



## Watching brief

<b>Title</b>	Blastomycosis outbreak in Escabana, Michigan, United States of America, 2023.
<b>Authors</b>	Braidy Sutton and Ashley Quigley
<b>Date of first report of the outbreak</b>	First reports emerged in February 2023 (1) of an atypical pneumonia.
<b>Disease or outbreak</b>	A fungal disease called blastomycosis stemming from inhalation of the fungus <i>Blastomyces</i> (3).
<b>Origin (country, city, region)</b>	The current outbreak is centred on a paper mill factory located in Escabana, Michigan, United States of America (4).
<b>Suspected Source (specify food source, zoonotic or human origin or other)</b>	The environmental pathogenic mycosis is <i>Blastomyces</i> , which is prevalent in moist soils rich with decomposing organic matter (2). The source of infection remains unknown, with the National Institute for Occupational Safety and Health (NIOSH) conducting a follow-up field investigation in late April (5).
<b>Date of outbreak beginning</b>	March 17, 2023 (2).
<b>Date outbreak declared over</b>	As of May 10, 2023 the outbreak is ongoing.
<b>Affected countries &amp; regions</b>	The current outbreak is limited to the port city of Escabana, Upper Peninsula, Michigan, United States of America (4).
<b>Number of cases (specify at what date if ongoing)</b>	As of May 10, 2023, there are 115 confirmed and probable cases, with 11.30% requiring hospitalisation ( $n = 13$ ) and one death reported (6).



<p><b>Clinical features</b></p>	<p>According to the Centres for Disease Control and Prevention (CDC), 3 clinical features of pulmonary blastomycosis are similar to that of other pulmonary infections and are presented in Table 1.</p> <p><b>Table 1.</b> Clinical features of pulmonary blastomycosis.</p> <table border="1" data-bbox="491 651 1418 779"> <tr> <td>Fever</td> <td>Cough</td> </tr> <tr> <td>Night sweats</td> <td>Muscle aches/joint pain</td> </tr> <tr> <td>Weight loss</td> <td>Chest pain</td> </tr> <tr> <td>Fatigue</td> <td>Skin lesions/blisters/ulcers</td> </tr> </table> <p>In severe cases (particularly the immunosuppressed) infection can become disseminated and spread to the skin, bones, joints, and central nervous system (3). Additionally, the CDC recommends accepting one or more of the following clinical features for positive case definition (7):</p> <ol style="list-style-type: none"> <li>1. Presence of pulmonary infiltrates/nodules/mass-like lesions</li> <li>2. Single or multiple verrucous or ulcerated skin lesions</li> <li>3. Lesion in any other body system</li> <li>4. Any bone or joint abnormality, including pathologic fracture</li> <li>5. Presentation of meningitis/encephalitis or focal brain lesions</li> </ol>	Fever	Cough	Night sweats	Muscle aches/joint pain	Weight loss	Chest pain	Fatigue	Skin lesions/blisters/ulcers
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<p><b>Mode of transmission (dominant mode and other documented modes)</b></p>	<p><i>Blastomyces</i> presents as a fungal spore-producing mould within the environment in soil and organic material (5). When disturbed or moved in some way, these spores became airborne and can be inhaled (8).</p>								
<p><b>Demographics of cases</b></p>	<p>Demographic details are currently unavailable from both formal and informal surveillance systems (9), with the only data available confirming all 115 confirmed and probable cases are employees of a paper mill in Escanaba (5, 6).</p>								
<p><b>Case fatality rate</b></p>	<p>The current (May 10, 2023) case fatality rate is 0.87% (<math>n = 1</math>) (6).</p>								
<p><b>Complications</b></p>	<p>There are four main complications of infection with <i>Blastomycosis</i>: the delayed incubation period; the length of the active treatment phase; differential diagnoses; and relapse.</p> <p>The incubation period can range from just three weeks (21 days) to three months (90 days) (3). This has epidemiological implications for the date of onset of the outbreak occurring, which, at a minimum, would be three weeks prior to the official date announced by the CDC (17 March, 2023). Additionally, this also implies that the period of active monitoring for symptom onset must extend for at least three months – and during this time it is probable that more cases will be detected. To complicate diagnosis further, asymptomatic infection is reported in 50% of cases (10).</p>								



	<p>The active treatment phase as recommended by the Infectious Diseases Society of America for mild to severe infection is between six to twelve months. This has significant health economic impacts (with an average course of treatment estimated to exceed US\$20,000) (8), though (11), blastomycosis is a notifiable disease in only four states (of which Michigan is one), and mild and moderate infection are most likely under-reported, indicating a higher-than-expected health burden (8).</p> <p>Differential diagnoses also complicates the process of successful early detection. Blastomycosis presents as chronic pneumonia that is clinically indistinguishable from tuberculosis, other fungal infections, and some types of cancer (10). Radiographic findings reveal fibronodular interstitial infiltrates, alveolar infiltrates, and mass lesions (in mimicry of bronchogenic carcinoma) also occurs frequently (10). Alarmingly, in chronic blastomycosis, extrapulmonary blastomycosis can occur, with the skin, bones, and genitourinary systems the most frequent sites of extrapulmonary disease.</p> <p>An exceedingly rare though documented complication is relapse following the completion of the antifungal drug regimen (10). Relapse within immunocompetent persons can occur up to six months following the end of treatment, with current guidelines recommending observation and follow up for at least six months (10) – this would extend the active treatment and follow up phase to between 9 and 18 months, increasing the overall burden of disease.</p>								
<p><b>Available prevention</b></p>	<p>No current prophylactic treatment exists to protect against infection, though initial recommendations from NIOSH are that N95 respirators be made freely available to all employees (5). Importantly, the current recommendation is that respirator use is voluntary (5).</p>								
<p><b>Available treatment</b></p>	<p>Pulmonary blastomycosis requires a significant antifungal regimen (10) which is outlined in Table 2.</p> <p><b>Table 2.</b> Anti-fungal regimen for mild to moderate, and moderately severe to severe blastomycosis infection.</p> <table border="1" data-bbox="491 1626 1417 1966"> <thead> <tr> <th data-bbox="491 1626 954 1686"><b>Mild to Moderate Infection</b></th> <th data-bbox="954 1626 1417 1686"><b>Moderately Severe to Severe Infection</b></th> </tr> </thead> <tbody> <tr> <td data-bbox="491 1686 954 1843">Oral itraconazole – 200mg 3 x per day for 3 days</td> <td data-bbox="954 1686 1417 1843">Lipid formulation of amphotericin B – 3-5mg/kg for 7 to 14 days Or Amphotericin B deoxycholate – 0.7-1mg/kg for 7 to 14 days</td> </tr> <tr> <td data-bbox="491 1843 954 1904">Oral itraconazole – 200mg 2 x per day for 6 -12 months</td> <td data-bbox="954 1843 1417 1904">Oral itraconazole – 200mg 3 x per day for 3 days</td> </tr> <tr> <td data-bbox="491 1904 954 1966"></td> <td data-bbox="954 1904 1417 1966">Oral itraconazole – 200mg 2 x per day for 6-12 months</td> </tr> </tbody> </table>	<b>Mild to Moderate Infection</b>	<b>Moderately Severe to Severe Infection</b>	Oral itraconazole – 200mg 3 x per day for 3 days	Lipid formulation of amphotericin B – 3-5mg/kg for 7 to 14 days Or Amphotericin B deoxycholate – 0.7-1mg/kg for 7 to 14 days	Oral itraconazole – 200mg 2 x per day for 6 -12 months	Oral itraconazole – 200mg 3 x per day for 3 days		Oral itraconazole – 200mg 2 x per day for 6-12 months
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	<p>This combination of drugs is recommended for both disseminated extrapulmonary blastomycosis (though the minimum recommended length of treatment for moderately severe to severe infection is extended to twelve months); and immunosuppressed cases (though lifelong suppressive therapy may be required) (10).</p> <p>Positive diagnosis is conferred when a culture of <i>Blastomyces</i> spp. is successfully grown from a clinical specimen or identification of <i>Blastomyces</i> spp. in tissue or body fluid by histopathology (8). Additionally, urine antigen tests are available for more rapid diagnosis (3).</p>
<p><b>Comparison with past outbreaks</b></p>	<p>For the latest available epidemiological data, Michigan reported an annual incidence rate of between 0.15-0.26/100,000 (11), and a case fatality rate (amongst the hospitalised) of 11.5%, with an age spread between 21 and over 80 (11). In 2019, Michigan reported 26 cases of blastomycosis (11), with the current 2023 outbreak four-times larger than total annual incidence (11). Hospitalisation rates in 2019 were 100% in Michigan, whereas in the current outbreak only 11.30% of cases have been hospitalised (5, 11). Additionally, the current outbreak's fatality rate is significantly lower than annual rates (0.87% and 11.30% respectively) (4, 11).</p> <p>This difference in current hospitalisation, fatality rates, and annualised rates could be explained by the early detection and enhanced surveillance systems recommended by NIOSH (5) and implemented by the paper mill that incorporates all case definitions – annualised hospitalisation rates would then apply only to those cases of severe infection.</p> <p>Unfortunately, no demographic data is available for epidemiological analysis, and no total employee data is available from the paper mill to compare incidence rates between years and populations to determine the root cause of the underlying difference between rates.</p>
<p><b>Unusual features</b></p>	<p>Despite a field investigation by NIOSH, current processes and points of exposure are not revealed (5). Usual exposure and infection occurs following inhalation of spores from disturbed soil (5, 8), however NIOSH is recommending that all heating, ventilation, air-conditioning systems, and ductwork is thoroughly inspected for either water incursion or microbial growth (8). This could represent an atypical dispersal method and require significant engineering controls to mitigate exposure.</p> <p>The current outbreak reports lower-than-expected hospitalisation and fatality rates when compared against annual rates (4, 11), and this is an unusual component of the current outbreak. This is potentially explained by the decision to count both probable and confirmed cases as 'current cases.' From the latest available data where confirmed cases were reported separately (as detected by EPIWATCH), 31 cases were confirmed (6, 12). This would yield a hospitalisation rate of 41.94% and a case fatality rate of 3.23%. Though significantly altered, these figures are still substantially lower than annualised epidemiological data would indicate (8).</p>



<p><b>Critical analysis</b></p>	<p>Blastomycosis infection is a relatively poorly understood mycosis (8). The overall distribution, burden of disease, and geographic endemicity are difficult to characterise (8). Differential diagnoses, the length of the incubation period, and the length of the active treatment phase further complicate both diagnosis and treatment (3, 8, 10). However, annualised epidemiological rates indicate that this outbreak has lower incidence, lower hospitalisation, and lower fatality than expected (4, 11).</p> <p>The ecological components needed for spore development include areas with acidic pH, high organic content, and a proximity to flowing water (13). Though little information is available following the field investigation by NIOSH, it is likely that the paper mill has received raw unprocessed material with significant masses of spores. It is unlikely that the heating, ventilation, air-conditioning, and ductwork servicing the paper mill are ideal environments for fungus development. Both situations though then would require significant engineering controls to remove the spores from the raw unprocessed materials and the heating, ventilation, air-conditioning, and ductwork.</p> <p>With a long incubation period, and a potential for relapse, significant resources are required to maintain surveillance systems. With urine antigenic tests being utilised to detect probable cases, this could be implemented as a daily pre-work check for all employees of the paper mill. To provide further prophylactic treatment, the use of N95 respirators should be updated from 'recommended' to 'required.' This mitigation strategy, combined with implemented NIOSH recommendations, and urine antigenic tests throughout the entire incubation and surveillance periods, would provide early detection.</p> <p>The average cost and length of the antifungal regimen is also potentially prohibitive for individuals and for the paper mill itself. This could foreseeably lead to treatment being foregone, truncated early, or prophylactic treatments and engineering controls being sporadically available or of reduced quality and efficacy.</p> <p>Given the lag between onset of infection, diagnosis, and several differential diagnoses, it is prudent to investigate surveillance data from June 2023. From the Michigan Disease Surveillance System Weekly Report (week ending July 8, 2023) the state has recorded an additional eight cases of blastomycosis, 280 cases of tuberculosis, and 1,342 cases of influenza (encompassing flu-like disease, influenza, novel influenza, and respiratory syncytial virus) (14). Interestingly, the Public Health Delta and Menominee Counties outbreak investigation reports a confirmed increase in cases by three and hospitalisations by one (15). Given the background incidence of respiratory viruses, and ongoing positive case identifications, this outbreak warrants ongoing surveillance.</p>
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<p><b>Key questions</b></p>	<ol style="list-style-type: none"> <li>1. What is the incidence of extrapulmonary disease within the current outbreak?</li> <li>2. What measures could be taken to expedite a positive diagnosis?</li> <li>3. Is there an enhanced risk of infection due to the type of work being performed?</li> <li>4. What current spore decontamination processes are in place?</li> </ol>
<p><b>References</b></p>	<ol style="list-style-type: none"> <li>1. Lynn J. Blastomycosis outbreak found in paper mill workers in Michigan’s Upper Penninsula. Patient Worthy. [Internet]. 2023 March 23 [cited 2023 May 12] [about 1 p]. Available from: <a href="https://patientworthy.com/2023/03/23/blastomycosis-outbreak-paper-mill-workers-michigan/">https://patientworthy.com/2023/03/23/blastomycosis-outbreak-paper-mill-workers-michigan/</a></li> <li>2. Jawarowski M. Blastomycosis – USA: (MI) Upper Penninsula, paper mill, RFI [Internet]. ProMED; 20230322.8709092</li> <li>3. Centres for Disease Control and Prevention. Fungal Diseases [Internet]. Georgia USA: Centres for Disease Control and Prevention; 2023 [reviewed 2023 Jan 17; cited 2023 May 01]. Available from: <a href="https://www.cdc.gov/fungal/diseases/blastomycosis/definition.html">https://www.cdc.gov/fungal/diseases/blastomycosis/definition.html</a></li> <li>4. Public Health Delta and Menominee Counties. Blastomycosis Outbreak Investigation Update [Internet]. Menominee Michigan; 2023 [cited 2023 May 01]. Available from: <a href="https://phdm.org/">https://phdm.org/</a></li> <li>5. The National Institute for Occupational Safety and Health. NIOSH Investigates Workplace Outbreak of Blastomycosis [Internet]. Washington, D.C.; 2023 [reviewed 2023 Apr 19; cited 2023 May 01]. Available from: <a href="https://www.cdc.gov/niosh/newsroom/alerts/blastomycosisshhe.html">https://www.cdc.gov/niosh/newsroom/alerts/blastomycosisshhe.html</a></li> <li>6. Bean M. Rare fungal outbreak in Michigan grows to 115 cases. Becker’s Healthcare. [Internet]. 2023 May 9 [cited 2023 May 12]; Clinical Leadership and Infection Control [about 1 p]. Available from: <a href="https://www.beckershospitalreview.com/public-health/rare-fungal-outbreak-in-michigan-grows-to-115-cases.html">https://www.beckershospitalreview.com/public-health/rare-fungal-outbreak-in-michigan-grows-to-115-cases.html</a></li> <li>7. Centres for Disease Control and Prevention. Blastomycosis 2020 Case Definition [Internet]. Georgia USA: Centres for Disease Control and Prevention; 2021 [reviewed 2021 Apr 16; cited 2023 May 01]. Available from: <a href="https://ndc.services.cdc.gov/case-definitions/blastomycosis-2020/">https://ndc.services.cdc.gov/case-definitions/blastomycosis-2020/</a></li> <li>8. Benedict K, Roy M, Chiller T, Davis J. Epidemiologic and ecologic features of blastomycosis: a review. Curr Fungal Infect Rep. 2012 Sep 27;6:327-225</li> </ol>

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