

To view an archived recording of this presentation please click the following link:

[https://youtu.be/j\\_yv27\\_hR1Q](https://youtu.be/j_yv27_hR1Q)

Please scroll down this file to view a copy of the slides from the session.

#### Disclaimer

**This document was created by its author and/or external organization. It has been published on the Public Health Ontario (PHO) website for public use as outlined in our Website Terms of Use. PHO is not the owner of this content. Any application or use of the information in this document is the responsibility of the user. PHO assumes no liability resulting from any such application or use.**

# Blastomycosis in Ontario: Public Health and Clinical Considerations

Dr. Austin Zygmunt, MSc, MD, CCFP, FRCPC ([Austin.Zygmunt@oahpp.ca](mailto:Austin.Zygmunt@oahpp.ca))

Dr. Julianne Kus, MSc, PhD, FCCM ([Julianne.Kus@oahpp.ca](mailto:Julianne.Kus@oahpp.ca))

Dr. Anthony La Delfa, MD, FRCPC ([aladelfa@msh.on.ca](mailto:aladelfa@msh.on.ca))

August 22, 2022

## Land Acknowledgment

- We wish to acknowledge the lands and waters of the traditional, unceded and treaty Indigenous territories on which Public Health Ontario operates.
- We respect and appreciate Ontario is now home to many diverse First Nations, Inuit, Métis and urban Indigenous peoples and cultures.
- We are grateful to have the opportunity to work on this land for the mutual benefit of all.

# Presentation Outline

- Background
- Epidemiology in Ontario
- Clinical Presentation & Treatment
- Laboratory-Based Diagnostic Testing
- Public Health Management
- Questions and Wrap-up

# Presentation Objectives

By the end of this session, participants will be able to:

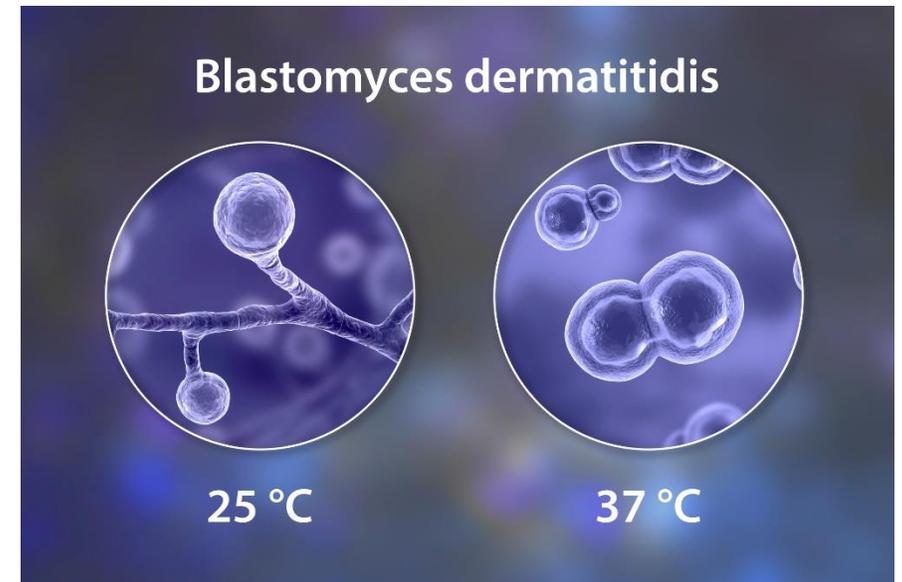
1. Describe the expected distribution of blastomycosis in Ontario
2. Understand the etiology, clinical presentation and diagnostics of blastomycosis
3. Explain the clinician's role in the management of blastomycosis



# Background

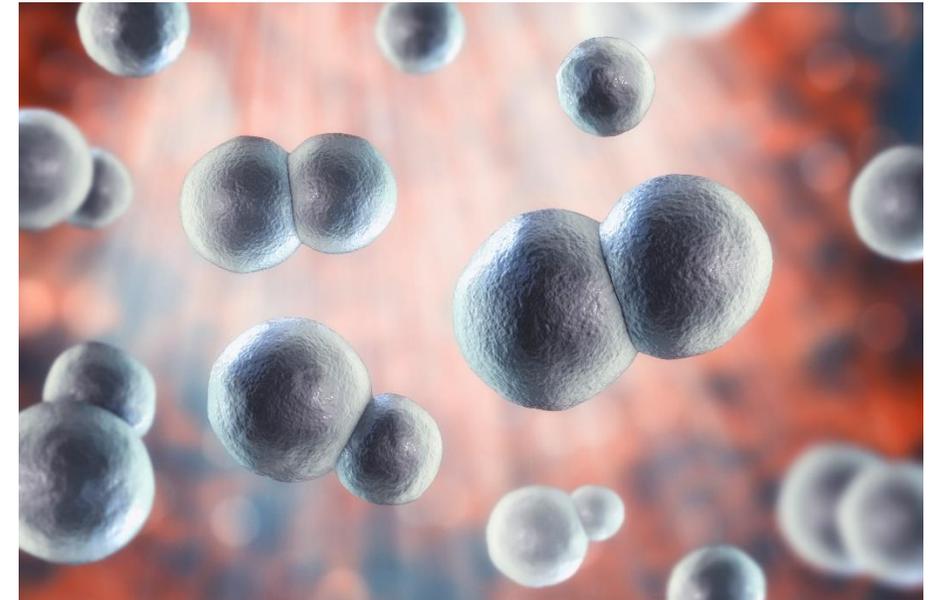
# What is blastomycosis?

- Blastomycosis is an infection caused by the fungus *Blastomyces*:
  - *Blastomyces dermatitidis*
  - *Blastomyces gilchristii*
- *Blastomyces spp.* are thermally dimorphic fungi
  - Grow in mould form in the environment (25°C) where they can produce spores
  - Grow in yeast form in human tissue (37°C)
- Other thermally dimorphic fungi include:
  - *Histoplasma capsulatum* (histoplasmosis)
  - *Coccidioides immitis* (coccidioidomycosis)



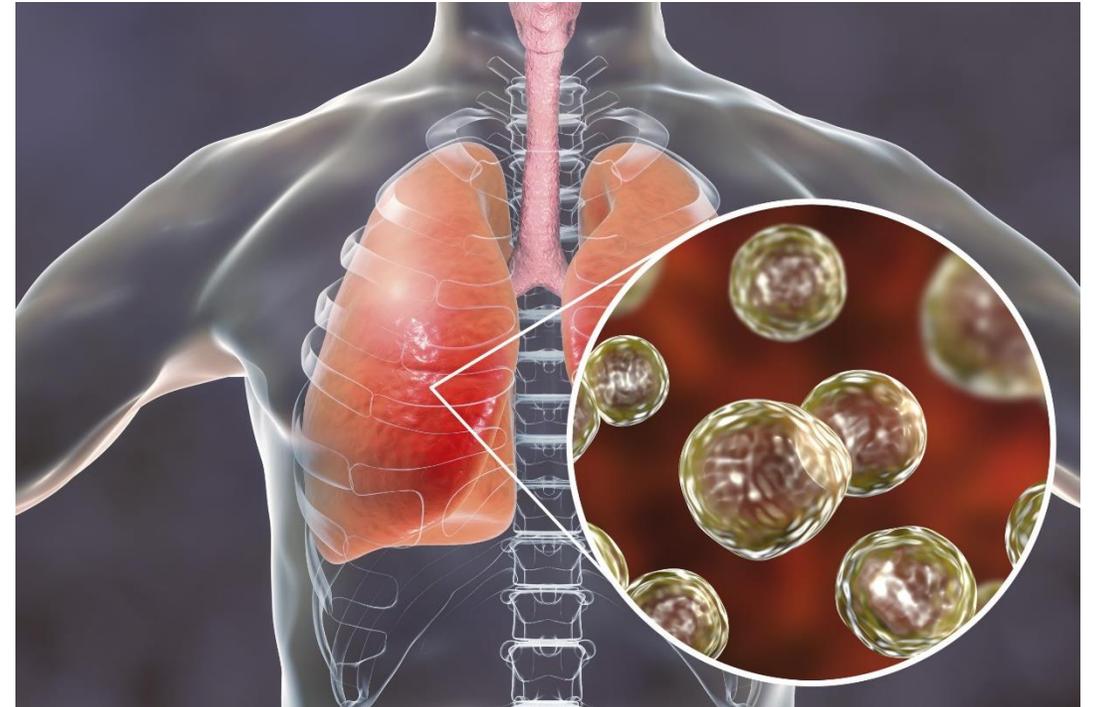
# Blastomycosis characteristics

- **Transmission**
  - Inhalation of spores in dust from the mould form
  - No person-to-person transmission
  - No animal-to-human transmission
    - Infection in animals such as cats and dogs have been identified
- **Incubation period:**
  - Average is 30 to 45 days
  - Range 21 – 106 days
- **Period of communicability:** not applicable
- **Reservoir:** soil (commonly along waterways, undisturbed places such as under a deck/porch), decaying organic matter (wood, leaves)



# Pathogenesis

- Infection occurs when fungal spores are inhaled into the lungs and settle into the pulmonary alveoli (air sacs) leading to an inflammatory response
- The yeast can remain in the lungs and can spread to other parts of the body through the blood stream (e.g. skin, bones, joints, organs).



## Risk factors

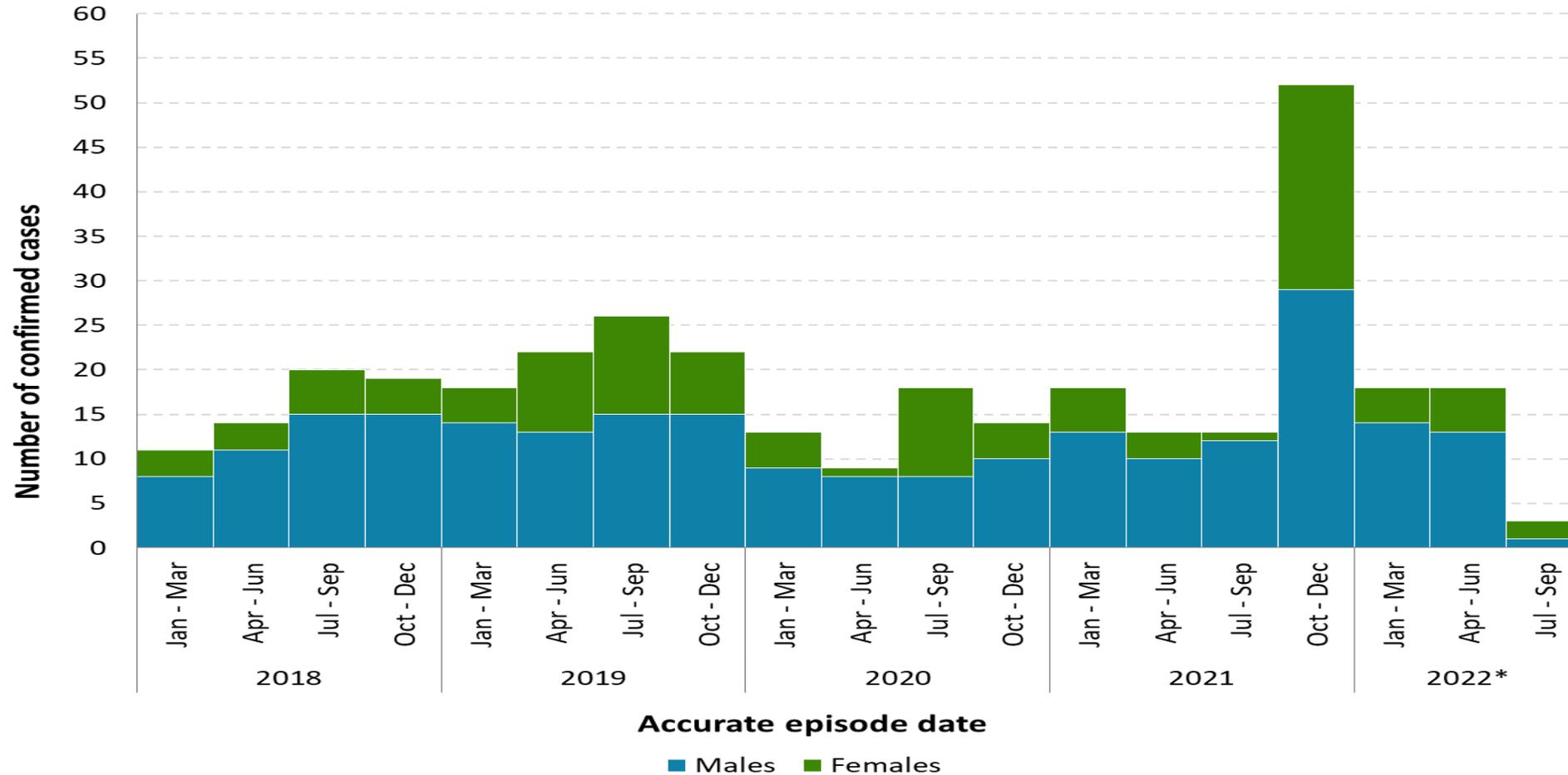
- Anyone can become infected with *Blastomyces* if they've been to an area where it is in the environment such as:
  - Participating in activities that disrupt soil (e.g. gardening, digging holes)
  - Participating in activities in wooded areas (e.g. hunting, farming, camping, forestry)
- Individuals who are immunocompromised are more likely to develop severe blastomycosis.





# Epidemiology in Ontario

# Confirmed cases of blastomycosis by gender: Ontario, 2018-2022\*



Source: Ontario. Ministry of Health. Integrated Public Health Information System (iPHIS) [database]. Toronto, ON: Queen's Printer for Ontario; c2020 [extracted 2022 Aug 10]

\*as of August 10, 2022

## Blastomycosis cases by severity and outcome: 2018-2022\*

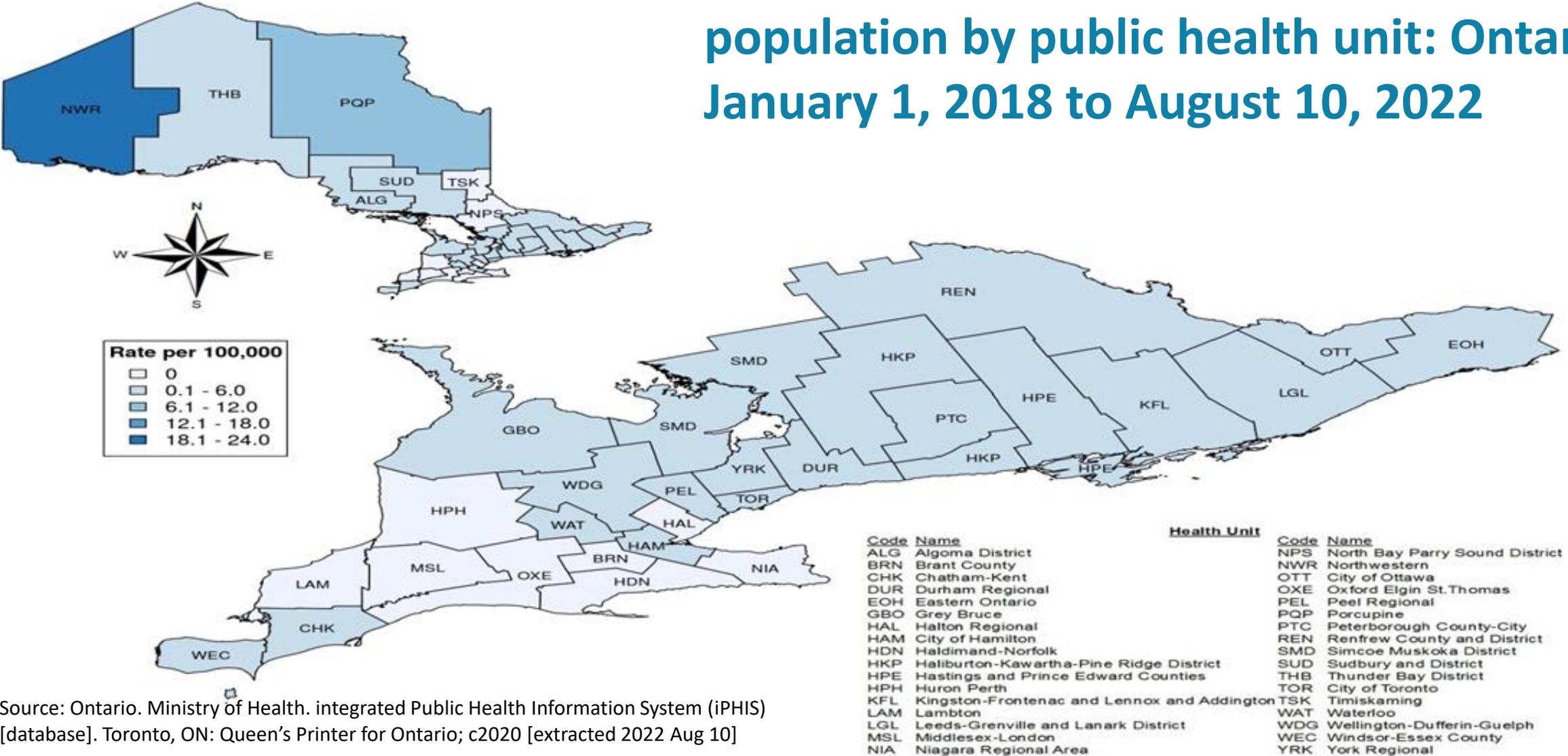
Year	Number (%) of cases ever hospitalized	Number (%) of cases with fatal outcome**
2018	28 (43.8)	3 (4.7)
2019	30 (34.1)	10 (11.4)
2020	23 (42.6)	6 (11.1)
2021	47 (49.0)	11 (11.5)
2022*	8 (20.5)	4 (10.3)

\*as of August 10, 2022

\*\* 16/34 indicate that reportable disease was underlying cause of death or contributed to death; 18/34 are missing cause of death; one additional fatal outcome did not have a date of death available and is not included in this table.

Source: Ontario. Ministry of Health. integrated Public Health Information System (iPHIS) [database]. Toronto, ON: Queen's Printer for Ontario; c2020 [extracted 2022 Aug 10]

# Blastomycosis rates per 100,000 population by public health unit: Ontario, January 1, 2018 to August 10, 2022



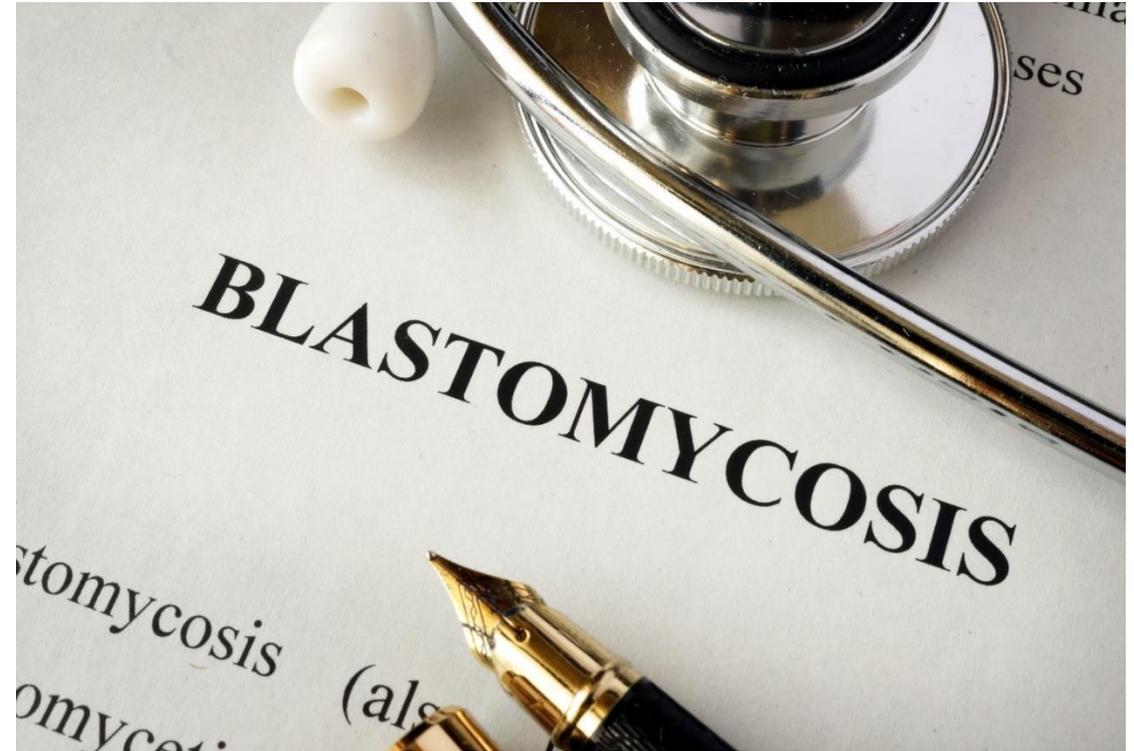
Source: Ontario. Ministry of Health. integrated Public Health Information System (iPHIS) [database]. Toronto, ON: Queen’s Printer for Ontario; c2020 [extracted 2022 Aug 10]



# Clinical Presentation & Treatment

# Clinical Presentation

- Wide range of clinical signs/symptoms
- Can be non-specific
- Severity widely variable
- Can mimic many other common conditions



# Clinical Features

- Pulmonary involvement (91%)
  - Cough, fever, sputum, chest pain, shortness of breath, weight loss, night sweats, chills, hemoptysis
  - Incubation 3-6 weeks from time of exposure
- Skin (18%)
  - Verrucous lesions, ulcers, subcutaneous nodules
- Bone/joint (4%)
  - Local swelling, sinus tract
- Genitourinary
- CNS
  - Meningitis, epidural abscess, intracranial abscess

Krumpelbeck E, Tang J, Ellis MW, Georgescu C. Disseminated blastomycosis with cutaneous lesions mimicking tuberculosis. *Lancet Infect Dis.* 2018;18(12):1410. Available from: [https://doi.org/10.1016/s1473-3099\(18\)30291-3](https://doi.org/10.1016/s1473-3099(18)30291-3)

# Case 1

- **Demographics:** Female under 20 years of age
- **Past Medical History:** none
- **Medications:** none
- **Social History:**
  - High school student
  - Part time job at fast food restaurant
- **Risk factors:**
  - No significant exposure to soil, outdoors, camping, animals

## Case 1

- Presented to family physician with isolated non-resolving chronic cough, intermittent hemoptysis for 3 months
- CT chest: Irregular mass-like consolidation in the right lower lobe
- Urgent Respiriology referral
- CT-guided biopsy: non-necrotizing granulomatous inflammation
- Bronchoscopy: fungal culture *Blastomyces dermatitidis/gilchristii*

## Case 2

- **Demographics:** Male over 65 years of age
- **Past Medical History:** Hypertension, steatohepatitis (known alcohol use), upper GI bleed, chronic hyponatremia (likely alcohol-related)
- **Medications:** amlodipine
- **Social History:**
  - Lives with wife, and has a dog and large bird
  - 1 bottle wine/day (more previously)
- **Risk factors:**
  - Lives on several acres of land in Southern Ontario
  - Frequently working outdoors
  - Traveled to over 95 countries in total

## Case 2

- **September:**
  - Query wasp bites to back and abdomen
- **October:**
  - Wounds opened, large wound/abscess to groin
  - Attended hospital for incision and drainage
  - Wound cultures taken, no formal diagnosis
  - Trial of amoxicillin/clavulanate with little improvement
- **Early November:**
  - Presented to Emergency Department with new right finger wound
  - Hand X-ray: ill-defined “aggressive” appearing lucencies to the index finger
- Wound swab = *Pseudomonas aeruginosa*
- Started on cefazolin then changed to ceftazidime by ID
- **Mid November:**
  - Reassessed in ID clinic
  - Bone culture from early November-now showing “Fungus”
  - Continue ceftazidime and watch closely
- **Late November:**
  - Reassessed in ID clinic
  - Wounds continuing to slowly improve
  - Bone culture: *Blastomyces dermatitidis*

## Case 3

- **Demographics:** Female between 40 to 50 years of age
- **Past Medical History:** none
- **Medications:** none
- **Social History:**
  - Lives with husband and children in Southern Ontario
  - No smoking, alcohol, substance use
- **Risk factors**
  - Works from home
  - “The least outdoorsy person”

## Case 3

- **December:**
  - Intermittent dry cough, worsened over next 3 months with small amounts of sputum
- **Mid March:**
  - Admitted with respiratory symptoms
  - Chest imaging showed Right Lower Lobe (RLL) mass with consolidation and small pleural effusion
  - Query lung cancer with superimposed pneumonia
  - Discharged to complete amoxicillin/clavulanate, but had minimal effect
- **Late March**
  - Presented to Emergency Department with worsening respiratory symptoms and new chest wall pain
  - Chest X-ray: progression of RLL infiltrates, nodular densities in the left mid-lung
  - Started on moxifloxacin for potential diagnosis non-resolving pneumonia
  - Bronchoscopy completed
    - Fungal Culture results: *Blastomyces dermatitidis/gilchristii*
  - Initiated on antifungal therapy that evening

# Blastomycosis Treatment

- **Pulmonary**
  - **Mild-moderate:** itraconazole or voriconazole x 6-12 months
  - **Severe:** amphotericin B x 1-2 weeks, then itraconazole/voriconazole x 6-12 months
- **Extrapulmonary**
  - **Mild-moderate:** itraconazole or voriconazole x 6-12 months
  - **Severe:** amphotericin B x 1-2 weeks, then itraconazole/voriconazole for  $\geq 12$  months
  - **Osteoarticular:** requires at least 12 months of treatment
  - **Central Nervous System:** amphotericin B x 4-6 weeks, then high dose fluconazole or voriconazole x 12 months

## Itraconazole Pearls

- Oral suspension has higher bioavailability than capsule
- Gastro-intestinal intolerance is common
- Requires serum itraconazole level at 2 weeks
- Poor Central Nervous System penetration

## Case 3

- Completed 2 weeks of amphotericin B but could not tolerate 6 months of itraconazole (due to gastro-intestinal intolerance)
- **October**
  - Noted some intermittent headaches and mild visual changes x 1 month (no change on/off itraconazole)
- **December**
  - Significant worsening of headache, presented to academic hospital
  - MRI: Posterior frontal ring enhancing lesion with restricted diffusion consistent with abscess or necrosis
- **Mid January**
  - Left-sided parietal craniotomy and evacuation of abscess: fungal culture positive for *Blastomyces dermatitidis*
  - Seen in ID clinic again, and started on voriconazole (better Central Nervous System penetration)
  - Two days post visit called into clinic with severe blurry vision x 24 hours
  - Voriconazole dose decreased, with some improvement in vision

## Treatment pearls

- **Fluconazole:** high rates of treatment failure
- **Itraconazole:** poor Central Nervous System penetration
- **Voriconazole:** severe visual side effects
- **Echinocandins:** poor activity against *Blastomyces*
- **Amphotericin B:** would require inpatient admission, cannot give prolonged course

# Isavuconazole

- Oral triazole antifungal, once daily
- Well tolerated
- Excellent Central Nervous System S penetration
- Superior or non-inferior to voriconazole and posaconazole for all studied indications
- Expensive medication
  - Exceptional Access Program denied for Case 3 because lack of published evidence for blastomycosis
  - Fortunately drug was covered under private drug plan and tolerating well now



# Laboratory-based diagnostics

# Laboratory-based Diagnostics for Blastomycosis

- **Microbiology:** Microscopy and Culture\*#
- **Histopathology:** Microscopy \*
- **Serology** \*#
- **Antigen testing**
  - Urine
  - Serum
  - Bronchoalveolar lavage (BAL)
  - Cerebrospinal fluid (CSF)
- **Direct Molecular Detection**
  - Detection of *Blastomyces* DNA
  - No commercial assays, not widely available, limited to laboratory-developed assays.



\*Routinely performed in Ontario

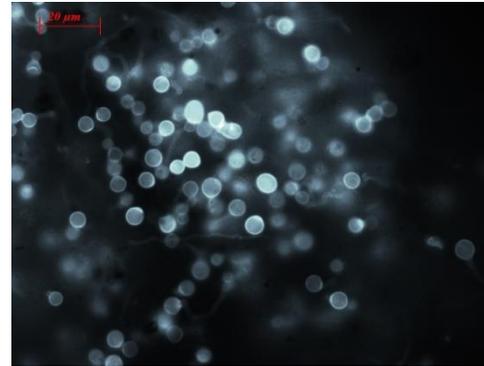
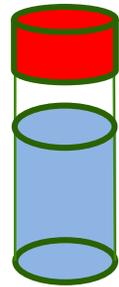
#Performed at PHO

# Blastomyces Diagnostics: Microscopy and Culture

- Detection of the fungus; indicates infection – definitive diagnosis
- Can be performed on any clinical specimen, site of infection (eg. sputum, BAL, tissue, skin)
- Culture Gold Standard; Sensitivity reported to be ~66-90% pulmonary, 77% extra-pulmonary.

## Direct Microscopy from Specimen

Set up and read within 24 hr of receipt at lab



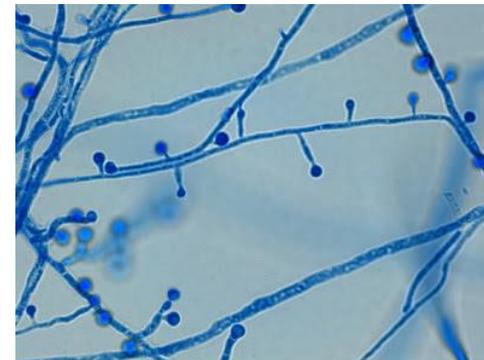
## Presumptive Identification

- Based on characteristic size and morphology – “broad-based budding yeast” 8-20 μm
- Rapid

## Culture (CL3)



Set up upon receipt at lab. Plates monitored regularly for growth for up to 4 weeks – growth typically <2 weeks



## Confirm Identification

- Phenotypic identification &
- Molecular probe OR
- PCR + Sequence analysis OR



## *Blastomyces* Diagnostics: Serology

- Detection of antibodies to *Blastomyces*; antibodies may take weeks to develop after exposure/infection
- The presence of antibodies is presumptive evidence that the patient was, or is, currently infected with, or was exposed to *Blastomyces*
- Methods include Complement Fixation (CF), Immunodiffusion (ID) and Enzyme Immunoassay (EIA)
  - CF and ID: classical/traditional assays
    - PHO uses ID: Specificity 100%; Sensitivity – 32-80%
  - EIA: currently no commercial EIA available in Canada, available in USA
    - More sensitive, slightly less specific: Specificity 94-99%; Sensitivity 88%.

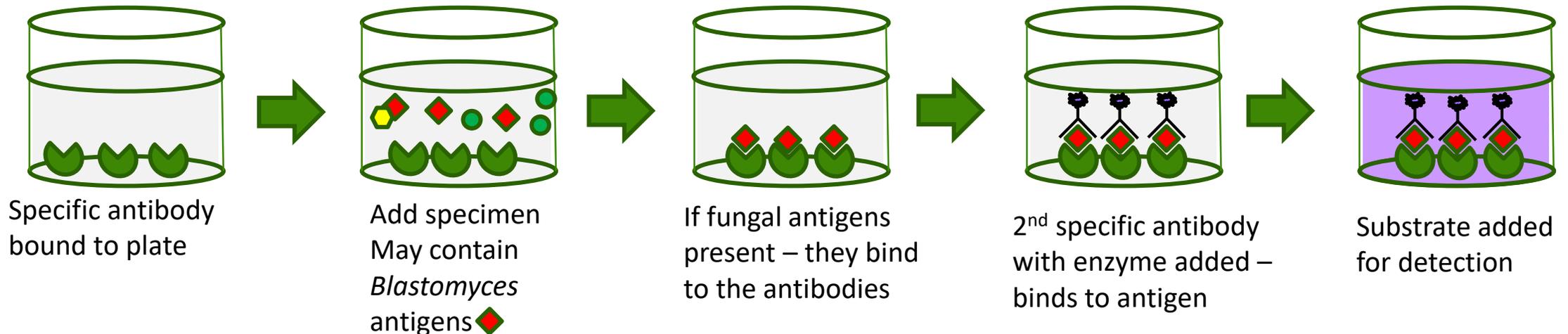


## ***Blastomyces* Diagnostics: Serology Caveats**

- Results should not be used in isolation for clinical diagnosis or patient management
- Samples may be collected too early resulting in negative serologic results - repeat testing in 1-2 weeks may be warranted
- Immunocompromised patients may fail to mount proper immune response resulting in negative results.

# Blastomyces Diagnostics Antigen Detection

- Detects small components of the pathogen itself, antigens
  - Quite sensitive (up to 93%; 89% in disseminated disease)
- Good for immunocompromised patients; positive earlier than serologic assays; can use several specimen types including urine (non-invasive)
- *Blastomyces* antigen detection assay has high degree of cross-reactivity (false positives) with other fungi (36-93% specific) and the assay is not available in Canada.



## Blastomyces Diagnostic Test Comparison (data for pulmonary infections)

Test	Sensitivity	Specificity	Strengths	Limitations
Sputum/BAL Culture	66-90%	~100%	Gold Standard Available in Ontario	Can be slow; diagnostic yield can vary by specimen type; Risk Group 3 organism, requires CL3 for culture
Direct Microscopy	48-90%	High	Rapid – can be hours Available in Ontario	Varied sensitivity
Histopathology/ Cytology	38-93%	High	Rapid – can be hours Available in Ontario	Varied sensitivity
Antibody CF	16-77%	30-100%	Fast result - days	May be negative early in infection; difficult to perform - reference labs
Antibody ID	32-80%	~100%	Fast result – days Available in Ontario	May be negative early in infection or in immunocompromised patients; difficult to perform
Antibody EIA	88%	94-99%	Increased sensitivity when combined with antigen	May be negative early in infection or in immunocompromised patients; not in Canada
Antigen Serum	36-82%	99% (non-fungal infx)	Can be rapid	Cross-reacts with other fungi (95.6% cross-reactivity with Histoplasma); not in Canada
Antigen Urine	76-93%	79-99%	Can be rapid; non-invasive;	Cross-reacts with other fungi including Histoplasma; not in Canada
Direct Molecular	Unknown; can be high	Unknown; can be high	Can be rapid	Various lab-developed tests, not widely-available; no evidence to date on role in patient care

# Summary: Laboratory-based diagnostics for Blastomycosis

- **Culture and Microscopy**
  - Remain the gold-standard for diagnostics; microscopy can be rapid however culture and confirmation can take weeks
- **Serology**
  - The assay in use in Canada is not very sensitive but is highly specific
  - Not suitable for acute diagnosis or for some immunocompromised patients
- **Antigen**
  - Where rapid diagnostic testing is needed (days), or collection of respiratory specimens is challenging, antigen testing may aid with diagnosis
  - Quite sensitive however considerable cross-reactivity with other endemic fungi including *Histoplasma* (also endemic in Ontario)
  - Antigen testing is a send-out test to the USA arranged by the treating physician/laboratory; PHO can support send-outs in the context of an outbreak.

# Recommendations

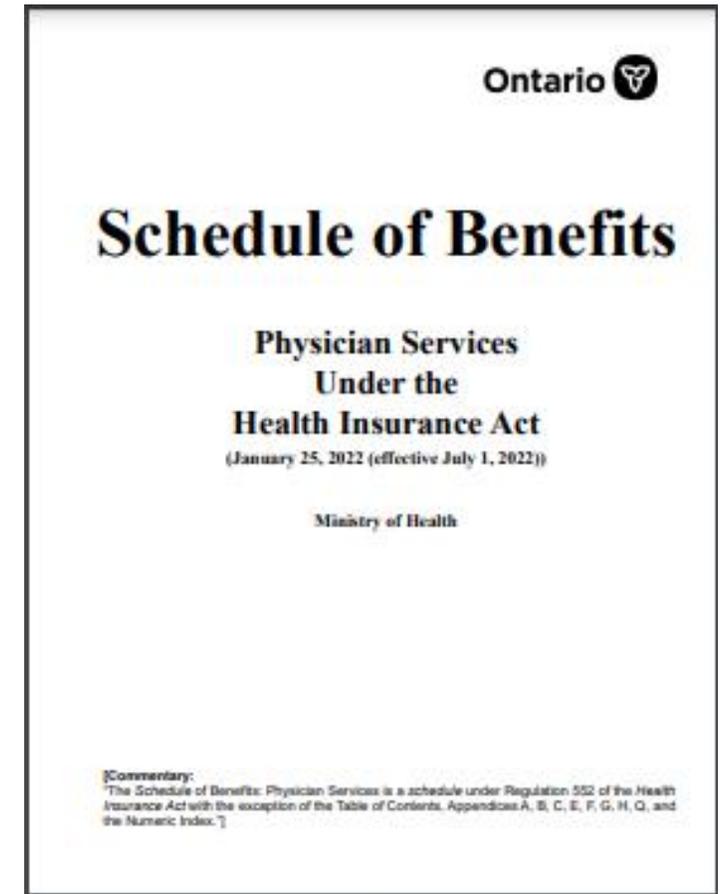
- Diagnosis is challenging
- Given each test's limitations and strengths, combined diagnostic approaches (including non-microbiology-based investigations) may be necessary for diagnosis
- Where possible, submit multiple specimens for microscopy/culture per patient over time to increase sensitivity
  - **Specimen quality is important!**
  - A poor “sputum” specimen which is mainly saliva is not an adequate specimen for diagnosis and may lead to false negative results and delayed diagnosis.



# Public Health Management

# Clinicians are required to report to Public Health

- Blastomycosis is reportable **by next business day** to your local Public Health Unit as per Ontario Regulation 135/18: Designation of Disease under the *Health Protection and Promotion Act*, R.S.O. 1990, c. H.7
- Reporting of blastomycosis is **not eligible** for physician billing code K034
  - K034 is for urgent telephone reporting of specified Diseases of Public Health Significance to a Medical Officer of Health.



*Designation of Diseases*, O Reg 135/18. Available from: <https://www.ontario.ca/laws/regulation/R18135>

*Health Protection and Promotion Act*, RSO 1990, c H.7. Available from: <https://www.ontario.ca/laws/statute/90h07>

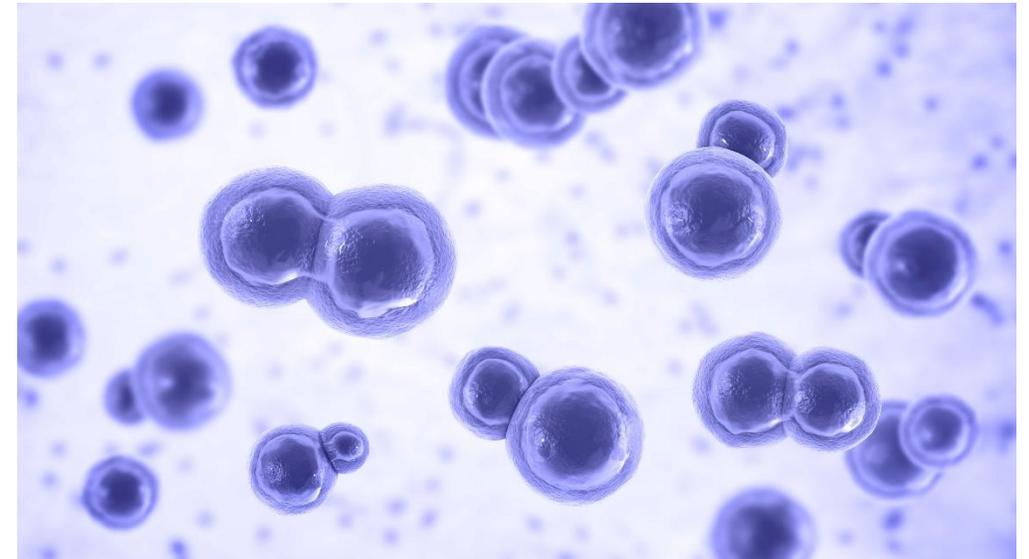
Source: Ontario. Ministry of Health. Schedule of benefits: physician services under the *Health Insurance Act* (January 25, 2022 (effective July 1, 2022)) [Internet].

Toronto, ON: Queen's Printer for Ontario; 2022 [cited 2022 Aug 18]. Available from:

[https://www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/sob\\_master.pdf](https://www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/sob_master.pdf)

# Blastomycosis surveillance case definitions

- **Confirmed case**
  - Laboratory confirmation of infection:
    - Positive *Blastomyces dermatitidis*/*Blastomyces gilchristii* (*B. dermatitidis*/*gilchristii*) culture with confirmation using a validated method
  - OR
  - Molecular confirmation by nucleic acid amplification test (NAAT) testing or through sequencing analysis
- **Probable case**
  - Laboratory evidence of infection by visualization of characteristic *B. dermatitidis*/*gilchristii* large, broad-based, budding yeast through direct microscopic examination of patient specimens.



## Blastomycosis outbreak definitions

- **Endemic areas:** an increase in blastomycosis case numbers above expected levels
- **Non-endemic areas:** two or more cases linked to a common location
- If your public health unit is concerned about a potential cluster/outbreak of blastomycosis please consult with Public Health Ontario and the Ministry of Health to develop outbreak specific case definitions (i.e. confirmed, probable, and suspect cases).

# Case and contact management

- **Case management**

- Treatment under direction of attending health care provider
- Consideration of the appropriateness of detailed case follow-up is based on local epidemiology of blastomycosis and knowledge of local endemic areas
- Detailed follow-up of cases occurring in areas that are not known to be endemic for *Blastomyces* spp. supports provincial surveillance for new and emerging risk areas for exposure

- **Contact management**

- Not required as no person-to-person transmission
- May consider follow-up of individuals exposed to the same sources as case to monitor for signs and symptoms of blastomycosis.

## Information to collect during a case investigation

- **Case details** (e.g. case classification, disposition, etc.)
- **Demographics** (e.g. age, gender)
- **Address** (e.g., for home, work, volunteering)
- **Medical risk factors** (e.g. immunocompromised, heart disease, lung disease, etc.)
- **Symptoms** (e.g., fever, cough, shortness of breath, skin lesions)
- **Clinical information** (e.g. ED visit, hospitalization, ICU, treatment)

## Ask questions about potential sources of exposure

- **Wood** (e.g., wood piles, wood chip/sawdust piles, chopping wood, hollow trees, decaying wood)
- **Disturbing soil** (e.g., digging holes, working with large machinery, working underneath a cottage/shed/house, planting trees, gardening)
- **Animals** (e.g., visiting beaver dams/houses or trapping beavers, hunting/trapping small animals, pelts/remains)
- **Outdoor recreational activities** (e.g., foraging, shorelines of streams/rivers/lakes, camping/sleeping on the ground outdoors, hiking, biking, ATVing/4-wheeling)
- **Other** (e.g., dirt basement, visiting cemetery, travel to a cabin/lodge)

## Environmental testing for *Blastomyces*

- Environmental sampling is primarily done for research purposes and has been mostly unsuccessful in isolating *Blastomyces*
- Testing the environment is not routinely recommended
- If testing is done:
  - A negative test does not rule out the fungus in the area
  - A positive test does not mean that it is the source of infection



# Questions?

## Public Health Resources

- Centers for Disease Control and Prevention. Fungal diseases: blastomycosis [Internet]. Atlanta, GA: Centers for Disease Control and Prevention; 2022 [cited 2022 Aug 18]. Available from: <https://www.cdc.gov/fungal/diseases/blastomycosis/index.html>
- Ontario. Ministry of Health. Ontario public health standards: requirements for programs, services and accountability. Infectious disease protocol. Appendix 1: case definitions and disease specific information disease: blastomycosis [Internet]. Toronto, ON: Queen's Printer for Ontario; 2022 [cited 2022 Aug 18] Available from: [https://www.health.gov.on.ca/en/pro/programs/publichealth/oph\\_standards/docs/Blastomycosis\\_chapter.pdf](https://www.health.gov.on.ca/en/pro/programs/publichealth/oph_standards/docs/Blastomycosis_chapter.pdf)
- Public Health Agency of Canada. Pathogen safety data sheets: infectious substances – *Blastomyces dermatitidis* [Internet]. Ottawa, ON: Government of Canada; 2010 [modified 2011 Aug 19; cited 2022 Aug 18]. Available from: <https://www.canada.ca/en/public-health/services/laboratory-biosafety-biosecurity/pathogen-safety-data-sheets-risk-assessment/blastomyces-dermatitidis.html>

## Clinical resources

- Chapman SW, Dismukes WE, Proia LA, Bradsher RW, Pappas PG, et al; Infectious Diseases Society of America. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. Clin Infect Dis. 2008;46(12):1801-12. Available from: <https://doi.org/10.1086/588300>
- Public Health Agency of Canada. For health professionals: blastomycosis [Internet]. Ottawa, ON: Government of Canada; 2016 [modified 2016 Mar 01; cited 2022 Aug 18]. Available from: <https://www.canada.ca/en/public-health/services/diseases/blastomycosis/health-professionals-blastomycosis.html>

## Testing resources

- Ontario Agency for Health Protection and Promotion (Public Health Ontario). Labstract - February 2009: systemic mycoses – change in specimen submission guidelines [Internet]. Toronto, ON: Queen’s Printer for Ontario; 2009 [cited 2022 Aug 18]. Available from: [https://www.publichealthontario.ca/-/media/Documents/Lab/lab-sd-050-systemic-mycoses-specimen-guidelines.pdf?la=en&sc\\_lang=en&hash=D11250FCF8C1074849DD2BCFFCD52AEF](https://www.publichealthontario.ca/-/media/Documents/Lab/lab-sd-050-systemic-mycoses-specimen-guidelines.pdf?la=en&sc_lang=en&hash=D11250FCF8C1074849DD2BCFFCD52AEF)
- Ontario Agency for Health Protection and Promotion (Public Health Ontario). Fungus culture – reference identification [Internet]. Toronto, ON: Queen’s Printer for Ontario; 2020 [modified 2020 Jul 20; cited 2022 Aug 18]. Available from: <https://www.publichealthontario.ca/en/Laboratory-Services/Test-Information-Index/Fungus-Culture-Reference-ID>
- Ontario Agency for Health Protection and Promotion (Public Health Ontario). Fungal – serology [Internet]. Toronto, ON: Queen’s Printer for Ontario; 2020 [modified 2020 Jul 20; cited 2022 Aug 18]. Available from: <https://www.publichealthontario.ca/en/Laboratory-Services/Test-Information-Index/Fungal-Serology>