Histoplasmosis-related healthcare use, diagnosis, and treatment in a commercially insured population, United States

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Abstract

Background: Infections with *Histoplasma* can range from asymptomatic to life-threatening acute pulmonary or disseminated disease. Histoplasmosis can be challenging to diagnose and is widely under-recognized. We analyzed insurance claims data to better characterize histoplasmosis testing and treatment practices and its burden on patients.

Methods: We used the IBM® MarketScan® Research Databases to identify patients with histoplasmosis (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 115.00–115.99) during 2012–2014. We analyzed claims in the 3 months before to the 1 year after diagnosis and examined differences between probable (hospitalized or >1 outpatient visit) and suspect (1 outpatient visit) patients.

Results: Among 1,935 patients (943 probable, 922 suspect), 54% had codes for symptoms or findings consistent with histoplasmosis and 35% had   2 healthcare visits in the 3 months before diagnosis. Overall, 646 (33%) had any fungal-specific laboratory test: histoplasmosis antibody test (n= 349, 18%), *Histoplasma* antigen test (n=349, 18%), fungal smear (n=294, 15%), or fungal culture (n=223, 12%); 464 (24%) had a biopsy. Forty-nine percent of probable patients and 10% of suspect patients were prescribed antifungal medication in the outpatient setting. Total, 19% were hospitalized. Patients' last histoplasmosis-associated healthcare visits occurred a median of 6 months after diagnosis.

Conclusions: Some histoplasmosis patients experienced severe disease, apparent diagnostic delays, and prolonged illness, whereas other patients lacked symptoms and were likely diagnosed incidentally (e.g., via biopsy). Low rates of histoplasmosis-specific testing also suggest incidental diagnoses and low provider suspicion, highlighting the need for improved awareness about this disease.

summary:

United States health insurance claims data show that histoplasmosis is associated with a wide spectrum of illness and a substantial burden for some patients. Low targeted testing rates suggest incidental diagnoses and low provider suspicion for histoplasmosis.

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Keywords

Histoplasmosis; Diagnosis; Antifungal treatment; Hospitalization; Outpatients

Introduction

Inhalation of the environmental fungus *Histoplasma capsulatum* can result in a wide range of outcomes, including asymptomatic, acute pulmonary, chronic pulmonary, and disseminated infections. In the United States, histoplasmosis is generally believed to be most common in areas surrounding the Ohio and Mississippi River Valleys [1], although the endemic range may be expanding, as cases also occur in other regions [2–4]. Public health surveillance for histoplasmosis is limited, with <1,000 cases identified annually in the 10 states where it is a reportable disease, but the true burden is likely far higher [3]. Recent studies describe the risk for severe illness in high-risk patient populations, such as those with HIV/AIDS, solid organ or stem cell transplant, and those who are taking immune-modulating medications [5–8]; however, characterizing histoplasmosis among the general population would improve understanding of the spectrum of illness.

Data on histoplasmosis testing practices are also limited. Like the other endemic mycoses, histoplasmosis can be challenging to diagnose because clinical findings are often similar to other conditions [9] and because non-invasive diagnostic testing often involves send-out tests to commercial laboratories, which can incur added cost and turnaround time (resulting in less frequent ordering). Acute pulmonary histoplasmosis (APH) is clinically indistinguishable from other respiratory conditions, including bacterial pneumonia [10]. Mild or asymptomatic histoplasmosis cases can be discovered incidentally during evaluation of pulmonary nodules detected on radiography, commonly via invasive biopsies done to evaluate for malignancy [11]. Although many *Histoplasma* infections are mild or asymptomatic, such consequent invasive procedures involve healthcare costs and risk of complications and death.

Histoplasmosis treatment practices are also poorly described. Published treatment recommendations are specific to the different forms of histoplasmosis and the resulting complications, although there is no consensus for optimal treatment of mild to moderate APH [12]. Empiric antibacterial use for suspected bacterial pneumonia might also occur in histoplasmosis patients, as shown for coccidioidomycosis [13] and blastomycosis [14]. Consequently, a comprehensive understanding of management practices, including testing, diagnosis, and treatment, is lacking. To better characterize patient burden of illness with the ultimate goal of informing early intervention strategies, we analyzed administrative data related to histoplasmosis diagnosis and treatment in a commercially insured population.

Methods

We used data from the 2011–2015 IBM® MarketScan® Research Databases. The MarketScan Commercial Database and the Medicare Supplemental Database contain individual-level insurance claims data representing a range of health services, including outpatient visits and prescriptions and hospitalizations for >230 million employees,

dependents, and retirees throughout the United States. Because these databases are fully de-identified, this analysis was not subject to review by the Centers for Disease Control and Prevention (CDC) institutional review board.

We identified patients with histoplasmosis using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes 115.00–115.99 (except histoplasmosis retinitis codes: 115.02, 115.12, and 115.92) during 2012–2014. The index date was the date this code was first used in the study period. Of >85 million enrollees, 8,169 patients had a histoplasmosis code during 2012–2014. We required continuous enrollment during the year before and the year after the index date (n=3,625 patients) or continuous enrollment during the year before the index date and in-hospital death (n=50). We subsequently excluded patients with any histoplasmosis code in the year before the index date (n=520), patients with insurance plans that did not contribute prescription drug data to MarketScan (n=483), and patients with ICD-9 codes for histoplasmosis retinitis or "unspecified histoplasmosis" at an eye care provider on the index date (n=736), for a final cohort of 1,935 patients. We limited the analysis to claims in the three months before to the year after the index date, creating a 15-month study window for each patient.

We used ICD and Current Procedural Terminology (CPT) codes to identify underlying conditions and immunocompromised status on or in the year before the index date; symptoms and clinical findings, focusing on the three months before the index date; histoplasmosis-specific and non-histoplasmosis specific laboratory tests ordered; chest imaging; outpatient prescriptions for systemic antifungal medications in the seven days before to the year after the index date; outpatient prescriptions for systemic antibacterial medications and corticosteroids; and other features likely related to histoplasmosis (Supplementary Table 1). Because we observed many patients with only one histoplasmosis-related outpatient visit, we stratified the cohort into those who had a histoplasmosis diagnosis code 1) during a hospitalization or at >1 outpatient visit ("probable" patients) vs. 2) at only 1 outpatient visit ("suspect" patients). Requiring multiple healthcare encounters with certain diagnosis code(s) is an established method in claims-based analyses to increase specificity by minimizing coding errors and "rule out" diagnoses coded on laboratory or radiology claims of patients who did not truly have the condition of interest [15].

We performed descriptive analyses and examined differences between these two groups and differences in age, sex, geography, and immune status using $\chi 2$ or Fisher exact tests for categorical variables and Wilcoxon rank-sum tests for continuous variables.

Results

In the final cohort of 1,935 patients, 943 (49%) were probable, and 922 (51%) were suspect. Probable patients were more likely than suspect patients to be male (51% vs. 45%, p=0.009), younger (median 55 vs. 58 years, p<.0001), and immunocompromised (24% vs. 13%, p<.0001) (Table 1). Forty-four percent resided in the East North Central Census Division.

In the three months before index date, 1,045 (54%) patients had ICD-9 codes for symptoms (45%) or clinical findings (28%) consistent with histoplasmosis (Table 2). Shortness of

breath (n=384, 20%), cough (n=318, 16%), and chest pain (n=290, 15%) were the most common symptoms. Twenty-four percent (n=456) had a pulmonary nodule or swelling, mass, or chest lump. Patients with symptoms or clinical findings were younger than those without (median 56 vs. 59 years, p<0.0001). Thirty-five percent had 2 visits for symptoms or clinical findings before the index date; median time between the first visit and the index date was 45 days (mean 45.6, range 1–89). Common respiratory diagnoses included "other unclassified lung disease" (n=387, 20%), "nonspecific abnormal finding of lung field" (n=375, 19%), and pneumonia (n=215, 11%), all more frequent among probable patients. Total, 689 (36%) patients had a total of 1,101 outpatient systemic antibacterial medication prescriptions in the three months before the index date, vs. 526 (27%) with 889 prescriptions in the three months after (Figure 1). The most common pre-index date antibacterials were azithromycin (n=214 patients) and amoxicillin (n=198).

Thirty-three percent (n=646) of patients had a fungal-specific test: a histoplasmosis antibody test (n=349, 18%), *Histoplasma* antigen test (n=349, 18%), fungal smear (n=294, 15%), or fungal culture (n=223, 12%) (Figure 2); probable patients were more likely to have a fungal-specific test (46% vs. 21%, p<0.0001) (Table 3). Twenty-four percent (n=464) had a biopsy (of the lung, lymph node, bone marrow, liver, or spleen), and 20% had cytopathology. Patients with a pulmonary nodule, swelling, mass, or chest lump, had higher rates of all test types than the overall cohort, including 63% with biopsy and 44% with cytopathology. The median time from pre-index date testing to index date was 3 days (mean 14.0, range 0–87) for antibody/antigen tests, 20 days (mean 24.6, range 0–89) for fungal culture or smear, and 15 days (mean 22.6, range 0–89) for biopsy (Figure 1). Immunocompromised patients were more likely than non-immunocompromised patients to have a *Histoplasma* antigen test (37% vs. 14%, p<0.0001), fungal culture (19% vs. 14%, p=0.0009), fungal smear (16% vs. 10%, p=0.0201), or biopsy (31% vs. 22%, p=0.0007). Total, 1,044 (54%) patients (340 [36%] probable and 704 [71%] suspect) had no fungal-specific test, biopsy, or cytopathology; 261 (13%) had no laboratory testing, no symptoms or clinical findings, no histoplasmosis-associated hospitalization, and no antifungal medication. Chest imaging was performed for 1,513 (78%) patients. Six percent underwent thoracoscopy, and 1.6% underwent thoracotomy.

Twenty-nine percent (n=554) were prescribed outpatient antifungal medication (49% of probable vs. 10% of suspect patients, p<0.0001) (Table 3, Figure 1). First antifungal prescriptions occurred a median of 10 days and a mean of 38 days after the index date (range −6–365). Immunocompromised patients were more likely to get antifungals than non-immunocompromised patients (48% vs. 24%, p<0.0001) and had longer treatment durations (median 238 vs. 98 days, p<0.0001). Patients with ICD-9 codes for symptoms or clinical findings were also more likely to get antifungals than those without (41% vs 14%, p<0.0001). Suspect patients with compatible symptoms or clinical findings spanning >30 days were more likely to get antifungals than those who had them for 30 days (14% vs. 7%, p=0.047); however, this association was not significant for probable patients.

Nineteen percent (n=377) were hospitalized for histoplasmosis (median 5 days, mean 8.8 [range 1–122]). Related inpatient diagnoses included pneumothorax (26%), pulmonary fibrosis (17%), and respiratory failure or hypoxemia (16%) (Supplementary Table 2). Fifty

(2.6%) patients died in the hospital. Males were more likely to be hospitalized than females (22% vs. 17%, p=0.006), and hospitalized patients were younger than non-hospitalized patients (median 55 vs. 58 years, p<0.0001). Histoplasmosis-related outpatient visits generated 18,869 claims, most of which were from acute care hospitals (47%), laboratories (9%), infectious disease providers (6%), and family practice (5%); of these 1,770 patients, 733 (41%) had >1 visit (mean 3.0 [range 1–93]). Among patients with >1 visit, median time between the index date and the last visit was 180 days (mean 175, IQR 45–295, with 100 (5.2%) patients having visits in the twelfth month.).

Discussion

This analysis of US health insurance claims data indicates that histoplasmosis encompasses a wide spectrum of illness, with some patients experiencing severe disease, requiring antifungal treatment, and having many healthcare encounters. In this large cohort, non-directed testing (i.e., culture, smear, biopsy) was more frequent than targeted *Histoplasma* antibody or antigen testing, suggesting that *Histoplasma*-specific tests were not commonly ordered for patients with histoplasmosis diagnosis codes. Also notable were potential opportunities for earlier diagnosis among symptomatic patients and those who initially received codes for other or unknown respiratory illnesses.

Our results show that histoplasmosis causes severe illness in some patients, with nearly 20% hospitalized and an overall in-hospital mortality rate of 2.6%. Because MarketScan data do not capture deaths outside the hospital, our study might be biased towards people with less severe cases who survived at least one year after the index date. Additionally, some patients may have been hospitalized for lung nodule resection rather than for acute illness. However, these findings are likely more representative of the spectrum of histoplasmosis than public health surveillance data, which typically detects more severe cases. For example, 57% of patients were hospitalized and 7% died in a recent surveillance summary [3]. Similar to those surveillance data and other studies [3, 11, 16], male sex was significantly associated with hospitalization but not with death in this analysis. We also observed a mean inpatient length of stay (8.8 days) comparable with national hospitalization data (8.5 days) [16].

Typical illness duration is not well described but varies from several weeks for APH to presumably months or years for the chronic forms. One of our primary limitations was the lack of detail available to classify different forms of histoplasmosis. We attempted to capture incident and more acute infections by excluding patients with histoplasmosis diagnosis codes in the year before the index date and found a median of six months between patients' first and last histoplasmosis-related healthcare encounters. However, this estimate could be falsely high if histoplasmosis diagnoses were recorded at visits after patients' illnesses resolved.

We found low histoplasmosis-specific testing rates overall, higher testing rates among probable patients, and many biopsies; these patterns suggest that histoplasmosis may commonly be a surprise diagnosis not previously considered. Such incidental—but not inconsequential—diagnoses likely reflect low provider awareness of the disease and its wide variety of manifestations, which can mimic cancer and tuberculosis, among many other

conditions. Notably, over half of patients did not have a histoplasmosis-specific test, fungal culture or smear, or biopsy or cytopathology. Some of these patients could have had *Histoplasma* detected on a non-fungal culture when testing for other infectious etiologies, but MarketScan data do not include laboratory test results, so exploring this hypothesis was not possible. Alternative explanations for low testing rates include 1) incomplete identification of incident histoplasmosis diagnoses where testing was done in previous years or 2) histoplasmosis diagnosis codes might have included "rule out" diagnoses; in claims-based analyses, diagnoses coded only on imaging or laboratory claims could represent suspected conditions that the provider is attempting to eliminate as a cause of illness. This explanation seems less likely because most claims were generated from provider types other than radiology departments and because healthcare providers' awareness of and suspicion for histoplasmosis is probably low. Our finding that immunocompromised patients were more likely to have antigen testing is consistent with the greater utility of this test vs. antibody tests in patients who might not mount an immune response [17]. The continued use of serologic testing after the index date among probable patients could indicate its use for monitoring disease progression or treatment response.

Incidental diagnoses of asymptomatic histoplasmosis could also occur based on findings like lymphadenopathy or nodules seen on imaging performed for other purposes. A previous study found that approximately half of all persons with histoplasmosis at a tertiary care center had asymptomatic histoplasmomas, which were typically discovered in this way [11]. The study also found that asymptomatic histoplasmosis was associated with older age, likely because older patients had more frequent radiology tests, allowing for more opportunities for incidental identification of histoplasmosis [11]. This is similar to our finding that younger patients were more likely to be symptomatic, which could also explain why younger patients were more likely to be hospitalized. Although asymptomatic histoplasmosis does not usually result in poor patient outcomes directly, it can incur substantial excess healthcare costs and morbidity during diagnostic workups to differentiate it from lung cancer [11]. Greater clinician awareness of histoplasmosis as a cause of lymphadenopathy and pulmonary nodules might reduce the need for invasive procedures. Additional research on non-invasive strategies to detect *Histoplasma* as a cause of abnormal radiologic findings, including pulmonary nodules, is needed [18]. Importantly, >80% of patients did not appear to have immunocompromising conditions (though we might have under-estimated their prevalence if they were not coded for during the year pre-index date), again highlighting the need for clinicians to also consider histoplasmosis in immunocompetent persons.

Over a third of patients had ≥2 visits with compatible symptoms or clinical findings before the index date, over a period of >6 weeks. Along with frequent diagnoses for other clinically similar respiratory illnesses and unknown or unspecified lung disease diagnoses, these results suggest that some patients experienced diagnostic delays. Substantial delays have previously been documented for central nervous system histoplasmosis [8], and multiple courses of empiric antibacterial treatment for suspected bacterial pneumonia are common with coccidioidomycosis and blastomycosis [13, 14]. In this cohort, antibacterial prescriptions were more frequent before the index date than after it. MarketScan data does not link prescriptions and diagnoses, so we could not determine the reason(s) why medications were prescribed; however, based on inappropriate antibacterial use documented

for other endemic mycoses and presence of nonspecific respiratory illness codes, some of the antibacterial use observed here is likely empiric treatment for bacterial pneumonia. Expanded access to rapid histoplasmosis diagnostics, coupled with greater clinician and patient awareness, might help reduce unnecessary antibacterial therapy in APH.

Less than one-third of patients received antifungal medications. This could be an underestimate because the datasets did not include inpatient medications, although nearly all inpatients with active infection likely also receive outpatient antifungals. Antifungal treatment is indicated for certain forms of histoplasmosis, including moderate to severe APH and chronic and extrapulmonary histoplasmosis [12]. Whether antifungals are useful for mild to moderate pulmonary infection is less clear; however, the Infectious Diseases Society of America (IDSA) guidelines state that antifungals could be considered for patients with symptoms lasting >1 month. In this analysis, apparent delays in antifungal treatment receipt (median 10, mean 38 days after the index date), along with the finding that suspect patients with symptoms or clinical findings spanning >30 days were more likely to get antifungals, suggest that the treatment practices we observed could be consistent with these guidelines, despite the limitations of using administrative data to detect specific forms of histoplasmosis and symptoms and clinical signs. Furthermore, the median antifungal duration (4.3 months) appears to be consistent with the IDSA recommendation of 12 weeks of treatment for APH, further suggesting that many treated patients likely had APH.

In addition to previously mentioned limitations, our analysis is subject to flaws inherent in administrative data, such as under-coding and misclassification. Furthermore, the healthcare experiences of patients in this convenience sample of the commercially-insured population might differ from those of people with other insurance types or the uninsured. Regardless, the healthcare burden of histoplasmosis is likely to be far greater than in this study, given that under-diagnosis, particularly of APH, is likely common, based on the high hospitalization rates and incidental diagnosis.

Our study provides insight into histoplasmosis-related healthcare use, testing, and treatment among privately-insured patients. Confirming the wide range of manifestations known to be associated with histoplasmosis, some patients experienced severe, prolonged illness, often after apparent diagnostic delays. A sizeable proportion appeared to lack symptoms and these patients were likely diagnosed based on histopathology or culture of biopsies. Based on the pathophysiology of *Histoplasma*-induced pulmonary nodules, lymphadenopathy, and mediastinitis, earlier symptomatic infection may have been common followed by longer-term persistence and more indolent symptoms. These results underscore the importance of considering APH in patients with lower respiratory symptoms, as well as those with lung nodules or chest lymphadenopathy, especially when no other etiology is found, and obtaining histoplasmosis-specific laboratory testing. Lastly, more than one-third of these patients resided outside the East North Central and East South Central Census Divisions, areas often associated with histoplasmosis, highlighting the need for healthcare providers and the public throughout the United States to be aware of the disease. In the future, more detailed data on the effects of histoplasmosis on patients and testing and treatment practices, will help to guide awareness efforts and inform early intervention strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

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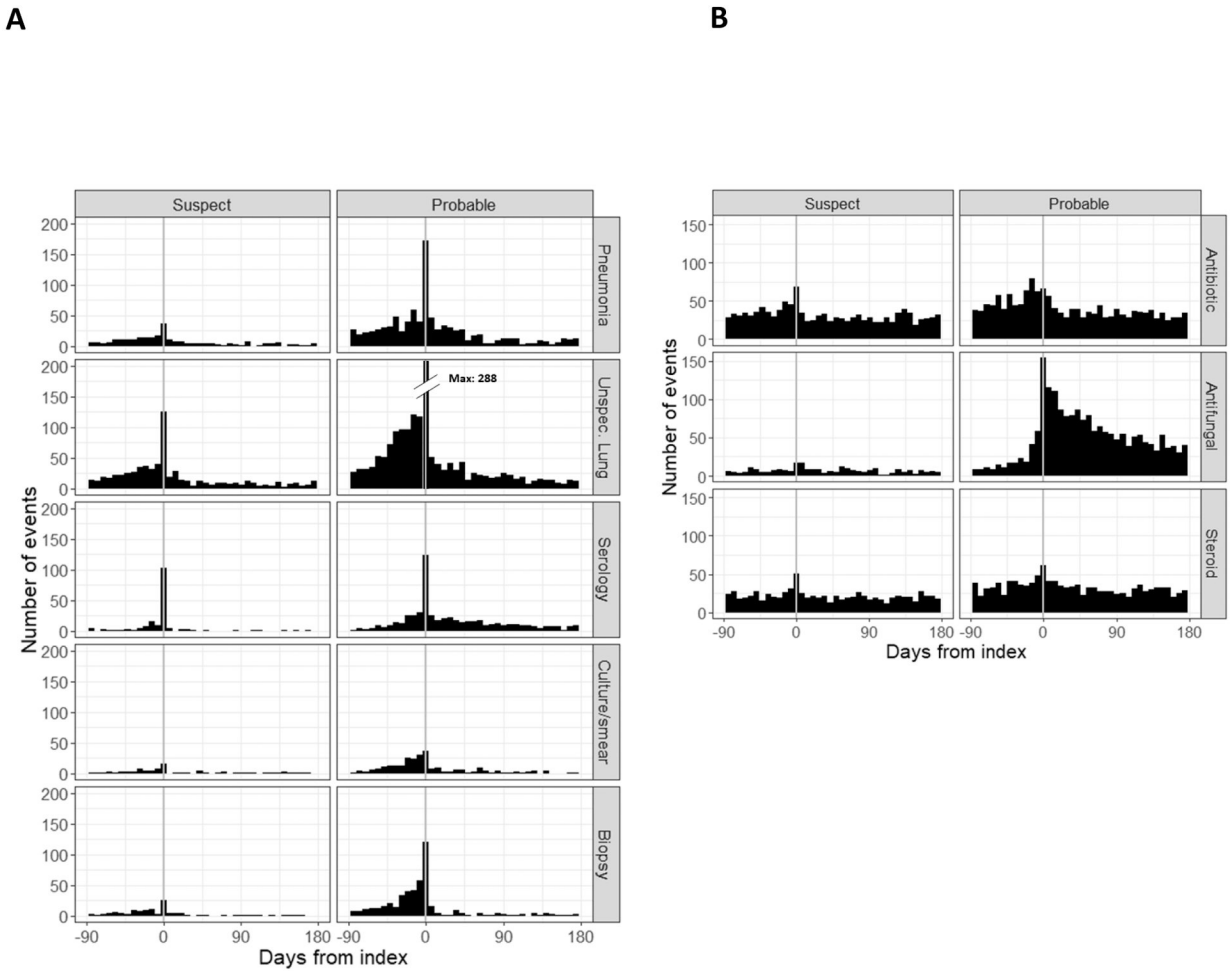
Figure 1: Days between index date and selected diagnoses and diagnostic tests (A) and prescription medications (B), suspect vs. probable histoplasmosis patients, 2012–2014
Histogram bars indicate the number of events on a given day before or after a patient's initial histoplasmosis diagnosis, or index date. Index dates are denoted by gray vertical lines. For readability, visits and prescriptions that occurred 181–365 days after index are not shown. These represent 2–25% of visits and 26–38% of prescriptions. Codes for pneumonia, unspecified lung disease, and diagnostic tests increased in the days leading up to the index date and declined sharply thereafter. Antibiotics were more commonly prescribed before the index date than after, whereas antifungals were prescribed much more commonly after the index date. Rates of corticosteroid prescriptions were generally similar before and after histoplasmosis diagnosis, with a minor peak on the index date.

Figure 2: Histoplasmosis antibody or antigen testing, fungal culture or smear, and biopsy, histoplasmosis patients, 2012–2014

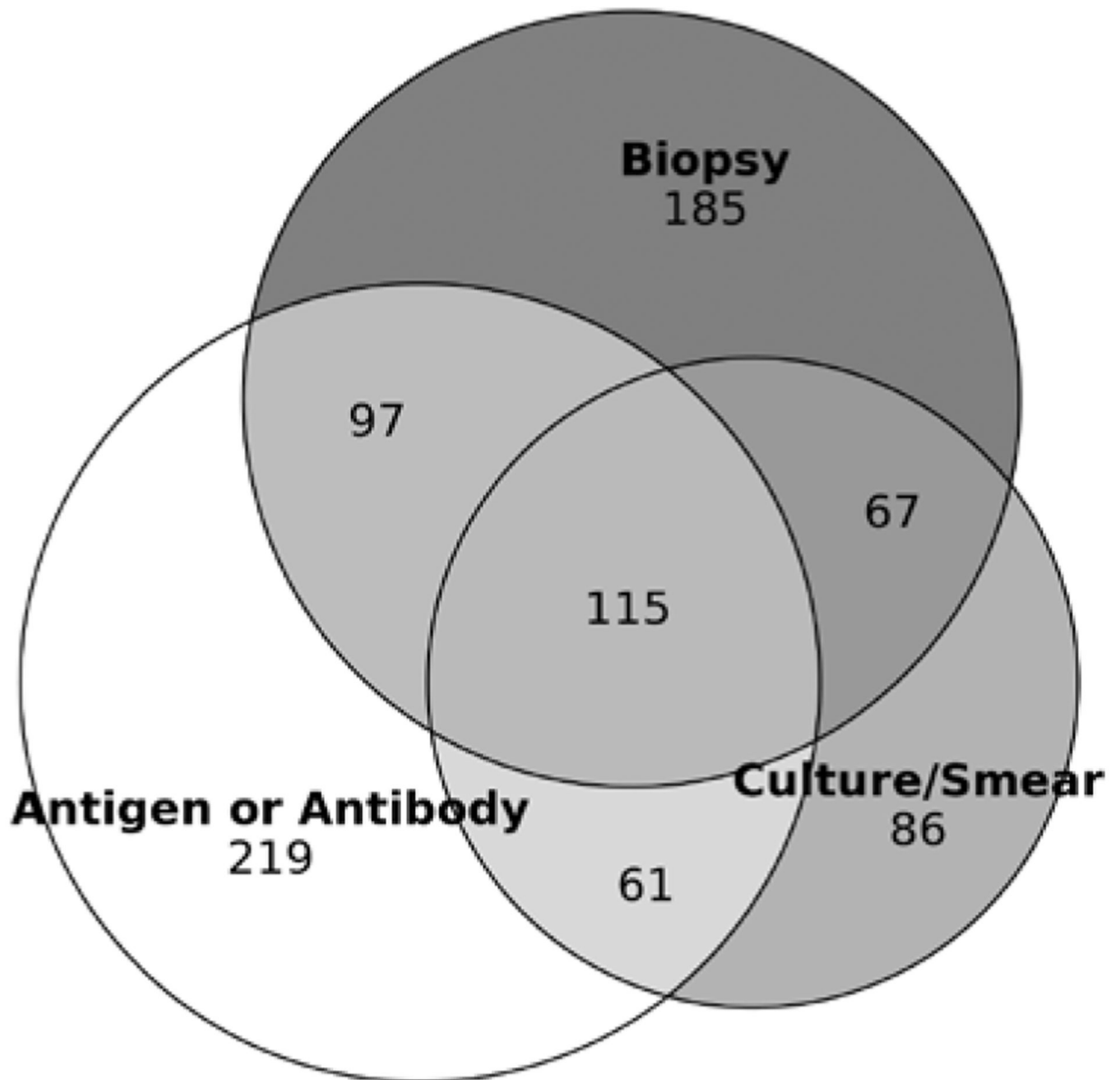Figure represents 890 unique patients with at least one of the following diagnostic tests:

fungal culture/smear, biopsy, or antibody or antigen test.

Table 1:

Demographic features and underlying conditions among histoplasmosis patients, 2012–2014

Characteristic	All patients		Probable		Suspect		
	n=1935	%	n=943	%	n=992	%	p-value
Age group, years							<0.0001
0–17	78	4.0%	44	4.7%	34	3.4%	
18–34	163	8.4%	99	10.5%	64	6.5%	
35–44	226	11.7%	124	13.1%	102	10.3%	
45–54	401	20.7%	200	21.2%	201	20.3%	
55–64	572	29.6%	274	29.1%	298	30.0%	
65	495	25.6%	202	21.4%	293	29.5%	
Sex							0.0088
Male	930	48.1%	482	51.1%	448	45.2%	
Female	1005	51.9%	461	48.9%	544	54.8%	
US Census Division of primary beneficiary's residence							0.0982
New England	21	1.1%	6	0.6%	15	1.5%	
Mid-Atlantic	91	4.7%	39	4.1%	52	5.2%	
East North Central	855	44.2%	432	45.8%	423	42.6%	
West North Central	113	5.8%	56	5.9%	57	5.7%	
South Atlantic	177	9.1%	73	7.7%	104	10.5%	
East South Central	391	20.2%	200	21.2%	191	19.3%	
West South Central	170	8.8%	89	9.4%	81	8.2%	
Mountain	35	1.8%	13	1.4%	22	2.2%	
Pacific	62	3.2%	27	2.9%	35	3.5%	
Unknown	20	1.0%	8	0.8%	12	1.2%	
Conditions on or in the year before index date [*]							
Diabetes	413	21.3%	209	22.2%	204	20.6%	0.3842
Chronic obstructive pulmonary disease	535	27.6%	300	31.8%	235	23.7%	<0.0001
HIV/AIDS	39	2.0%	27	2.9%	12	1.2%	0.0096
Tuberculosis	13	0.7%	8	0.8%	5	0.5%	0.3530
Immune-mediated inflammatory disease	205	10.6%	117	12.4%	88	8.9%	0.0113
Solid organ or stem cell transplant	53	2.7%	42	4.5%	11	1.1%	<0.0001
Hematologic malignancy	75	3.9%	53	5.6%	22	2.2%	<0.0001
Immunocompromised [**]	348	18.0%	223	23.7%	125	12.6%	<0.0001
Type of histoplasmosis [*]							
Unspecified	1663	85.9%	822	87.2%	841	84.8%	0.1305
Pulmonary	467	24.1%	363	38.5%	104	10.5%	<0.0001
Disseminated	78	4.0%	26	2.8%	52	5.2%	0.0055
Histoplasma duboisii infection	57	3.0%	39	3.9%	18	1.9%	0.0085

*
Patients could have received diagnosis codes for multiple conditions

**
HIV/AIDS, immune-mediated inflammatory disease, transplant, or hematologic malignancy

Table 2:

Symptoms, clinical findings, and other respiratory diagnoses in the 3 months before diagnosis among histoplasmosis patients, 2012–2014

Characteristic	All patients		Probable		Suspect		
	n=1935	%	n=943	%	n=992	%	p-value
Symptoms or clinical findings consistent with histoplasmosis	1045	54.0%	641	68.0%	404	40.7%	<0.0001
Symptoms consistent with histoplasmosis	875	45.2%	529	56.1%	346	34.9%	<0.0001
Fever/chills	160	8.3%	130	13.8%	30	3.0%	<0.0001
Cough	318	16.4%	197	20.9%	121	12.2%	<0.0001
Headache	98	5.1%	63	6.7%	35	3.5%	0.0015
Malaise/fatigue	203	10.5%	129	13.7%	74	7.5%	<0.0001
Chest pain	290	15.0%	193	20.5%	97	9.8%	<0.0001
Shortness of breath/wheezing	384	19.8%	240	25.5%	144	14.5%	<0.0001
Myalgia/arthralgia	69	3.6%	34	3.6%	35	3.5%	0.9200
Clinical findings consistent with histoplasmosis	549	28.4%	380	40.3%	169	17.0%	<0.0001
Swelling, mass, or lump in chest	272	14.1%	209	22.2%	63	6.4%	<0.0001
Lymphadenopathy	270	14.0%	199	21.1%	71	7.2%	<0.0001
Pulmonary nodule	339	17.5%	229	24.3%	110	11.1%	<0.0001
Number of visits for symptoms or clinical findings consistent with histoplasmosis							
0	918	47.4%	318	33.7%	600	60.5%	
1	344	17.8%	168	17.8%	176	17.7%	
2	191	9.9%	113	12.0%	78	7.9%	
3	482	24.9%	344	36.5%	138	13.9%	
Mean, median days between first symptom or clinical finding and index date (range)	45.6, 45.0	(1–89)	45.1, 44.0	(1–89)	46.3, 46.5	(1–89)	0.5294
Other respiratory diagnoses							
Influenza	13	0.7%	8	0.8%	5	0.5%	0.3540
Pneumonia	215	11.1%	153	16.2%	62	6.3%	<0.0001
Bronchitis	147	7.6%	89	9.4%	58	5.8%	0.0029
Acute sinusitis	102	5.3%	53	5.6%	49	4.9%	0.5029
Allergic rhinitis	75	3.9%	31	3.3%	44	4.4%	0.1909
Asthma	130	6.7%	68	7.2%	62	6.3%	0.3986
Lung cancer	76	3.9%	59	6.3%	17	1.7%	<0.0001
Sarcoidosis	26	1.3%	16	1.7%	10	1.0%	0.1885
Unspecified acute respiratory infection	68	3.5%	39	4.1%	29	2.9%	0.1477
Other unclassified lung disease	387	20.0%	275	29.2%	112	11.3%	<0.0001
Nonspecific abnormal finding of lung field	375	19.4%	266	28.2%	109	11.0%	<0.0001
Systemic outpatient antibacterial medication	689	35.6%	388	41.1%	301	30.3%	<0.0001

Table 3:

Testing and treatment among histoplasmosis patients, 2012–2014

	All patients		Probable		Suspect		
Characteristic	**n=1935**	**%**	**n=943**	**%**	**n=992**	**%**	**p-value**
Fungal-specific test	646	33.4%	435	46.1%	211	21.3%	<0.0001
Histoplasma antibody test	349	18.0%	241	25.6%	108	10.9%	<0.0001
Histoplasma antigen test	349	18.0%	261	27.7%	88	8.9%	<0.0001
Fungal smear	294	15.2%	207	22.0%	87	8.8%	<0.0001
Fungal culture	223	11.5%	163	17.3%	60	6.0%	<0.0001
Biopsy	464	24.0%	366	38.8%	98	9.9%	<0.0001
Cytopathology	382	19.7%	274	29.1%	108	10.9%	<0.0001
More than one laboratory test type [*]	549	28.4%	403	42.7%	146	14.7%	<0.0001
Systemic outpatient antifungal medication in the year after index date	554	28.6%	460	48.8%	94	9.5%	<0.0001
Mean, median duration in days (range)	167.1, 129.0	(1–438)	178.6, 156.0	(1–438)	110.7, 54.0	(1–372)	<0.0001
Itraconazole	377	19.5%	353	37.4%	24	2.4%	<0.0001
Mean, median duration in days (range)	173.1, 128.0	(2–438)	177.4, 142.0	(2–438)	109.1, 42.5	(14–372)	0.0049
Fluconazole	170	8.8%	111	11.8%	59	5.9%	<0.0001
Mean, median duration in days (range)	94.3, 31.5	(1–384)	83.2, 30.0	(1–384)	115.1, 56.0	(1–371)	0.3316
Voriconazole	48	2.5%	41	4.3%	7	0.7%	<0.0001
Mean, median duration in days (range)	152.4, 111.0	(10–380)	159.2, 130.0	(10–380)	112.4, 63.0	(31–291)	0.4956
Posaconazole	13	0.7%	13	1.4%	0	0.0%	n/a
Mean, median duration in days (range)	197.2, 218.0	(14–365)	197.2, 218.0	(14–365)	n/a	n/a	n/a
Amphotericin B	22	1.1%	2	0.2%	20	2.1%	<0.0001
Mean, median days from index date to first systemic outpatient antifungal medication	38.0, 10.0	(−6–365)	29.7, 9.0	(−6–365)	78.6, 26.5	(−6–363)	<0.0001

[*] *Histoplasma* antibody test, *Histoplasma* antigen test, fungal smear, fungal culture, biopsy, or cytopathology