

Clinical Diagnostic Algorithms for Blastomycosis, Coccidioidomycosis, and Histoplasmosis

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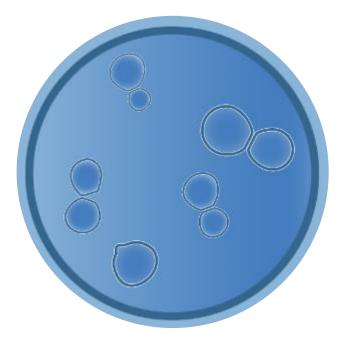
Mycotic Diseases Branch, Centers for Disease Control & Prevention

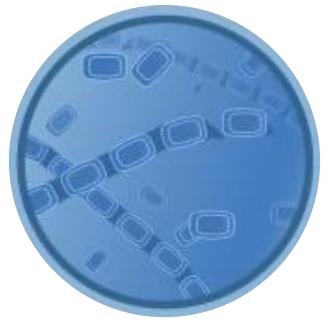
Dallas Smith, PharmD, MAS Epidemiologist Mycotic Diseases Branch, Centers for Disease Control & Prevention

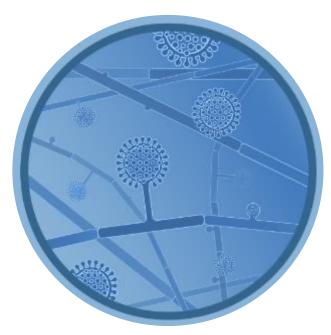
Agenda

- Blastomycosis, coccidioidomycosis, and histoplasmosis overview
- Diagnostic challenges
- Impact of underdiagnosis
- Diagnostic algorithms

Blastomyces, Coccidioides, and Histoplasma are fungal pathogens that are endemic in certain areas





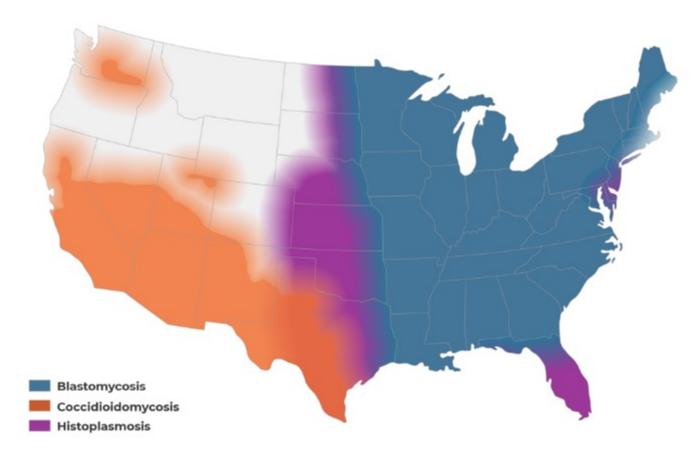


Blastomyces

Coccidioides

Histoplasma

Their combined distribution spans most of the country



Hospitalizations

- Coccidioidomycosis (~6,700)
- Histoplasmosis (~4,600)
- Blastomycosis (~1,000)

Direct medical costs

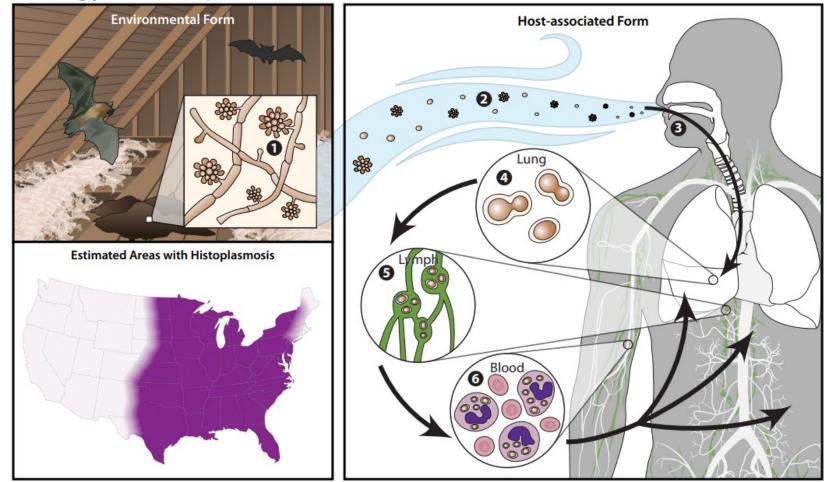
- Coccidioidomycosis (~\$200m)
- Histoplasmosis (~\$200m)
- Blastomycosis (~\$23m)

Fungi that cause these diseases live in the environment, particularly in soil

Exposure typically occurs through inhalation of microscopic spores

These fungi are dimorphic, with mycelial and yeast phases

Biology of Histoplasmosis

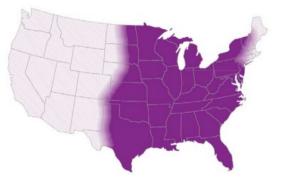


Each fungus is associated with a geographic range

Estimated areas of endemicity:







Blastomycosis

Coccidioidomycosis

Histoplasmosis

Trends are monitored through national surveillance in select states where any of these disease are reportable

- In states where a disease is reportable, healthcare professionals, laboratories, hospitals, and other providers must tell public health departments when a person is diagnosed.
- Case data is voluntarily submitted to CDC when a patient meets standardized criteria to be classified as a case according to the Council of State & Territorial Epidemiologists case definition.



Blastomycosis, coccidioidomycosis, and histoplasmosis are not reportable in all states

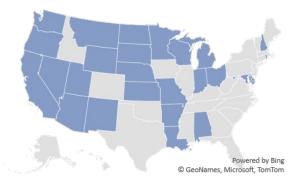
Estimated areas of endemicity:

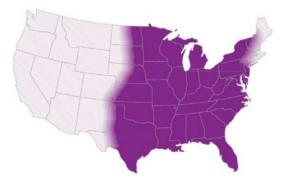


States where disease is reportable:









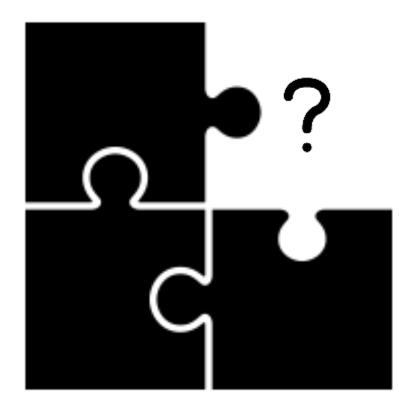


Blastomycosis

Coccidioidomycosis

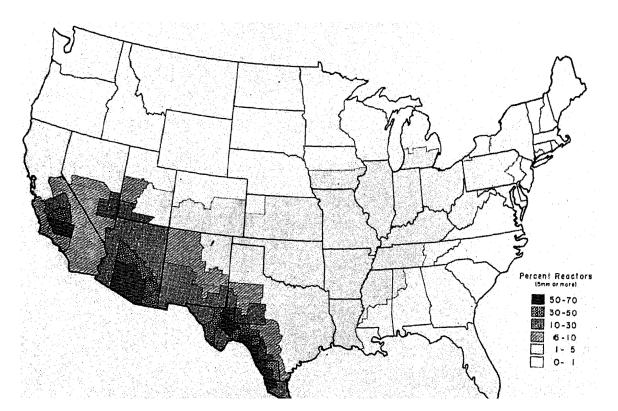
Histoplasmosis

Surveillance limitations result in incomplete understanding of disease

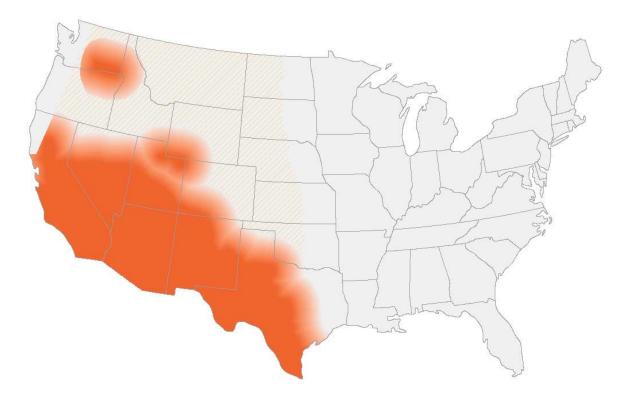


Geographic range likely wider than currently recognized

Coccidioidomycosis skin testing in 1940s-1950s New map of coccidioidomycosis endemicity



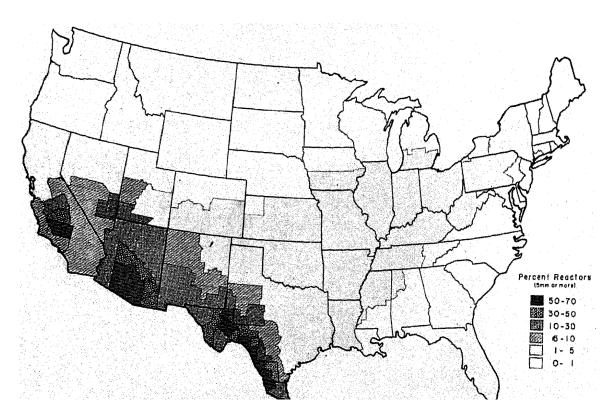
Distribution of counties and groups of counties by frequency of coccidioidin reactors in 48,676 young adults. *Edwards et al* 1957.



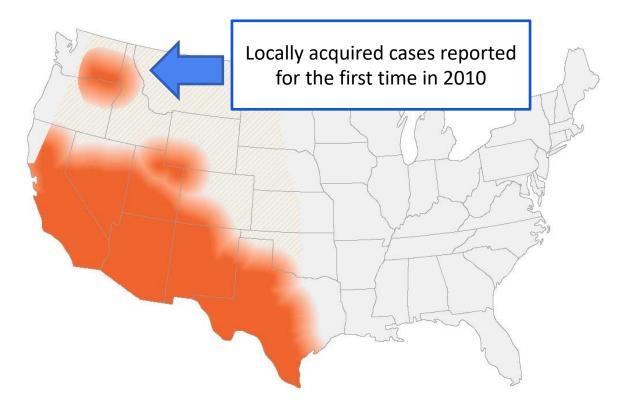
https://www.cdc.gov/fungal/diseases/coccidioidomycosis/maps.html

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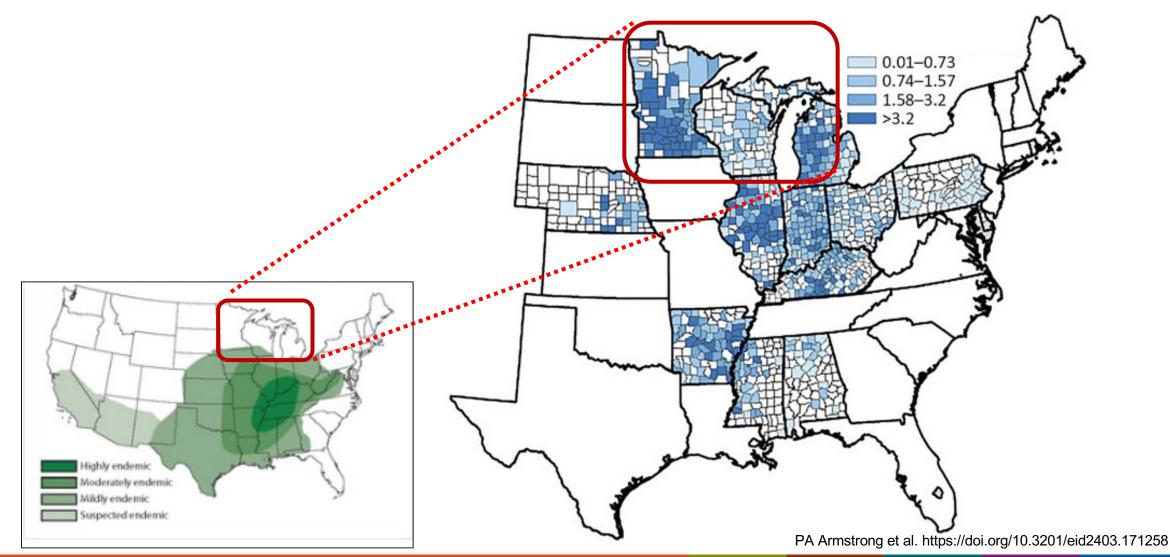
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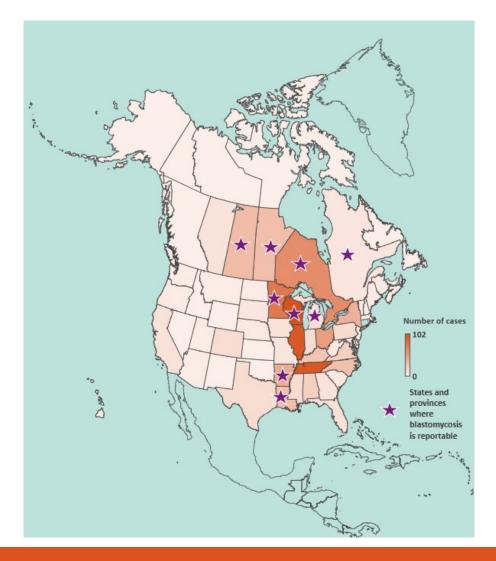
https://www.cdc.gov/fungal/diseases/coccidioidomycosis/maps.html

Geographic range likely wider than currently recognized

Histoplasmosis incidence, 2011-2014

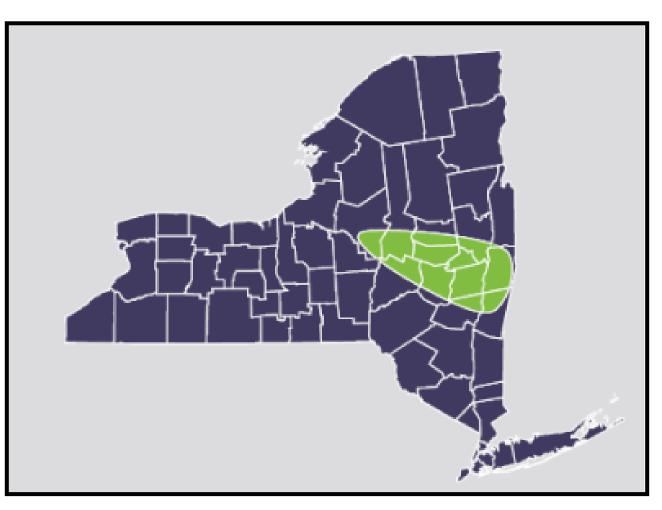


Limited blastomycosis surveillance hinders ability to assess geographic trends



- Reviewed blastomycosis case reports from 1970-2020, mapped where cases were diagnosed.
- Most published blastomycosis cases were diagnosed within the estimated endemic range.
- Over half of published cases occurred in jurisdictions without public health surveillance.

New York investigation indicated potential local acquisition of blastomycosis



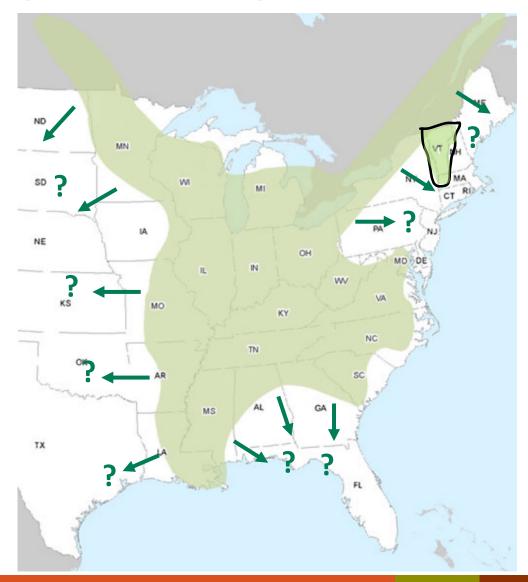
McDonald R, Dufort E, Jackson BR, Tobin EH, Newman A, Benedict K, Blog D. Notes from the Field: Blastomycosis Cases Occurring Outside of Regions with Known Endemicity - New York, 2007-2017. MMWR Morb Mortal Wkly Rep. 2018 Sep 28;67(38):1077-1078

Recent analyses suggest *Blastomyces* may be endemic in Vermont



Borah B, EIS Conference, 2023 Benedict et al., 2012, *Current Fungal Infection Reports*

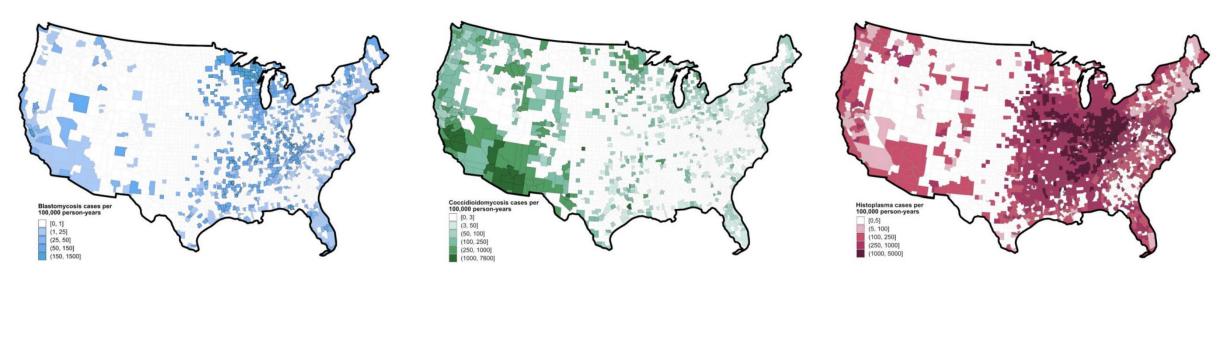
Endemicity may extend beyond historical regions



Borah B, EIS Conference, 2023 Benedict et al., 2012, *Current Fungal Infection Reports*

Cases are identified outside of traditionally established endemic regions

Incidence from 2007–2016 in Medicare fee-for-service beneficiaries by U.S. county Reported as cases per 100,000 person-years



Blastomycosis

Coccidioidomycosis

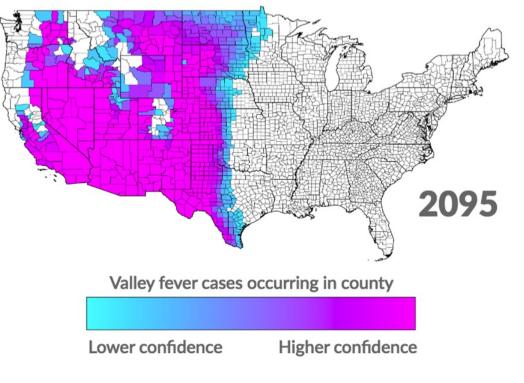
Histoplasmosis

Mazi, P. B., Sahrmann, J. M., Olsen, M. A., et al., (2022). The Geographic Distribution of Dimorphic Mycoses in the United States for the Modern Era. *Clinical infectious diseases*, https://doi.org/10.1093/cid/ciac882

Climate change may further impact the geographical distribution of coccidioidomycosis

- Climate niche model for coccidioidomycosis based on temperature and precipitation
- Predicted areas affected by coccidioidomycosis under different climate warming scenarios

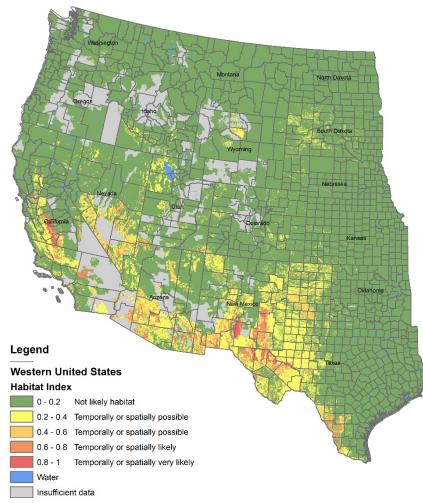
High climate warming scenario



Estimated ranges of coccidioidomycosis (Gorris et al, GeoHealth 2019)

Climate change may further impact the geographical distribution of coccidioidomycosis

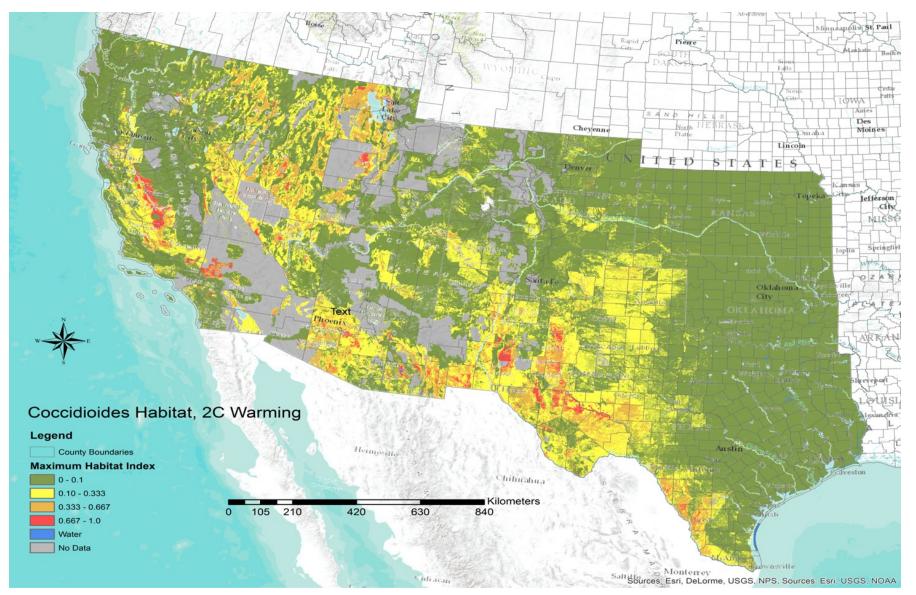
- Model predicted suitable soil habitat for coccidioidomycosis based on USDA data
 - Electrical conductivity, pH, temperature, precipitation, organic matter, water holding capacity, surface morphology.





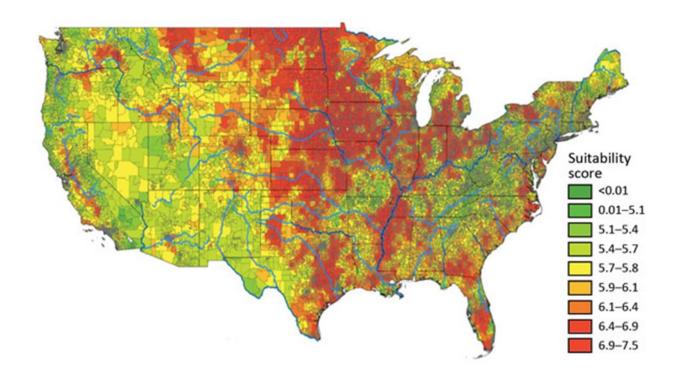
https://doi.org/10.1371/journal.pone.0247263

What if we impose a 2^o Celsius warming?



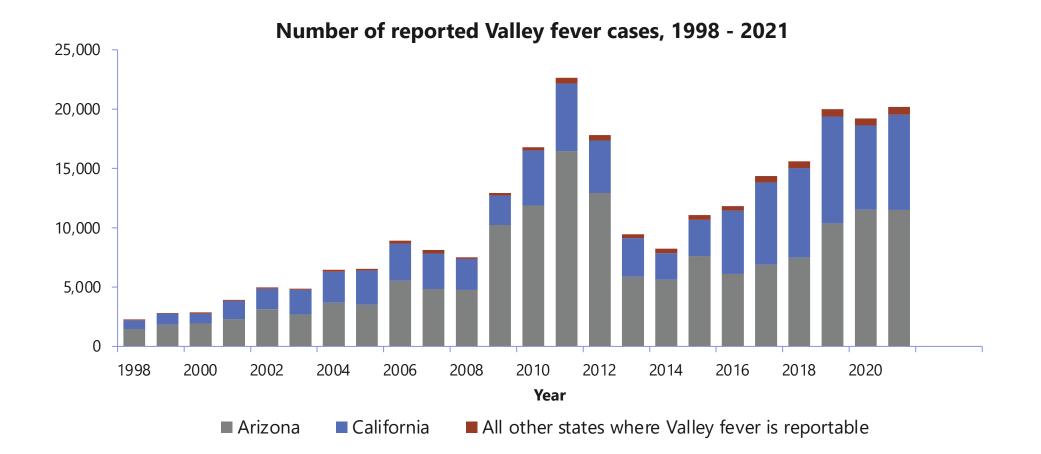
Climate change may further impact the geographic suitability for *Histoplasma*

- Geographic suitability model to predict areas favorable to *Histoplasma* presence
 - Land cover use
 - Distance to water
 - Soil pH



Estimated ranges of histoplasmosis (Maiga et al, EID 2018)

Reported coccidioidomycosis cases have increased considerably since 2014



Steady rise in histoplasmosis hospitalization rates

Annual rates of all-listed and primary histoplasmosis-associated hospitalizations per 100,000 persons

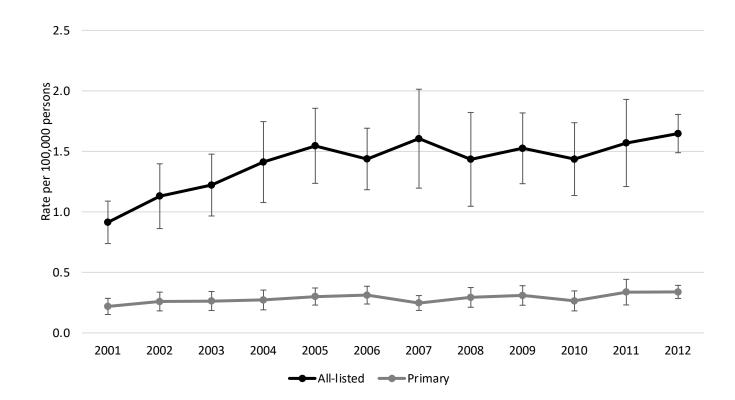
Open Forum Infectious Diseases

BRIEF REPORT

Histoplasmosis-Associated Hospitalizations in the United States, 2001–2012

Kaitlin Benedict,¹ Gordana Derado,² and Rajal K. Mody¹

¹Mycotic Diseases Branch and ²Biostatistics and Information Management Office, Division of Foodborne, Waterborne and Environmental Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia



Surveillance reports characterized epidemiology from 2019–2021



Morbidity and Mortality Weekly Report (MMWR)

Surveillance for Coccidioidomycosis, Histoplasmosis, and Blastomycosis – United States, 2019

Surveillance Summaries / August 19, 2022 / 71(7);1-14

Surveillance for Coccidioidomycosis, Histoplasmosis, and Blastomycosis During the COVID-19 Pandemic — United States, 2019– 2021

Weekly / March 21, 2024 / 73(11);239-244

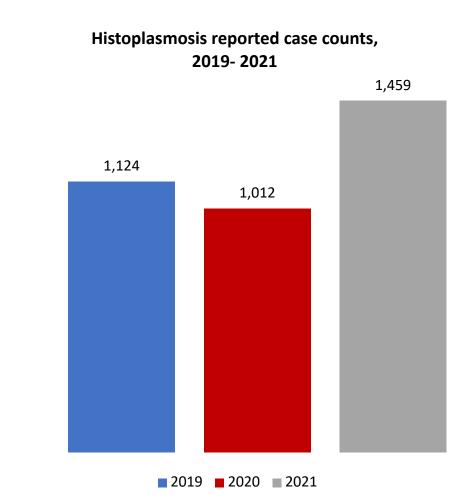
Histoplasmosis cases increased substantially from 2020 to 2021

1,500

500

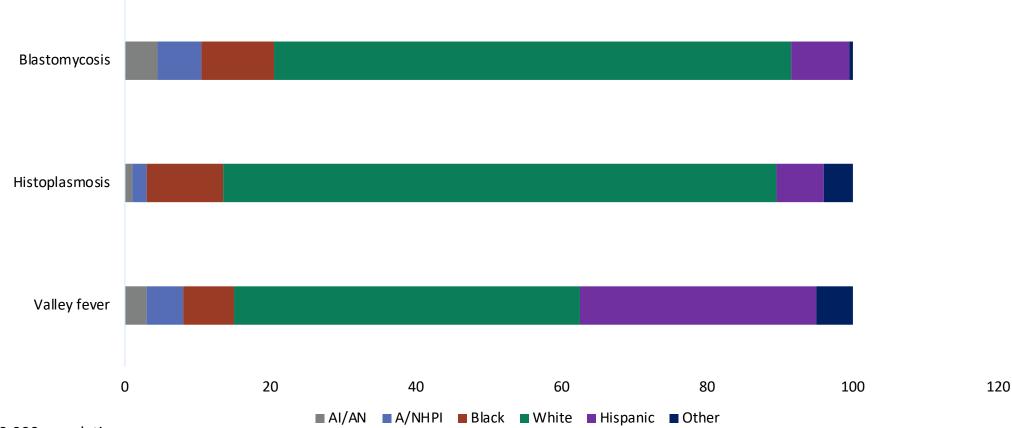
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- Reported cases of histoplasmosis declined by 10% from 2019 to 2020, then increased 44% from 2020 to 2021
- Several factors may have contributed ^{1,000} to the substantial increase in 2021
 - Possible increased risk of exposure due to time spent outdoors
 - Increased clinical suspicion of fungal diseases
 - Weather patterns favorable to fungal growth and dispersal



Greatest proportion of cases occurred among non-Hispanic White populations for all three diseases

Percent of Valley fever, histoplasmosis, blastomycosis by race/ethnicity, 2020–2021



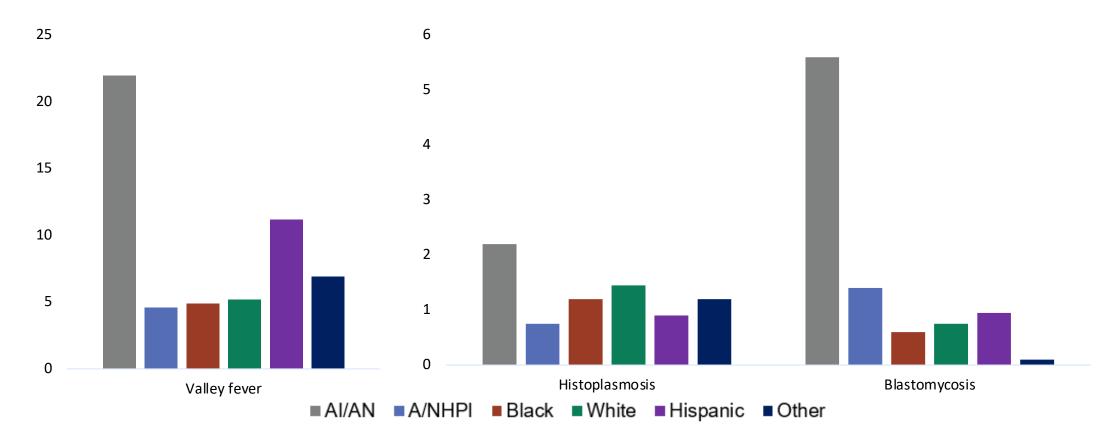
*Cases per 100,000 population

AI/AN=American Indian/Alaska Native; A/NHPI=Asian, Native Hawaiian, Pacific Islander

Williams SL, Smith DJ, Benedict K, et al. DOI: <u>http://dx.doi.org/10.15585/mmwr.mm7311a2</u>

Annual incidence highest among American Indian/Alaska Native populations

Incidence* of Valley fever, histoplasmosis, blastomycosis by race/ethnicity, 2020–2021



*Cases per 100,000 population

AI/AN=American Indian/Alaska Native; A/NHPI=Asian, Native Hawaiian, Pacific Islander

Williams SL, Smith DJ, Benedict K, et al. DOI: <u>http://dx.doi.org/10.15585/mmwr.mm7311a2</u>

American Indian/Alaska Native populations had highest hospitalization rate of any racial/ethnic group

Coccidioidomycosis Among American Indians and Alaska Natives, 2001–2014 doi:

Orion McCotter ख़, Jordan Kennedy, Jeffrey McCollum, Michael Bartholomew, Jonathan Iralu, Brendan R Jackson, Dana Haberling, Kaitlin Benedict

Open Forum Infectious Diseases, Volume 6, Issue 3, March 2019, ofz052, https://doi.org/10.1093/ofid/ofz052

Published: 11 March 2019 Article history •

Hospitalization rate for American Indian/Alaska Native population was >4 times the rate for non-Hispanic White populations

Reported case counts are likely a substantial underestimation of true disease burden

Several factors limit the ability to detect cases of coccidioidomycosis, histoplasmosis and blastomycosis

Underreporting

Underdiagnosis

Care-seeking Behavior







Reported case counts are likely a substantial underestimation of true disease burden

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Underreporting



Underdiagnosis

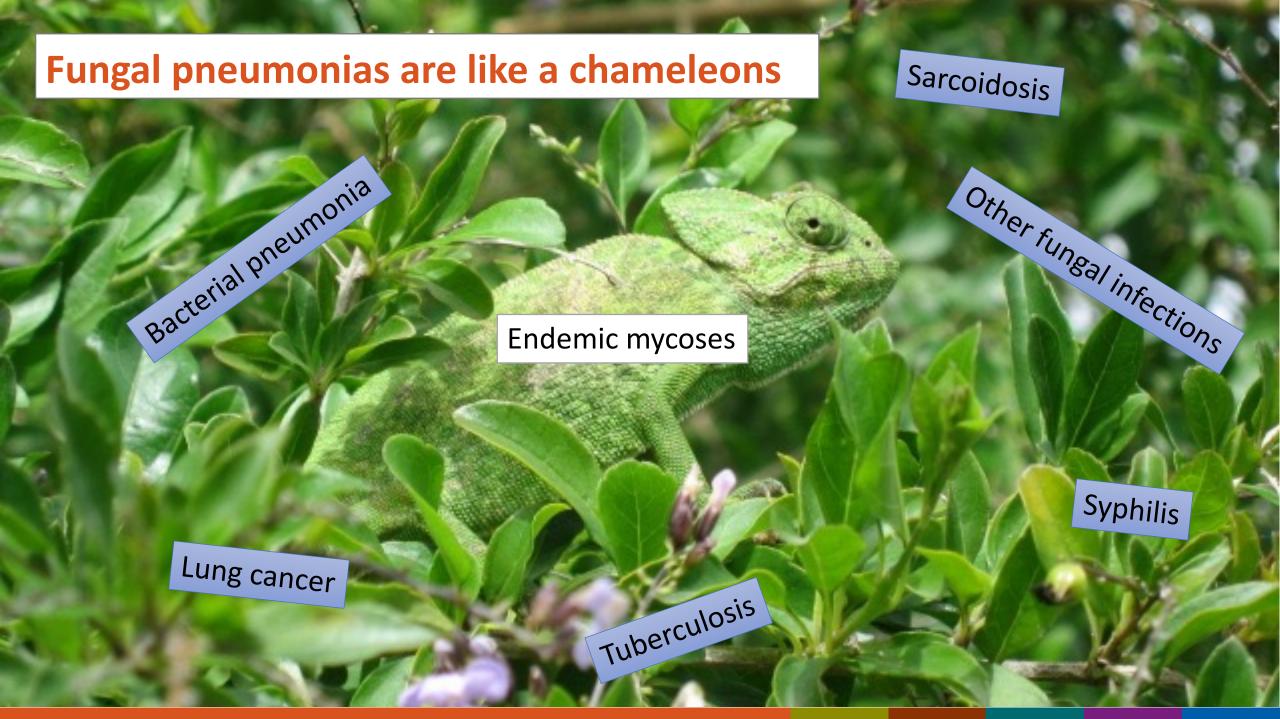


Care-seeking Behavior

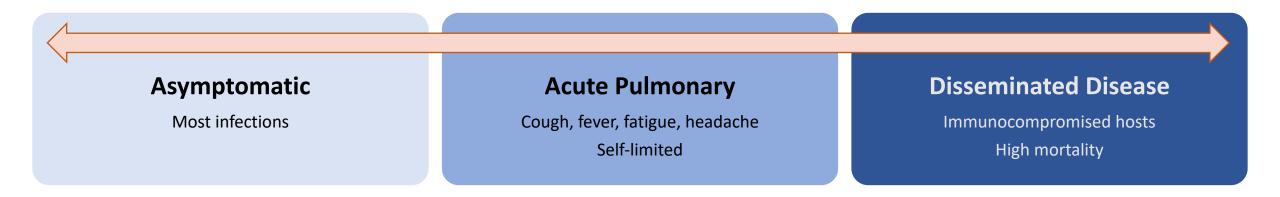


Missed or delayed diagnosis can have wide-reaching implications.

Diagnostic challenges



Clinical manifestations vary substantially



Severity of illness depends principally on:

- 1. Fungal inoculum
- 2. Host immunity

Hospitalization and mortality rates are of concern

Morbidity and Mortality Weekly Report (*MMWR*)

Surveillance for Coccidioidomycosis, Histoplasmosis, and Blastomycosis — United States, 2019

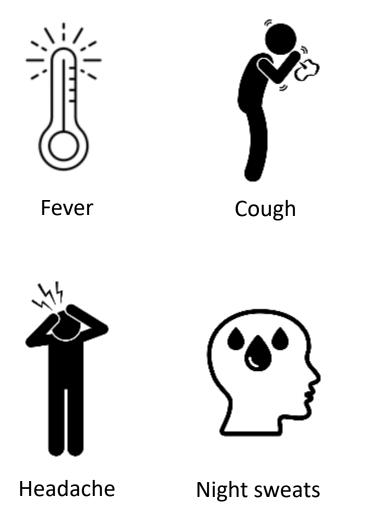
Surveillance Summaries / August 19, 2022 / 71(7);1-14

Dallas J. Smith, PharmD^{1,2}; Samantha L. Williams, MPH²; Endemic Mycoses State Partners Group; Kaitlin M. Benedict, MPH²; Brendan R. Jackson, MD²; Mitsuru Toda, PhD² (<u>VIEW AUTHOR AFFILIATIONS</u>)

54% of histoplasmosis patients were hospitalized and 5% died

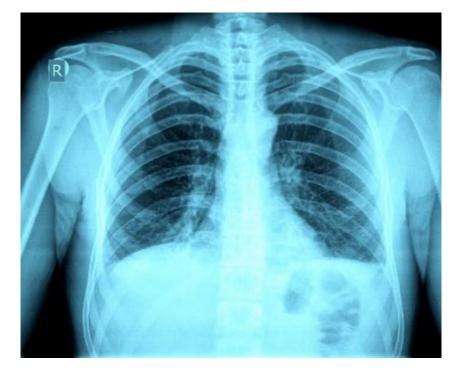
65% of blastomycosis patients were hospitalized and 9% died

Symptoms may be mild and are generally nonspecific





Fatigue

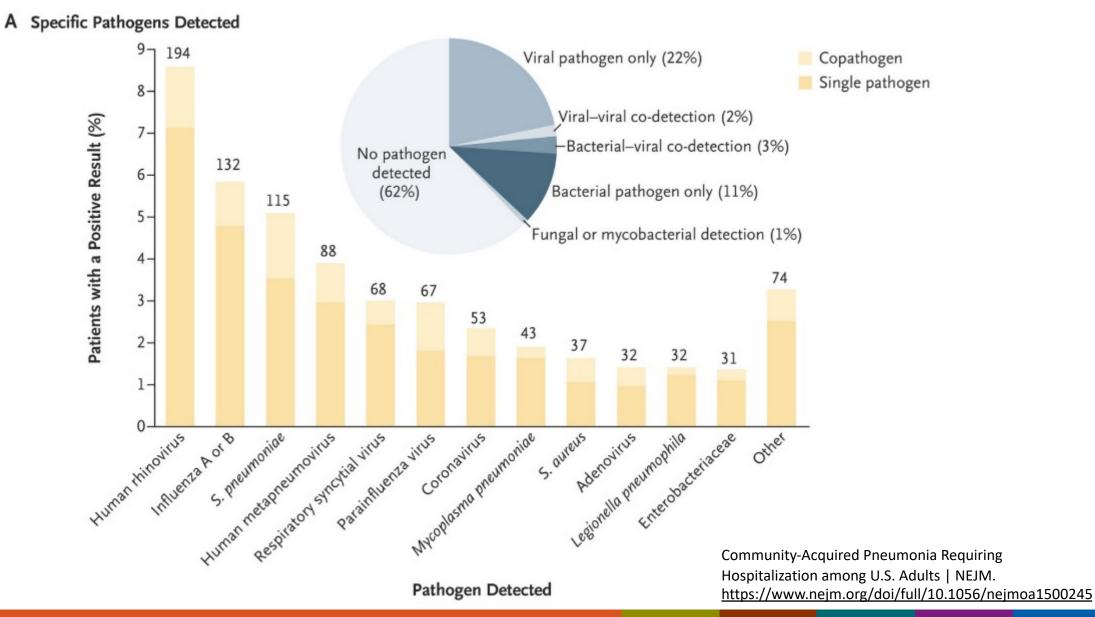


Muscle aches

These diseases are often misdiagnosed as communityacquired pneumonia (CAP) of bacteria or viral etiology



Etiology of pneumonia in the community (EPIC)



Current clinical practice guidelines for CAP do not recommend testing for coccidioidomycosis, histoplasmosis, and blastomycosis

AMERICAN THORACIC SOCIETY DOCUMENTS

Diagnosis and Treatment of Adults with Community-acquired Pneumonia

An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America Guidelines state that endemic mycoses are uncommon pathogens

IDSA GUIDELINES

- The Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age: Clinical Practice Guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America
- True burden likely higher

Survey of healthcare providers asked frequency of testing for these fungal diseases with CAP

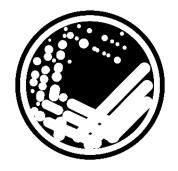
	Primary care providers sometimes or frequently	Infectious disease physicians sometimes or frequently
Blastomycosis	Not surveyed	35%
Coccidioidomycosis	19%	36%
Histoplasmosis	22%	58%

Selecting the optimal laboratory test(s) is complex and nuanced

Antibody/Antigen detection



Culture



Molecular methods



Histopathology



Methods	Pros	6	Cons
Antibody/ Antigen	 Quick turnard Antigen testin disease progr 	ng useful early in •	

Methods		Pros	Cons
Antibody/ Antigen		 Quick turnaround times Antigen testing useful early in disease progression 	 Cross-reactivity Sensitivity dependent on host immune status and disease course
Molecular	DODODA	Quick turnaround times	 Not widely available Few performance-related studies

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Histopathology	- Contraction of the second se	Highly specificRelatively quick turnaround times	Requires invasive proceduresPersonnel training

Test performance varies based on specimen, disease course, and immune status

Sensitivities and specificities of histoplasmosis diagnostic tests

Test	Sensitivity	Specificity	Population Studied
Antigen tests		I	
EIA Urine antigen ⁷	79%	99%	Adult population, people living with HIV
EIA Serum antigen ⁷	82%	97%	Adult population, people living with HIV
Antibody tests			
EIA antibody ⁸	98%	97% (high cross- reactivity with <i>Blastomyces</i>)	Immunocompromised & healthy populations
Complement fixation (CF) antibody ^{9,10}	66%–95%	70%–80%	Adult populations
Immunodiffusion (ID) antibody ^{9,10}	63%–95%	100%	Adult populations
Other tests		ł	
Culture ¹¹	15%-85%	100%	Acute or subacute, disseminated disease
Microscopy/histopathology ¹¹	9%–43%	100%	Acute or subacute, disseminated disease

Impact of underdiagnosis

Unresolved illness, repeat healthcare visits

23–38 days (median time between seeking healthcare and diagnosis)

Benedict K, Ireland M, Weinberg MP, Gruninger R, Weigand J, Chen L, et al. Enhanced Surveillance for Coccidioidomycosis, 14 U.S. States, 2016. *Emerging Infectious Diseases*. 2018 Aug; 24(8). Alpern JD, Bahr NC, Vazquez-Benitez G, Boulware DR, Sellman JS, Sarosi GA. Diagnostic Delay and Antibiotic Overuse in Acute Pulmonary Blastomycosis. *Open Forum Infect Dis*. 2016 Apr 19;3(2):ofw078. Benedict K, McCracken S, Signs K, Ireland M, Amburgey V, et al. Enhanced Surveillance for Histoplasmosis–9 States, 2018–2019. *Open Forum Infect Dis*. 2020 Sept; 7(9):ofaa343.

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56%–70% receive **another diagnosis** before being tested for an endemic fungal infection

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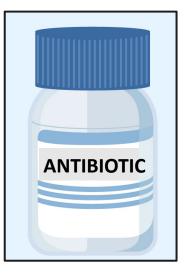
54%–60% see provider ≥**3 times** before tested for an endemic fungal infection

Benedict K, Ireland M, Weinberg MP, Gruninger R, Weigand J, Chen L, et al. Enhanced Surveillance for Coccidioidomycosis, 14 U.S. States, 2016. *Emerging Infectious Diseases*. 2018 Aug; 24(8). Alpern JD, Bahr NC, Vazquez-Benitez G, Boulware DR, Sellman JS, Sarosi GA. Diagnostic Delay and Antibiotic Overuse in Acute Pulmonary Blastomycosis. *Open Forum Infect Dis*. 2016 Apr 19;3(2):ofw078. Benedict K, McCracken S, Signs K, Ireland M, Amburgey V, et al. Enhanced Surveillance for Histoplasmosis–9 States, 2018–2019. *Open Forum Infect Dis*. 2020 Sept; 7(9):ofaa343.

Overuse of unnecessary antibiotics

>50% receive antibiotics before diagnosis of histoplasmosis or coccidioidomycosis

Most patients receive ≥2 rounds of antibiotics before being tested for an endemic fungal infection



Chi GC, Benedict K, Beer KD, Jackson B, et al. Antibiotic and antifungal treatment among persons with confirmed coccidioidomycosis – Southern California, 2011. *Medical Mycology*. 2020, 58, 411–413. doi: 10.1093/mmy/myz073

Alpern JD, Bahr NC, Vazquez-Benitez G, Boulware DR, Sellman JS, Sarosi GA. Diagnostic Delay and Antibiotic Overuse in Acute Pulmonary Blastomycosis. *Open Forum Infect Dis*. 2016 Apr 19;3(2):ofw078. Benedict K, McCracken S, Signs K, Ireland M, Amburgey V, et al. Enhanced Surveillance for Histoplasmosis–9 States, 2018–2019. *Open Forum Infect Dis*. 2020 Sept; 7(9):ofaa343.

Limits accurate surveillance

 Hinders the true understanding of disease epidemiology, with downstream effects on messaging and risk mitigation



Resources are needed to improve provider awareness and testing practices to promote early diagnosis

Diagnostic algorithms

Diagnostic algorithms were developed

In partnership with the Mycoses Study Group, CDC created diagnostic algorithms for blastomycosis, coccidioidomycosis, and histoplasmosis in patients with CAP to:

- Increase levels of testing, particularly among primary care and outpatient providers
- Aid in the accurate interpretation of diagnostic test results
- Offer a **standard** diagnostic approach for the endemic mycoses

Focus on improving awareness and testing among primary care and outpatient providers

Considerable testing gap for patients presenting with CAP between primary care providers and infectious disease physicians

	Primary care providers Test sometimes or frequently	Infectious disease physicians Test sometimes or frequently
Coccidioidomycosis	19%	36%
Histoplasmosis	22%	58%

Focus on improving awareness and testing among primary care and outpatient providers

Clinician Practice Patterns That Result in the Diagnosis of Coccidioidomycosis Before or During Hospitalization

Jie Pu, Fariba M Donovan, Kate Ellingson, Gondy Leroy, Jeff Stone, Edward Bedrick, John N Galgiani ⊠

Clinical Infectious Diseases, ciaa739, https://doi.org/10.1093/cid/ciaa739

- Less than one-third of new diagnoses occurred outside the hospital
 - 73% of during hospitalization
 - Only 22% at ambulatory clinics, 3% in emergency departments, and 0.5% in urgent care

Focus on improving awareness and testing among primary care and outpatient providers

Enhanced Surveillance for Histoplasmosis—9 States, 2018–2019 👌

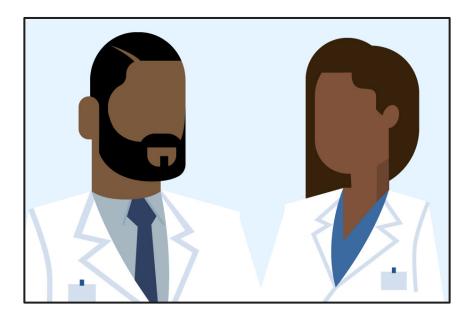
Kaitlin Benedict ➡, Stephanie McCracken, Kimberly Signs, Malia Ireland,
Victoria Amburgey, Jose Antonio Serrano, Natalie Christophe,
Suzanne Gibbons-Burgener, Sara Hallyburton, Kimberly A Warren, Alison Keyser Metobo,
Racheal Odom, Matthew R Groenewold, Brendan R Jackson
Author Notes

Open Forum Infectious Diseases, Volume 7, Issue 9, September 2020, ofaa343,

- 43% of patients first sought care in a primary care facility
- Primary care providers made up just 11% of providers who first tested for histoplasmosis

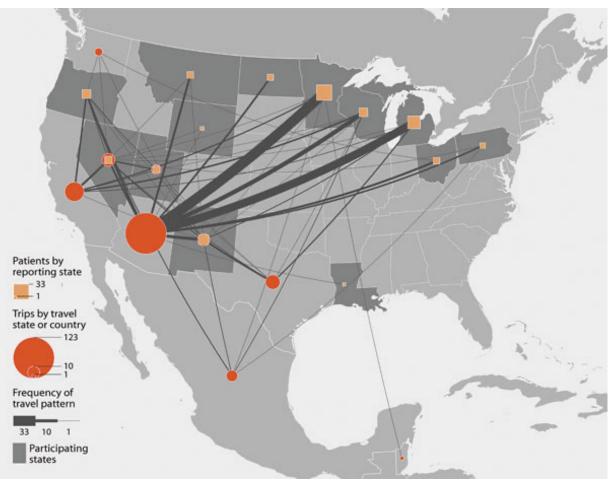
Reach providers across the United States, not just endemic areas

- Providers who live or train in low or non-endemic areas may have less awareness of disease
- Providers may move to practice in endemic areas



Travel-associated infections occur regularly

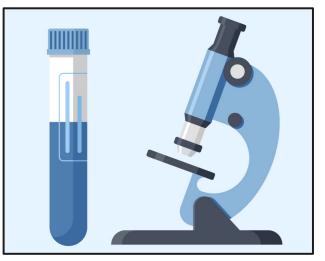
Reported cases of coccidioidomycosis related to travel, 2016

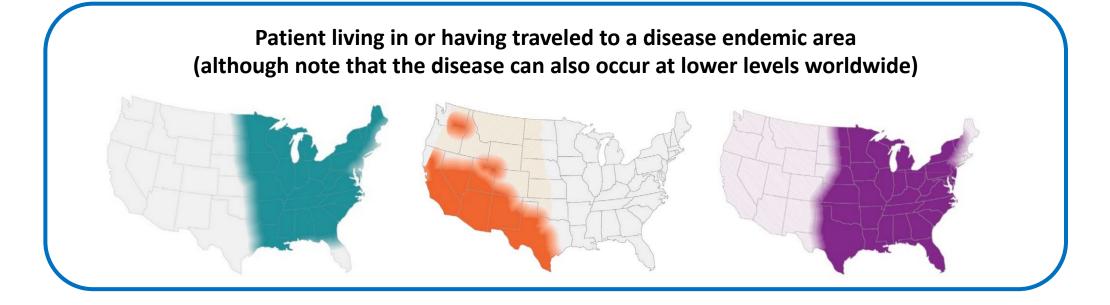


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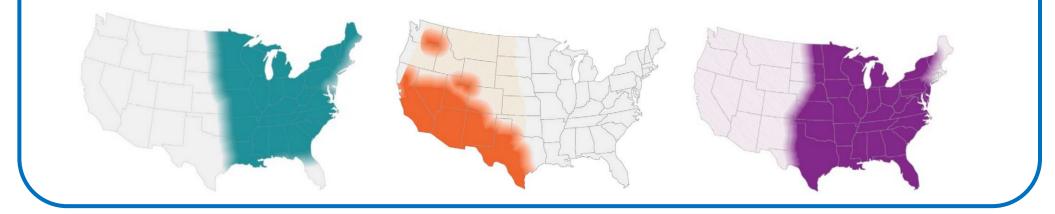
Algorithm development process

- 1. In consultation with experts, reviewed performance characteristics of available diagnostic tests
- 2. Synthesized learnings into a draft diagnostic algorithms
- 3. Presented to specialty groups and experts both within and external to CDC to solicit feedback
- 4. Revised algorithms accordingly and finalized

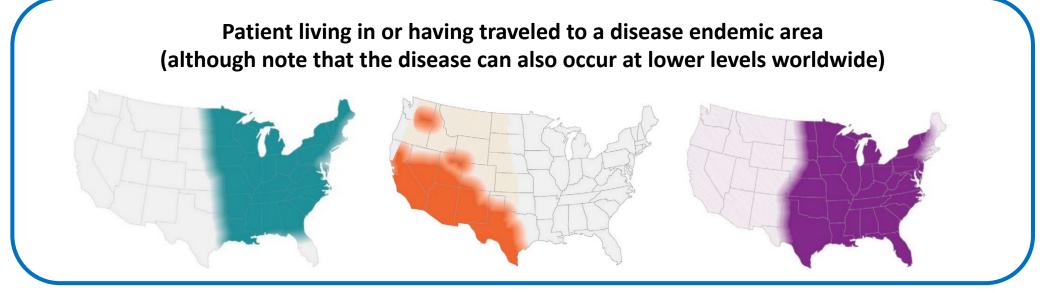




Patient living in or having traveled to a disease endemic area (although note that the disease can also occur at lower levels worldwide)



CAP of unknown etiology not responding to a course of empiric antibiotics







Patient living in or having traveled to a disease endemic area (although note that the disease can also occur at lower levels worldwide)

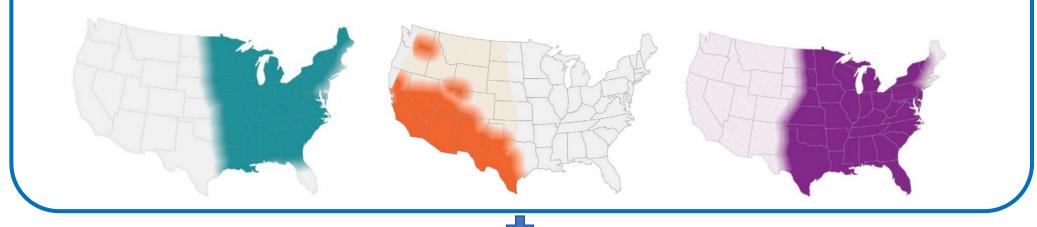
Blastomycosis

Initial CAP visit if:

- Skin lesions present* OR
- Link to known blastomycosis outbreak

*Skin lesions could be indicative of late disease or traumatic inoculation rather than acute pulmonary blastomycosis

Patient living in or having traveled to a disease endemic area (although note that the disease can also occur at lower levels worldwide)



Coccidioidomycosis

Initial presentation of CAP (or erythema nodosum in the setting of recent respiratory symptoms if people have:

- Lived in or traveled to the highly endemic desert regions of Arizona (i.e., South-Central Arizona) or the San Joaquin Valley of California OR
- Link to known coccidioidomycosis outbreak

Patient living in or having traveled to a disease endemic area (although note that the disease can also occur at lower levels worldwide)

Histoplasmosis

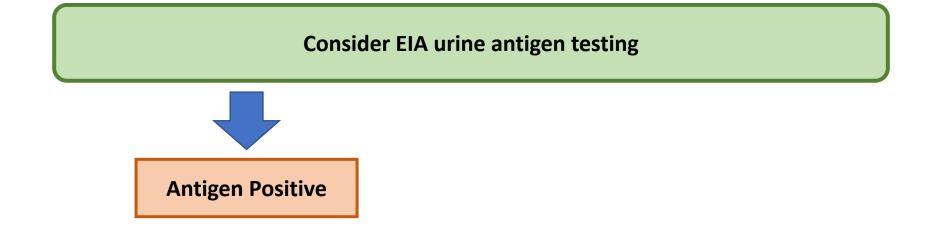
Initial CAP visit if:

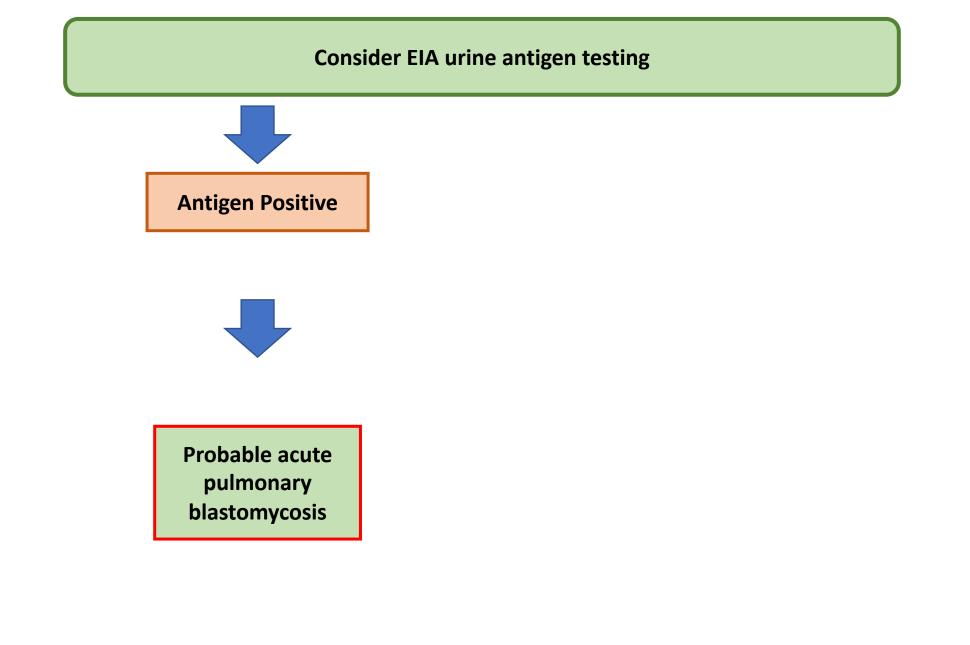
- Notable exposure to bird or bat droppings (cave or demolition/ remodeling exposure; note that many patients do not recall a specific exposure) OR
- Chest x-ray showing new nodules or lymphadenopathy OR
- Link to known histoplasmosis outbreak

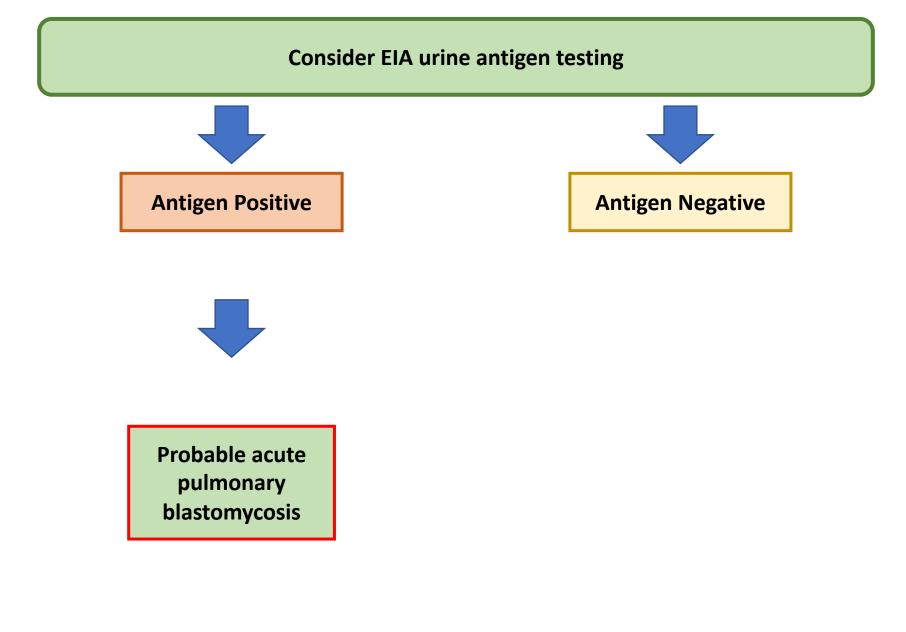
Blastomycosis Algorithm

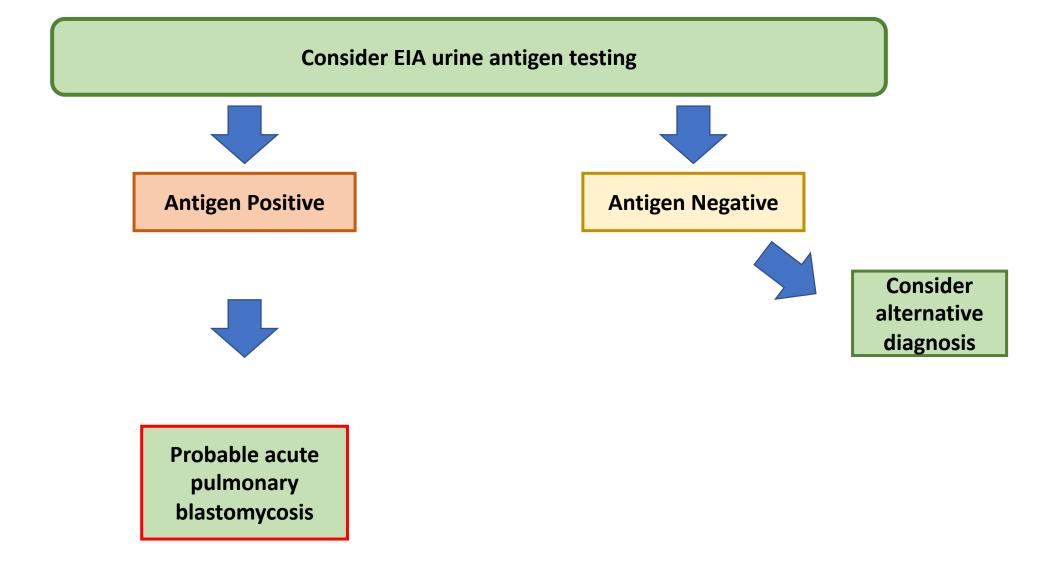
Consider EIA urine antigen testing

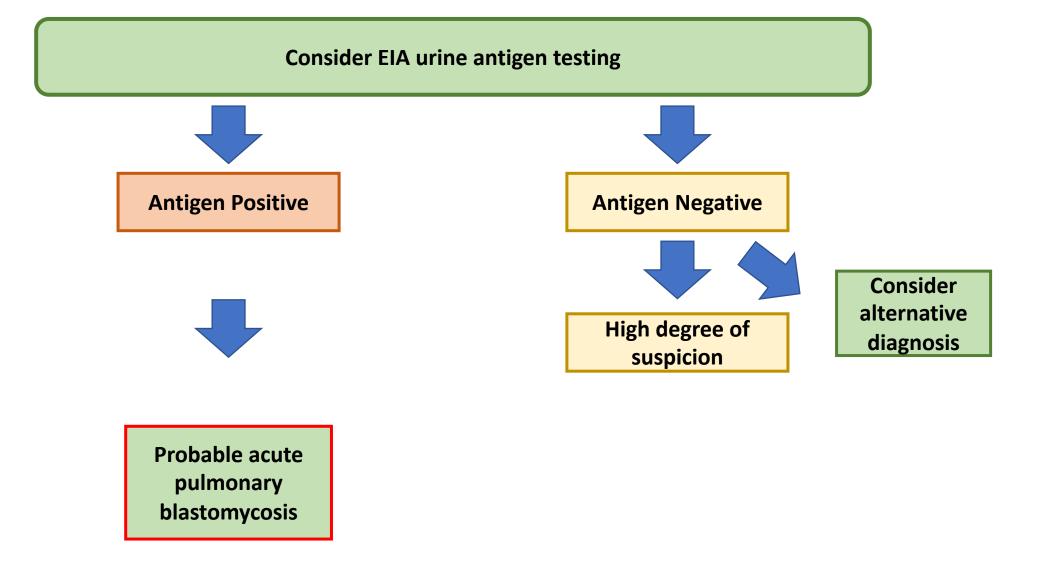
EIA = enzyme immunoassay

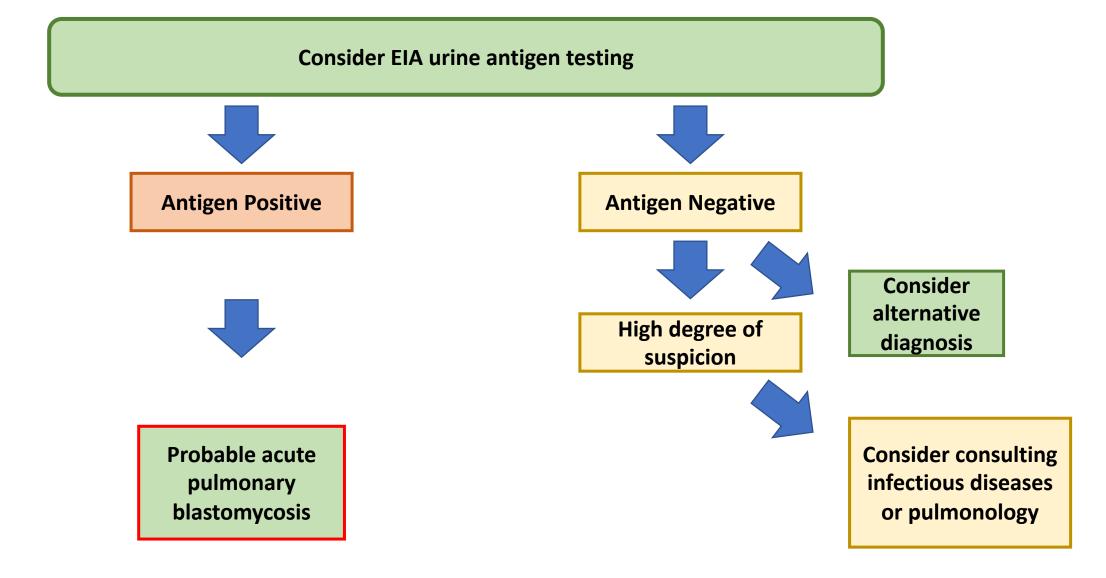


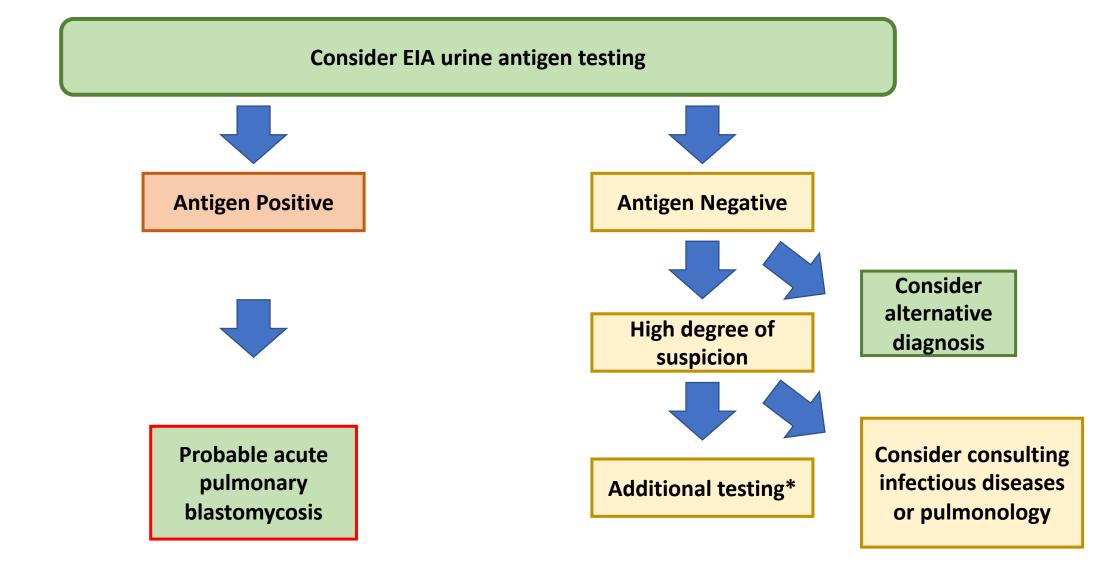




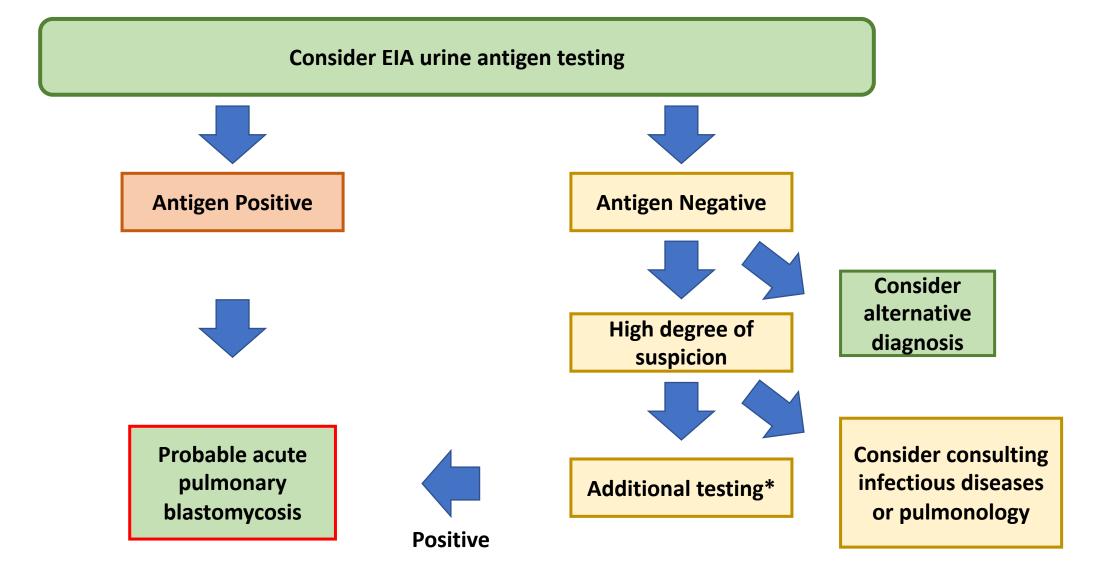


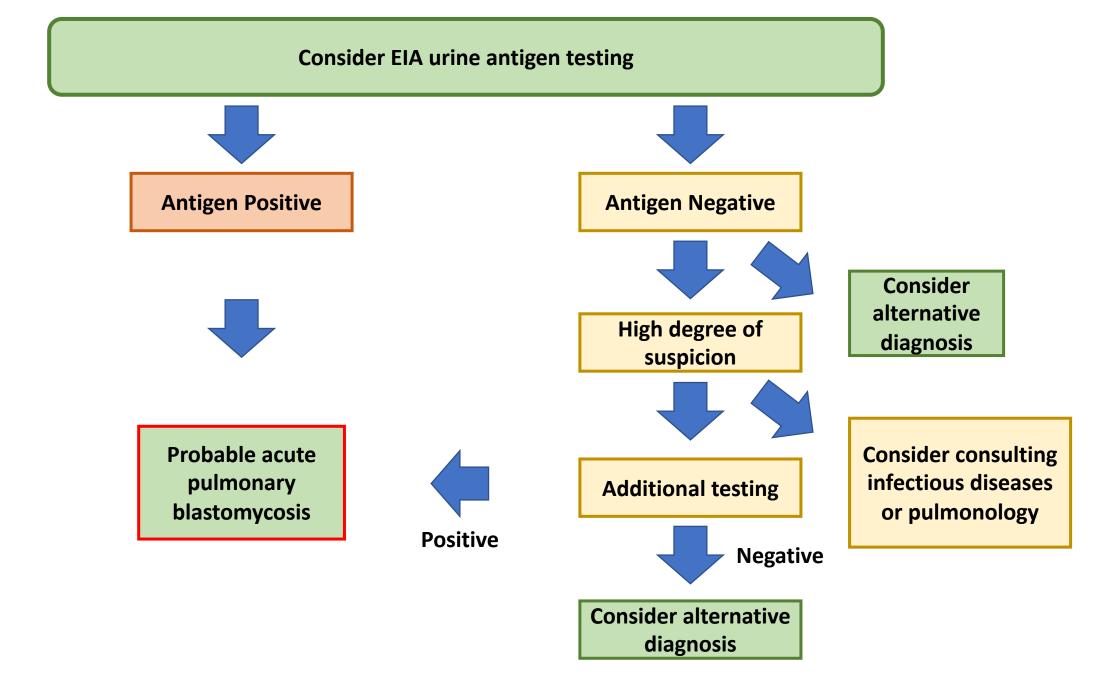






*Sputum or bronchoalveolar lavage culture and microscopy, skin biopsy (if lesion exists), serologic antibody testing

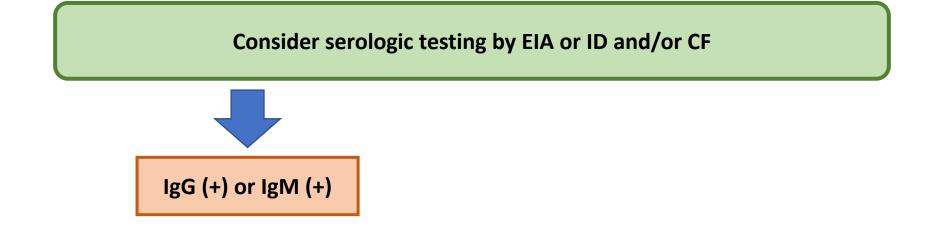


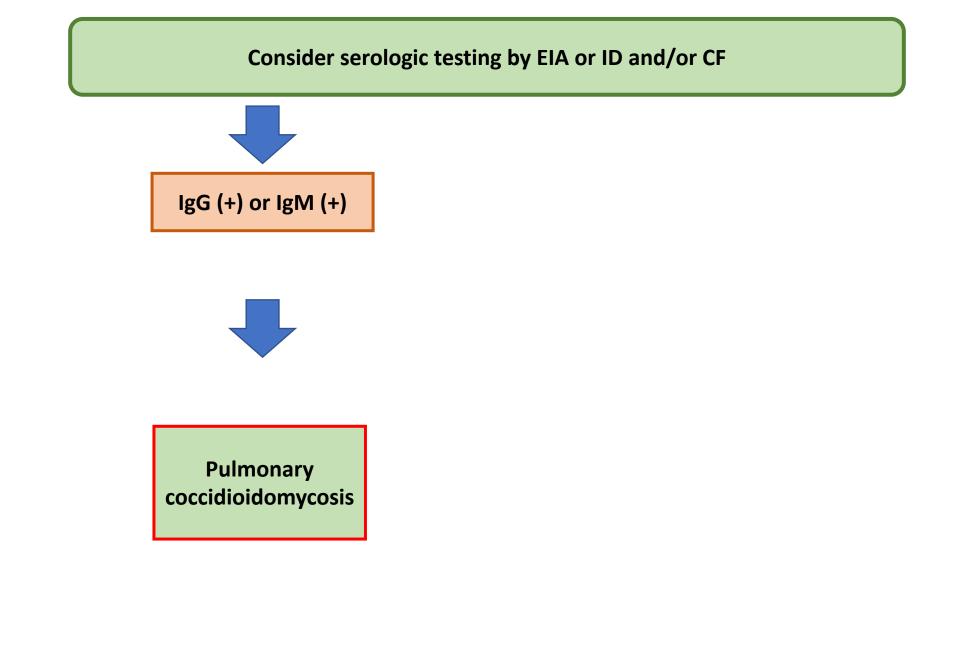


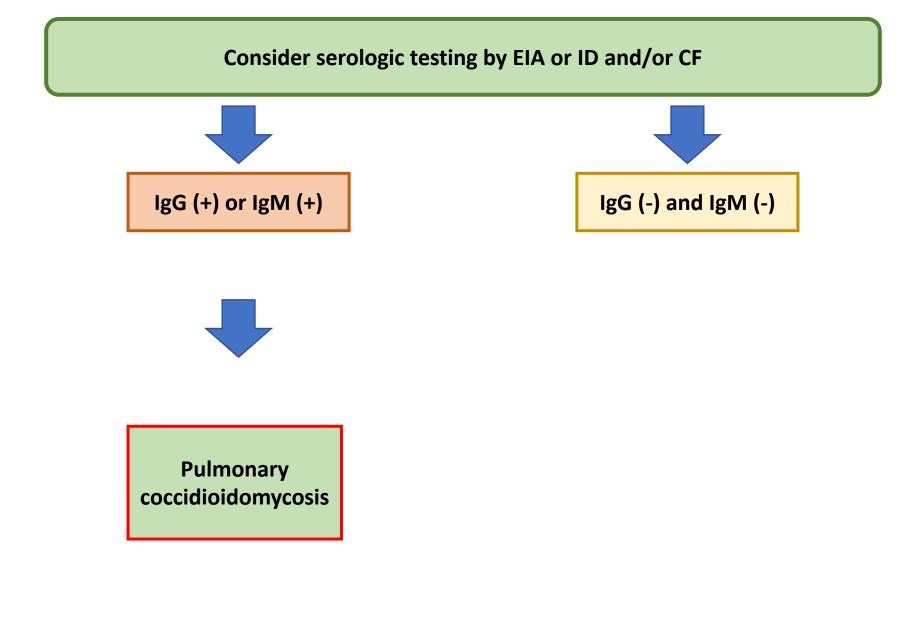
Coccidioidomycosis Algorithm

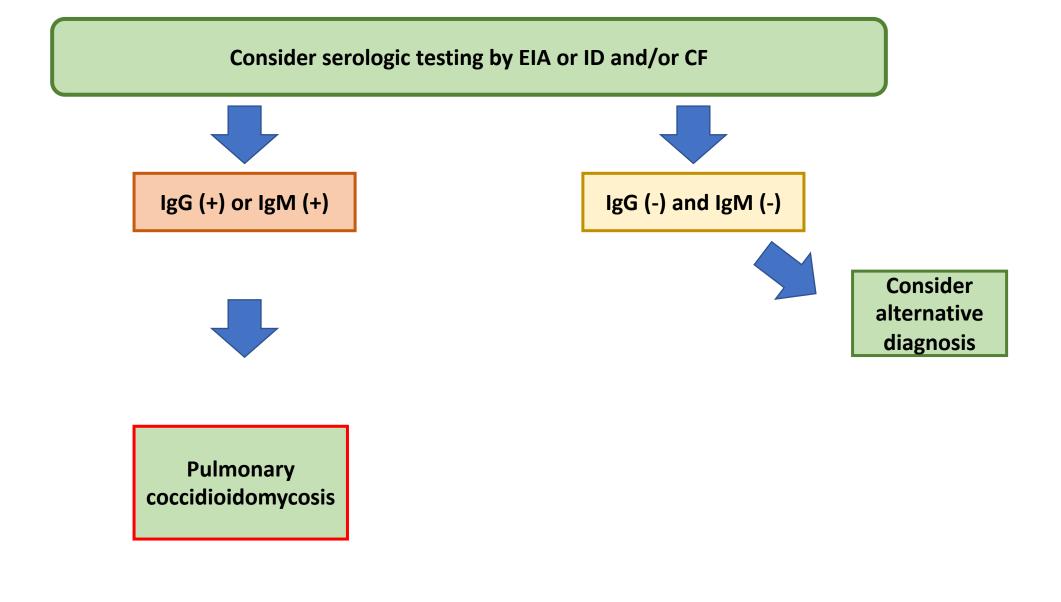
Consider serologic testing by EIA or ID and/or CF

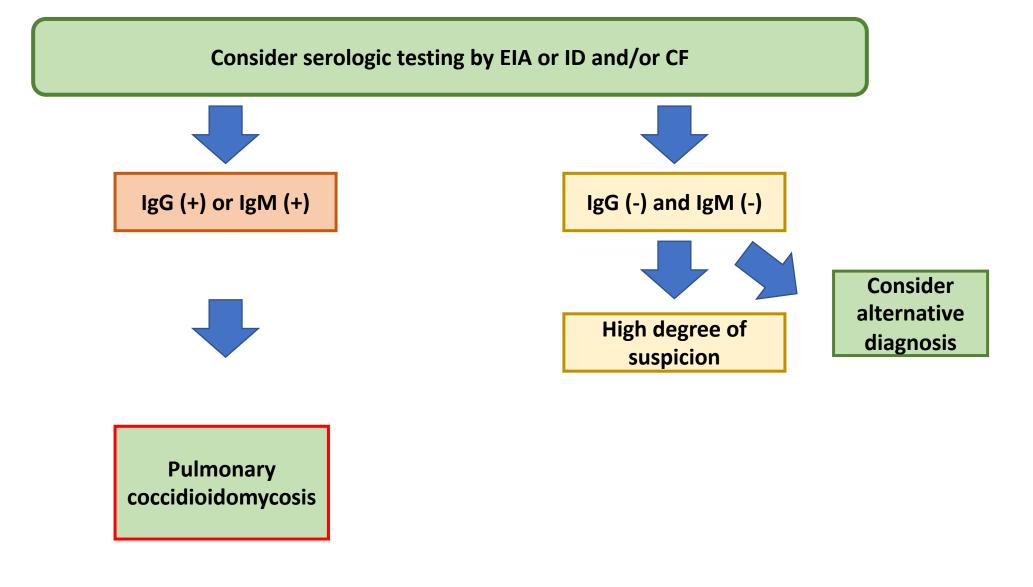
EIA = enzyme immunoassay ID = immunodiffusion CF = complement fixation

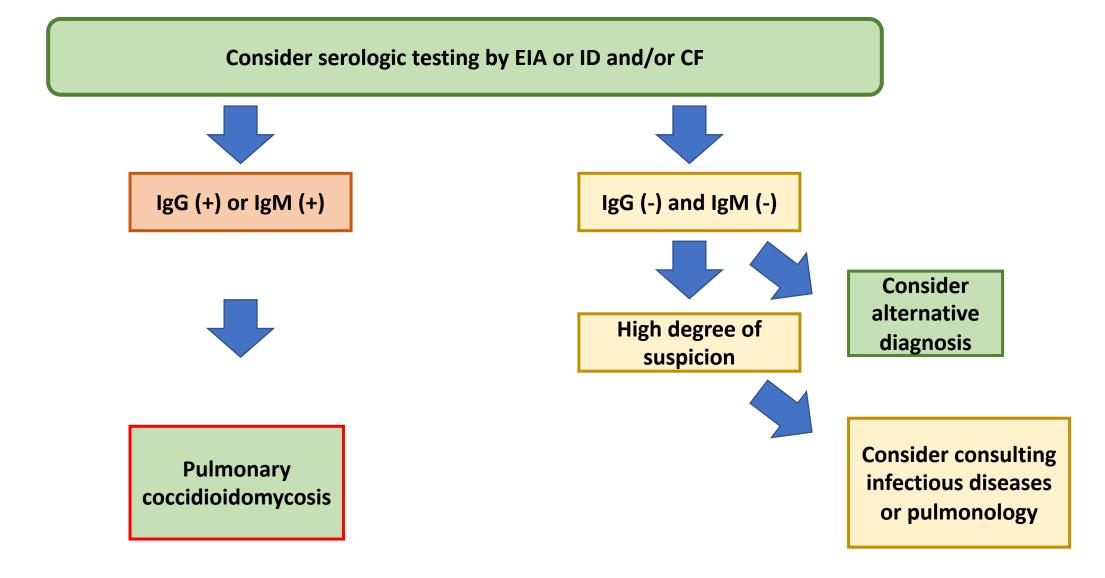


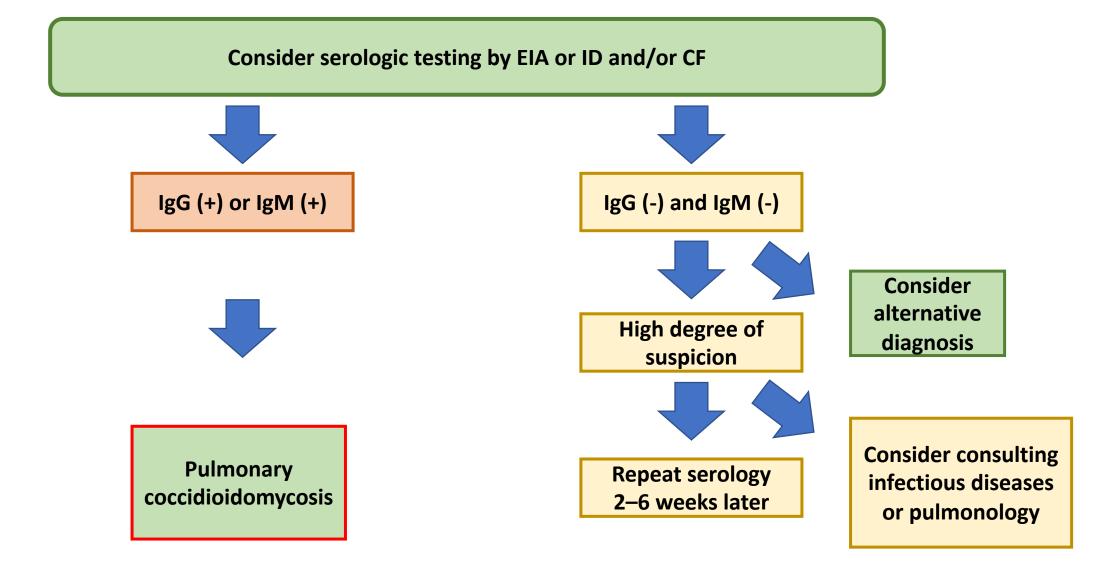


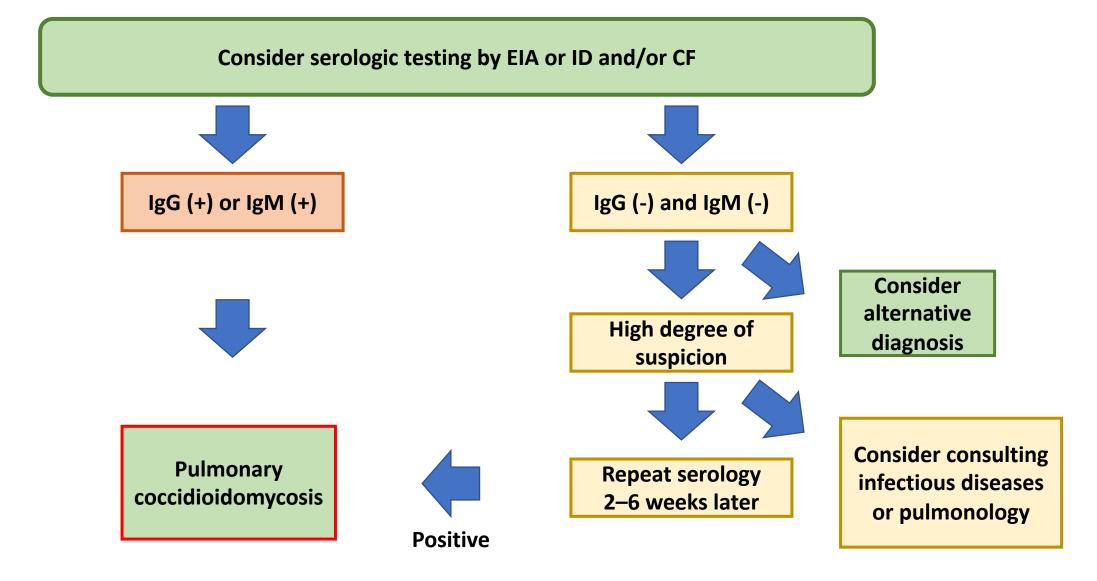


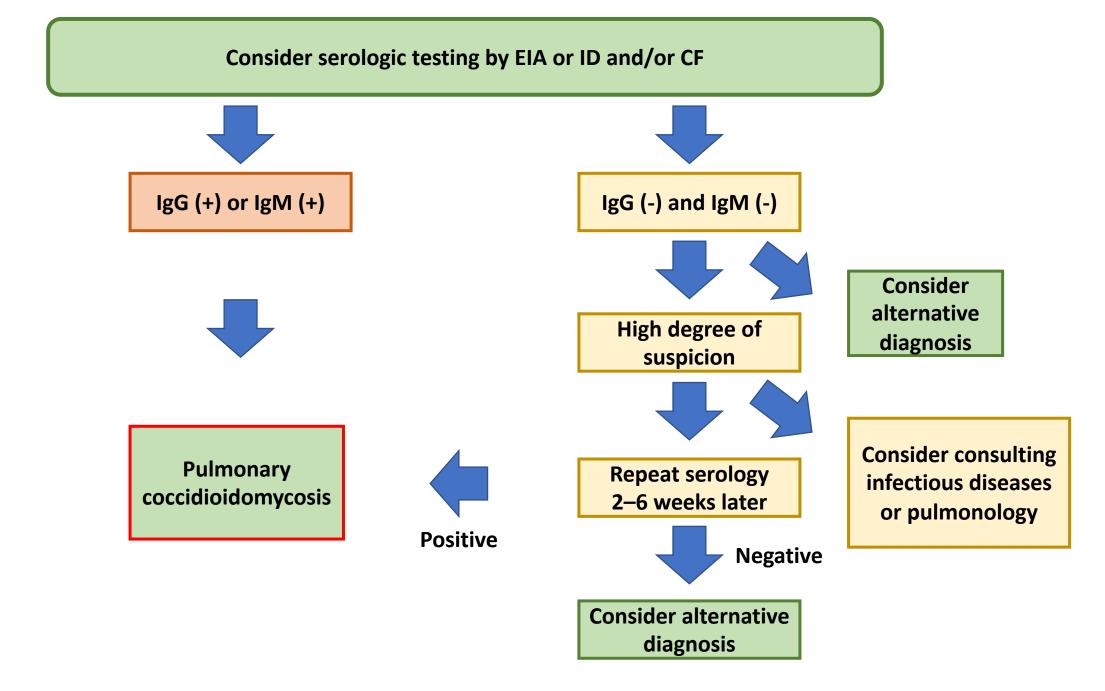








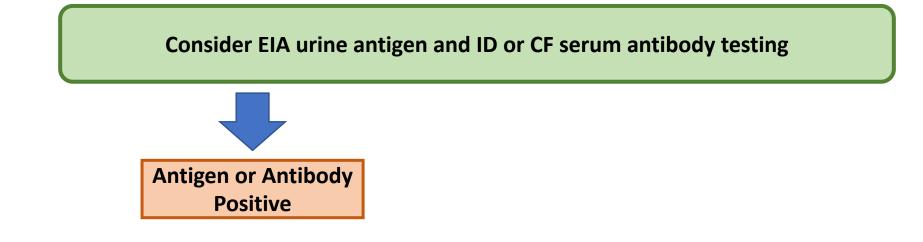


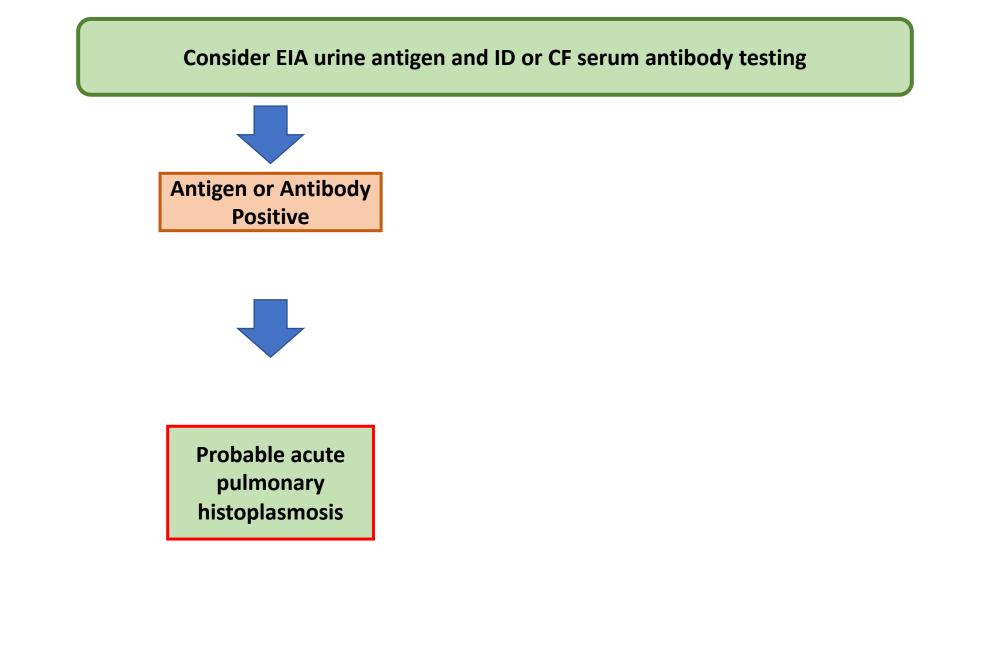


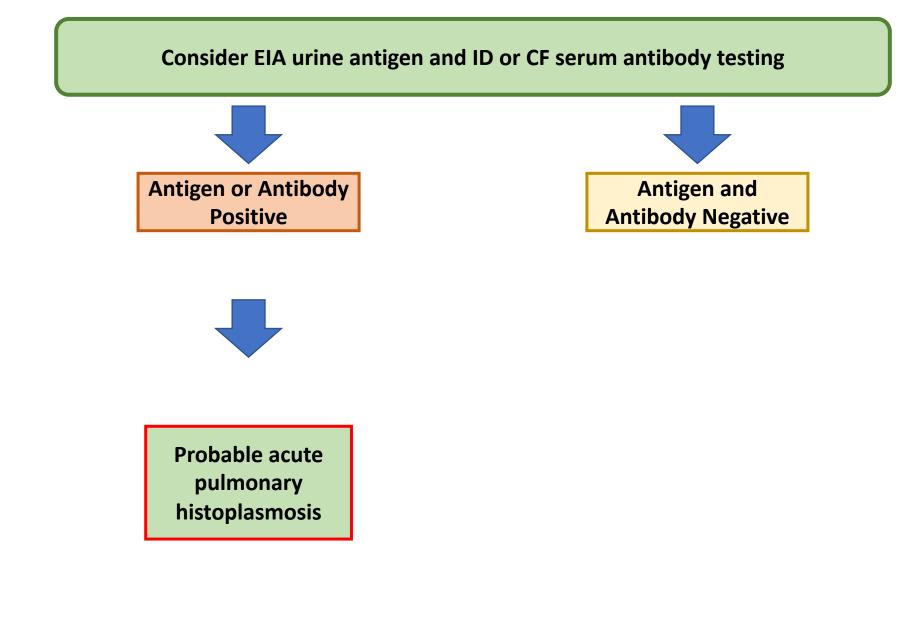
Histoplasmosis Algorithm

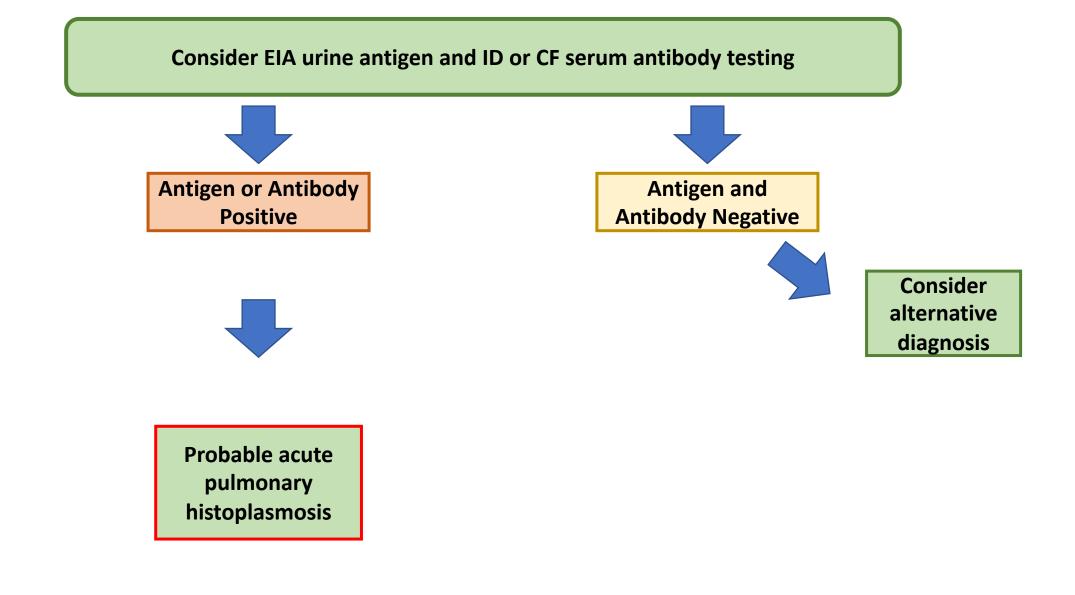
Consider EIA urine antigen and ID or CF serum antibody testing

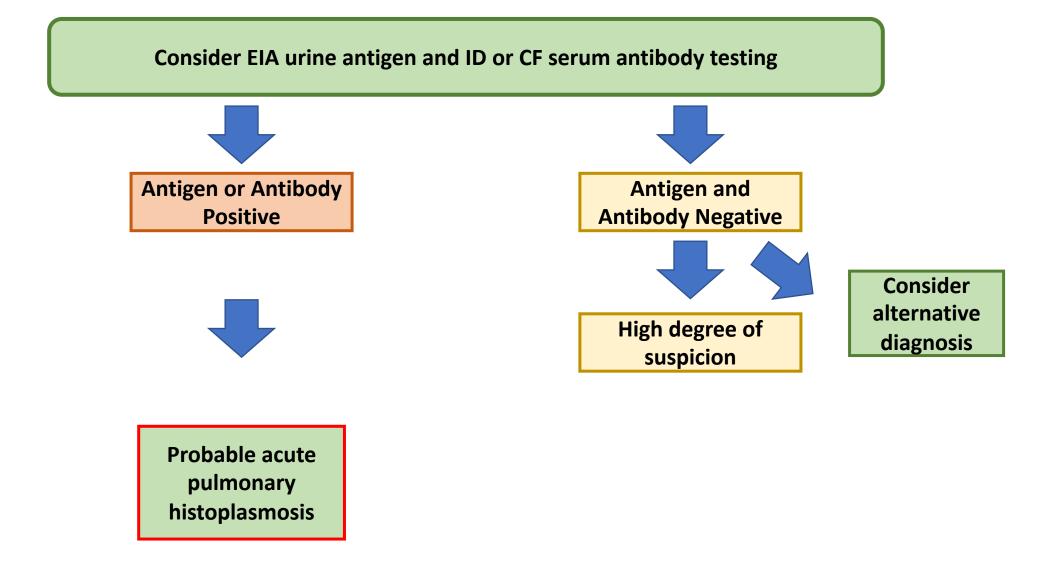
EIA = enzyme immunoassay ID = immunodiffusion CF = complement fixation

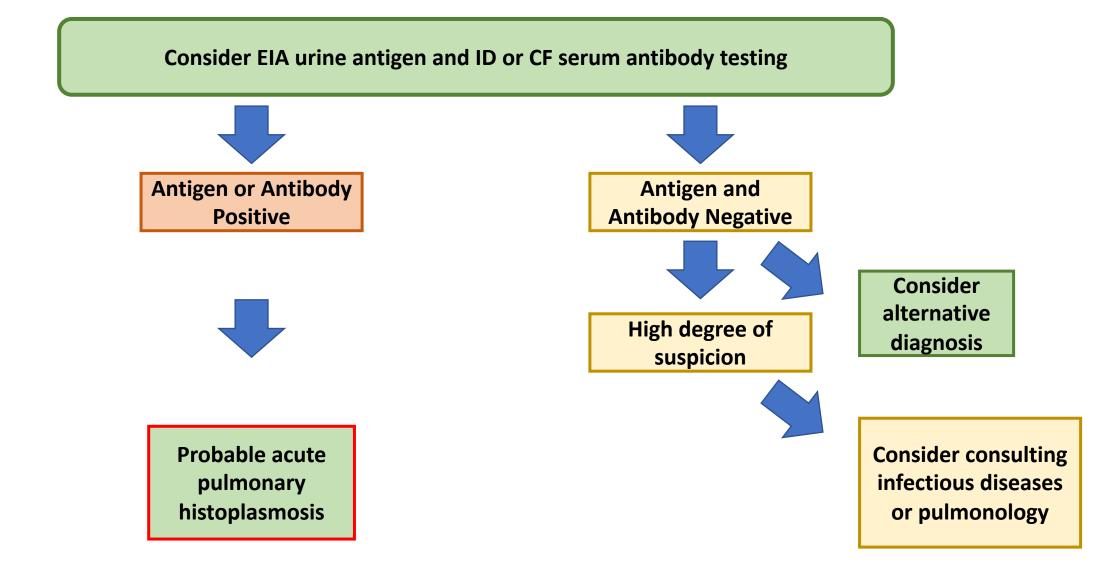


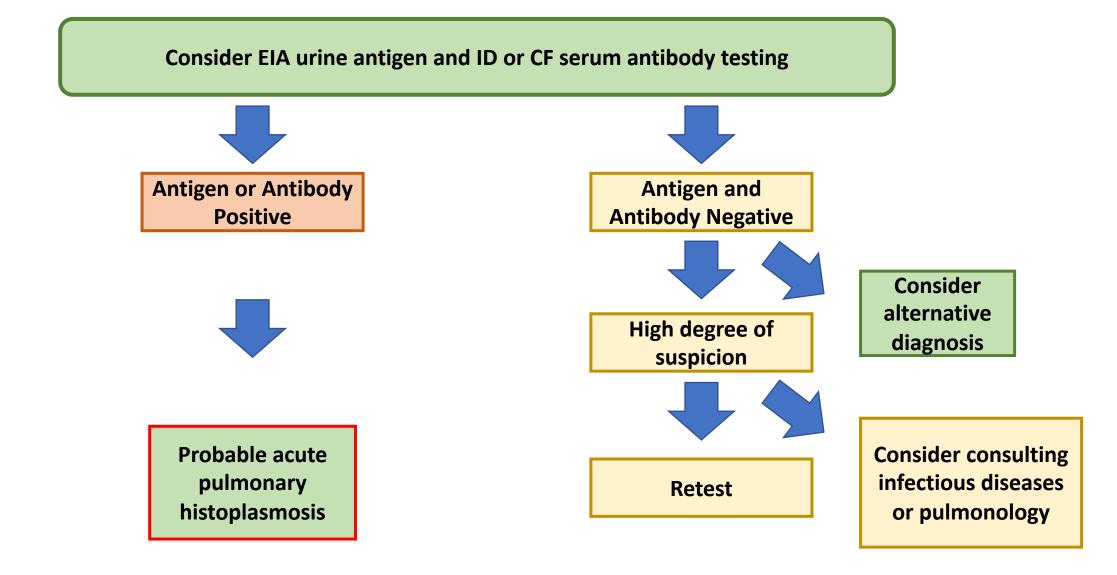


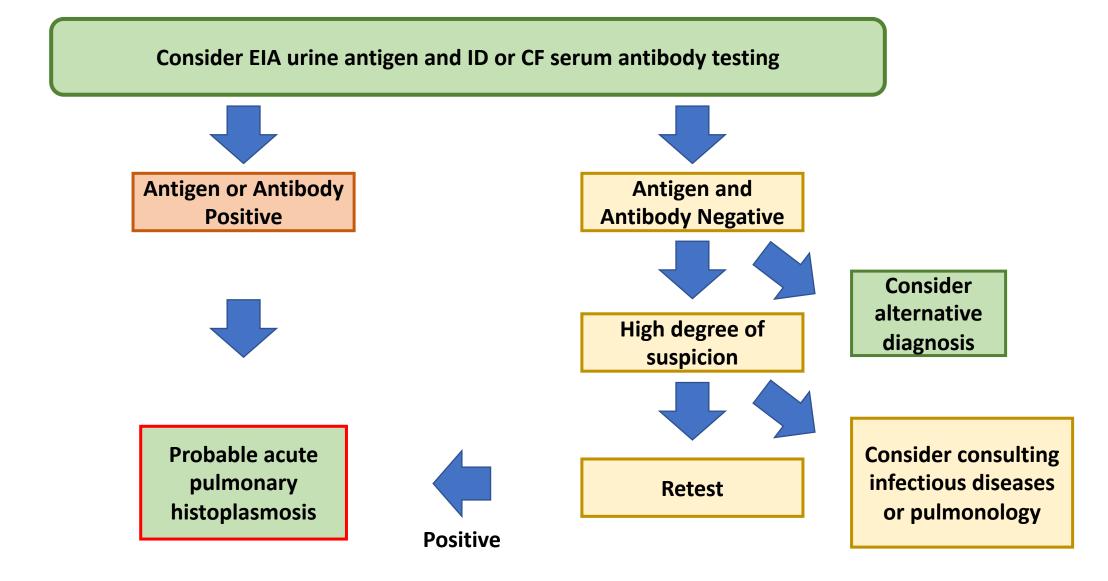


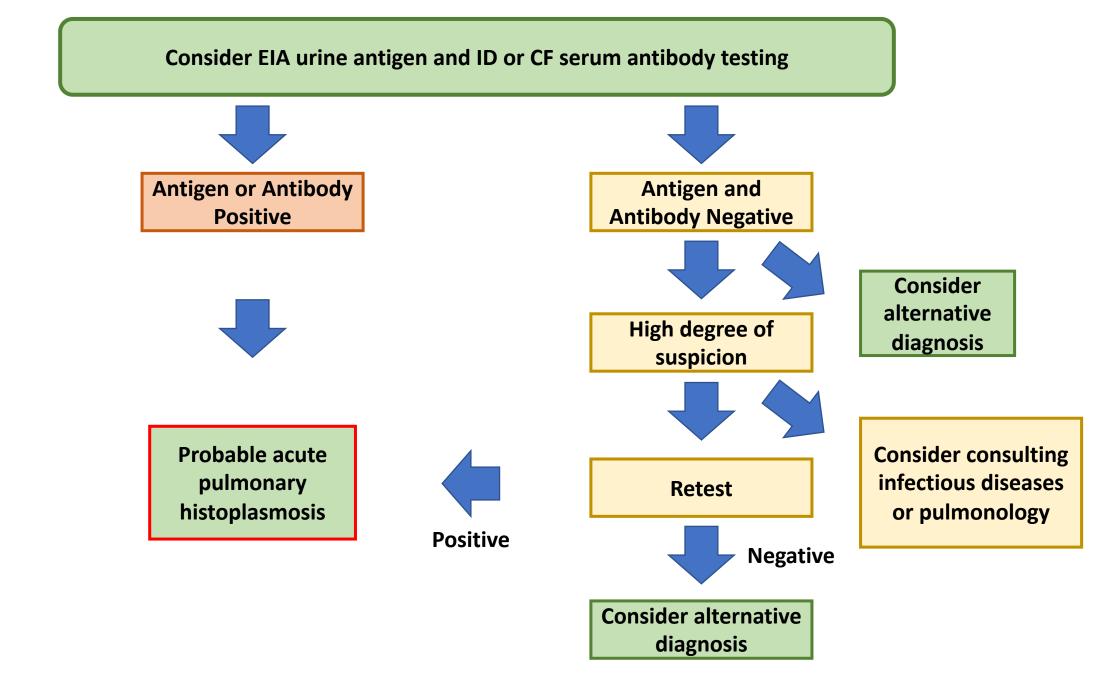












Diagnostic algorithms aim to:

- 1. Improve early diagnosis and reduce misdiagnoses
- 2. Reduce unnecessary antibacterial use
- 3. Improve patient outcomes

Algorithms are available on CDC's website

- <u>Community-Acquired Pneumonia (CAP): Clinical Testing Algorithm for</u> <u>Blastomycosis | Fungal Diseases | CDC</u>
- <u>Community-Acquired Pneumonia (CAP): Clinical Testing Algorithm for</u> <u>Coccidioidomycosis | Fungal Diseases | CDC</u>
- <u>Community-Acquired Pneumonia (CAP): Clinical Testing Algorithm for</u> <u>Histoplasmosis | Fungal Diseases | CDC</u>
- Continuing Medical Education activity jointly provided by Postgraduate Institute for Medicine; Terranova Medica, LLC; and the Mycoses Study Group Education & Research Consortium

http://www.funguscme.org/CAP2022/index.html

Future directions

- Assess uptake and impact of diagnostic algorithms
- Incorporate new diagnostic methods as available
- Quantify proportion of CAP and other lower respiratory infections attributable to these endemic mycoses
- Further assess test performance (i.e. inter-laboratory and intermanufacturer)
- Consider development of guidelines for diagnosis of CAP of various etiologies that do not respond to initial antibiotics

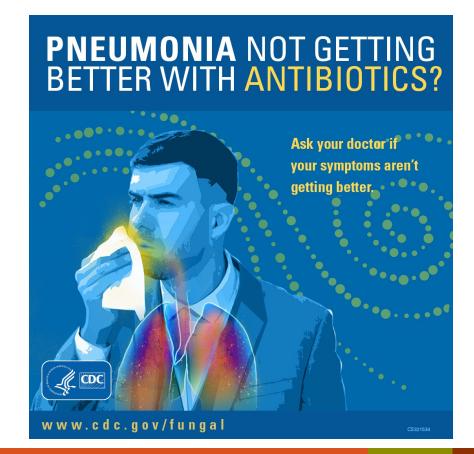
Coccidioidomycosis, histoplasmosis, and blastomycosis are fungal diseases that can be diagnosed any where in the U.S.



Increased awareness and testing practices can improve health outcomes

Early diagnosis and treatment can help prevent severe disease

If a patient is experiencing symptoms consistent with these fungal diseases and does not improve on antibiotics, consider fungal testing



Thank you

CDC's fungal disease webpage: https://www.cdc.gov/fungal/index.html

For more information, contact CDC 1-800-CDC-INFO (232-4636) TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

THINK FUNGUS. SAVE LIVES.

