RA. The epidemiology of histoplasmosis: a review. Semin Respir Infect **2001**; 16:109–18.
4. Benedict K, Thompson GR 3rd, Deresinski S, Chiller T. Mycotic infections acquired outside areas of known endemicity, United States. Emerg Infect Dis **2015**; 21:1935–41.
5. Maiga AW, Deppen S, Scaffidi BK, et al. Mapping *Histoplasma capsulatum* exposure, United States. Emerg Infect Dis **2018**; 24:1835–9.
6. Armstrong PA, Jackson BR, Haselow D, et al. Multistate epidemiology of histoplasmosis, United States, 2011–2014. Emerg Infect Dis **2018**; 24:425–31.
7. Benedict K, Mody RK. Epidemiology of histoplasmosis outbreaks, United States, 1938–2013. Emerg Infect Dis **2016**; 22:370–8.
8. Hajjeh RA, Pappas PG, Henderson H, et al; National Institute of Allergy and Infectious Diseases Mycoses Study Group. Multicenter case-control study of risk factors for histoplasmosis in human immunodeficiency virus-infected persons. Clin Infect Dis **2001**; 32:1215–20.
9. Kauffman CA, Freifeld AG, Andes DR, et al. Endemic fungal infections in solid organ and hematopoietic cell transplant recipients enrolled in the Transplant-Associated Infection Surveillance Network (TRANSNET). Transpl Infect Dis **2014**; 16:213–24.
10. Myint T, Al-Hasan MN, Ribes JA, et al. Temporal trends, clinical characteristics, and outcomes of histoplasmosis in a tertiary care center in Kentucky, 2000 to 2009. J Int Assoc Provid AIDS Care **2014**; 13:100–5.
11. Vergidis P, Avery RK, Wheat LJ, et al. Histoplasmosis complicating tumor necrosis factor-α blocker therapy: a retrospective analysis of 98 cases. Clin Infect Dis **2015**; 61:409–17.
12. Centers for Disease Control and Prevention. Histoplasmosis: 2017 case definition. **2019**. Available at: https://wwwn.cdc.gov/nndss/conditions/histoplasmosis/case-definition/2017/. Accessed 8 November 2019.
13. Centers for Disease Control and Prevention. National Health Interview Survey 2018 data release: sample adult file variable layout. **2019**. Available at: ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Dataset_Documentation/NHIS/2018/samadult_layout.pdf. Accessed 23 January 2020.
14. US Census Bureau. Public Use Microdata Sample (PUMS) documentation. **2019**. Available at: https://www.census.gov/programs-surveys/acs/technical-documentation/pums.html. Accessed 23 January 2020.
15. Benedict K, Ireland M, Weinberg MP, et al. Enhanced surveillance for coccidioidomycosis, 14 US states, 2016. Emerg Infect Dis **2018**; 24:1444–52.
16. Tsang CA, Anderson SM, Imholte SB, et al. Enhanced surveillance of coccidioidomycosis, Arizona, USA, 2007–2008. Emerg Infect Dis **2010**; 16:1738–44.
17. Benedict K, Derado G, Mody RK. Histoplasmosis-associated hospitalizations in the United States, 2001–2012. Open Forum Infect Dis **2016**; 3:1–4.
18. Ledtke C, Tomford JW, Jain A, et al. Clinical presentation and management of histoplasmosis in older adults. J Am Geriatr Soc **2012**; 60:265–70.
19. Benedict K, Beer KD, Jackson BR. Histoplasmosis-related healthcare use, diagnosis, and treatment in a commercially insured population, United States. Clin Infect Dis **2020**; 70(6):1003–10.
20. Kauffman CA. Histoplasmosis: a clinical and laboratory update. Clin Microbiol Rev **2007**; 20:115–32.
21. Deppen SA, Massion PP, Blume J, et al. Accuracy of a novel histoplasmosis enzyme immunoassay to evaluate suspicious lung nodules. Cancer Epidemiol Biomarkers Prev **2019**; 28:321–6.
22. Ratcliffe M, Burd C, Holder K, Fields A. Defining Rural at the U.S. Census Bureau: American Community Survey and Geography Brief. United States Census Bureau; **2016**. Available at: https://www2.census.gov/geo/pdfs/reference/ua/Defining_Rural.pdf.
23. Edwards LB, Acquaviva FA, Livesay VT, et al. An atlas of sensitivity to tuberculin, PPD-B, and histoplasmin in the United States. Am Rev Respir Dis **1969**; 99:Suppl:1–132.
24. Centers for Disease Control and Prevention. Histoplasmosis: Protecting Workers at Risk. Atlanta: Centers for Disease Control and Prevention; **2004**.
25. Serrano JA, Sokol T, Pagan D, Smith A. Outbreak of histoplasmosis associated with geocaching among a group of campers—Louisiana, November 2018. Paper presented at: 2019 Council of State and Territorial Epidemiologists Annual Conference; June 2-6, 2019; Raleigh, NC.
26. Khan M, Brady S, Adame G, Komatsu K. Awareness and knowledge of coccidioidomycosis in Arizona: findings from the 2016 Behavioral Risk Factor Surveillance System. Paper presented at: International Conference on Emerging Infectious Diseases; August 26-29, 2018; Atlanta, GA.
27. Wheat LJ, Wass J, Norton J, et al. Cavitary histoplasmosis occurring during two large urban outbreaks. Analysis of clinical, epidemiologic, roentgenographic, and laboratory features. Medicine (Baltimore) **1984**; 63:201–9.
28. Centers for Disease Control and Prevention. Basics about COPD. **2019**. Available at: https://www.cdc.gov/copd/basics-about.html. Accessed 14 February 2020.
29. Centers for Disease Control and Prevention. Most recent national asthma data. **2019**. Available at: https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm. Accessed 14 Febraury 2020.
30. Centers for Disease Control and Prevention. U.S. histoplasmosis maps. **2020**. Available at: https://www.cdc.gov/fungal/diseases/histoplasmosis/maps.html. Accessed 14 February 2020.