1. What was known about the problem at the beginning of the investigation?

Mucormycosis (formerly referred to as zygomycosis) is a rare, often fatal infection, caused by a group of angioinvasive molds. These infections typically occur in persons with marked immunosuppression, and commonly manifest as rhinocerebral, pulmonary, and cutaneous disease.

On September 17, 2015, the Centers for Disease Control and Prevention (CDC) was notified by the Pennsylvania Department of Health (PA DOH) of mucormycosis infections among three solid organ transplant recipients in Hospital A in Pennsylvania during September 2014 – September 2015, including one pulmonary and two cutaneous infections. A fourth infection was identified on September 18, 2015 in Hospital B, within the same healthcare system. All infections were suspected to be healthcare-associated. At the request of the United Network for Organ Sharing (UNOS), Hospitals A and B voluntarily suspended their solid organ transplantation program pending further investigation of the infections.

PA DOH requested CDC technical assistance with the following activities: 1) investigation of presence and scope of potential outbreak; 2) assessment of infection prevention activities related to the care of solid organ transplant patients at Hospitals A and B; 3) investigation of possible sources of infections, common exposures, and potential risk factors for infections; 4) provide recommendations to reduce the risk of healthcare-associated mucormycosis at Hospitals A and B, including recommendations for establishing prospective surveillance to assess the impact of prevention measures.

2. What was accomplished in the field (investigation methods)?

The Epi-Aid team included Amber Vasquez and Shannon Novosad (EISOs, Division of Healthcare Quality Promotion (DHQP)), Erick Christensen (Epi-Elective Medical Student), Rajal Mody (Epidemiology Team Lead, Mycotic Diseases Branch), Matthew Arduino (Branch Chief, DHQP Clinical and Environmental Laboratory), Heather Moulton-Meissner (DHQP Outbreak Lab Coordinator) and M. Shannon Keckler (LLS Fellow, DHQP).

To identify other possible mucormycosis infections, microbiology records from Hospitals A and B were queried for mucormycete organisms. In addition, histopathology records were queried, first for evidence of fungal elements and then for findings consistent with mucormycosis on final report.

A probable healthcare-associated mucormycosis case-patient was defined as any individual who (1) had a history of solid organ transplantation, (2) had a diagnostic mucormycosis specimen identified by culture or molecular testing, and (3) was admitted to either Hospital A or B for ≥ 14 days at the time of diagnosis or had a recent admission of ≥ 14 days within 30 days prior to mucormycosis diagnosis during June 2014-September 2015.

A suspect case-patient was defined as any individual who met the probable case definition but either (1) had a diagnostic mucormycosis specimen identified by histopathology only, or (2) had an admission duration of 7 – 14 days.

Microbiology and histopathology records were queried from January 2011 through September 2015.
The case definitions were applied to these records to establish a baseline rate of mucormycosis at Hospitals A and B. Epidemiologic curves were created to show cases of mucormycosis among all hospitalized patients, cases among solid organ transplant patients, and probable compared with suspect cases over time.

Preliminary information indicated a possible association with room X of the cardiothoracic intensive care unit (CTICU) in Hospital A. To assess statistical significance of room X exposure, the team analyzed a cohort of 124 patients who received a heart or lung transplant at Hospital A or B from June 17, 2014 to September 3, 2015 and compared rates of mucormycosis in those exposed to room X and those unexposed to room X.

A nested case-control study was conducted to evaluate risk factors for mucormycosis in the CTICU. Five controls were chosen for each case. A control was defined as a solid organ transplant recipient without clinical suspicion or laboratory confirmation of mucormycosis with an admission to the CTICU for at least 14 consecutive days, from May 1, 2014 to August 20, 2015.

Unstructured interviews were conducted with hospital staff, including physicians, nurses, pharmacists, environmental services, facilities management, construction crew, and infection control team.

Maps were created and photographs taken to highlight areas of construction relative to the case-patient locations at the time of their diagnoses. Timelines for patient hospitalization and location in comparison to timing of construction projects were also created.

Environmental assessments and observations of conditions inside or in proximity to Hospitals A and B were conducted. Observations included the ongoing deconstruction of Hospital A’s CTICU, the adjacent hallway and family room, construction on the nearby pediatric hospital, bed and linen storage areas, loading docks, operating rooms, respiratory equipment storage areas, air ventilation intake and output locations, and continuous renal replacement therapy (CRRRT) equipment units for both Hospitals A and B. Observations were also made on Hospital B’s transplant intensive care unit (TICU), where the fourth patient (suspect case-patient) had been admitted. Environmental samples were collected from the CTICU room X (which was undergoing deconstruction for remediation), the adjacent hallway and family room, bed storage area (hospital A), pediatric hospital construction, and the TICU.

Interim findings were presented to PA DOH, Health Resources and Services Administration (HRSA), and UNOS on September 27. Subsequently, transplant services were reopened at Hospitals A and B.

Initial findings and recommendations were presented to the hospital administrators and the PA DOH on October 8, 2015.

3. What are the initial findings and recommendations?

Three probable cases of mucormycosis and one suspect case were identified at Hospitals A and B from June 2014 to September 2015. Three of the four case-patients died. All case-patients had undergone solid organ transplantation. All four patients were severely ill and receiving voriconazole prophylaxis, an antifungal that lacks coverage against mucormycetes. The three probable case-patients (two heart transplant recipients and one lung transplant recipient) all received care in room X of Hospital A’s CTICU during their stay (median time in CTICU 33 days, range 16 – 58 days). The fourth case-patient
was admitted for 13 days, thus was classified as a suspect case and was not included in the cohort or case-control analyses.

The four patients differed with respect to the species of mucormycete detected, with *Rhizopus oryzae (arrhizus)*, *Rhizopus microsporus* and *Lichtheimia corymbifera* recovered in culture from three of the cases, respectively, and *Lichtheimia* DNA detected by an unaffiliated laboratory in a clinical sample from the fourth case. Given their differing clinical syndromes (two pulmonary, one cutaneous, and one disseminated infection with an unknown primary site), the four patients might also have differed with respect to mode of transmission.

In the cohort analysis of CTICU room X exposure, 124 transplant patients receiving either a heart or lungs met our inclusion criteria; 7 patients were cared for in room X during their admission. Three of these seven went on to develop mucormycosis, an attack rate of 43%, compared with 0 of the 117 who were not exposed to the room (Fishers exact p-value of 0.0001). Of the 7 patients exposed to room X, only the three mucormycosis case-patients had received CRRT during their admission. The subsequent case-control study did not reveal CRRT to be a statistically significant exposure for cases, with all three cases and 8 of 15 controls exposed to CRRT (p-value 0.52). In addition, at CDC’s request, FDA checked its Medical Device Reporting post-market surveillance system and found no reports of infection for CRRT devices. Other exposures of interest that were analyzed in the case-control study included severity of illness by APACHE II and SOFA scoring, co-morbidities, immunosuppressive therapy, respiratory therapy, nutritional status, and re-exploration of surgical site. The only exposure, to date, which has been shown to be statistically significant in the case-control study is exposure to room X (all three case-patients, zero controls, p-value of 0.0012).

Upon environmental assessment of room X, several factors were noted to potentially increase the risk of acquiring mucormycosis. Room X was the only negative pressure isolation room in the CTICU. Room X was also located adjacent to an exit that was frequently used by visitors and led to a carpeted hallway and a nearby family area. Heavy foot traffic through this exit may have aerosolized spores that could have been drawn into room X due to the negative pressure condition. Modular toilet units stored under the sink were present in each room throughout the CTICU, including room X. Staff members recalled visible black mold on the inside of these toilet units, which had the potential for aerosolization of water upon flushing. During deconstruction of the room, Hospital A management observed mold accumulation behind a panel on a wall in room X. This may have been related to past reports of a leaking wall-mounted dialysis fixture.

Multiple environmental samples obtained during the investigation are still pending. To date, a mucormycete has been recovered from only one air sample collected by hospital personnel from room X prior to its deconstruction. This organism has been identified as *Mucor circinelloides*.

Prior to CDC’s arrival, the facility began remediation of the CTICU and room X. The facility also made adjustments to antifungal prophylaxis in transplant patients by switching to a therapy that includes coverage of mucormycetes. CDC agreed with these changes and further recommended the following to the facility:

1. Avoid housing immunocompromised solid organ transplant patients in a negative pressure room unless otherwise indicated.
2. Replacement of the frequently used door adjacent to room X with an emergency exit in order to limit foot traffic between the family room and the CTICU.
(3) Removal of carpet from the hallway and family room adjacent to the CTICU.
(4) Routinely monitor for and appropriately remediate any moisture damage at Hospitals A and B.
(5) Consider recording ID numbers for CRRT machines to track possible associations between specific machines and adverse events.
(6) Enhanced surveillance for mucormycosis cases, including microbiology and pathology results during review of all possible cases and inclusion of any recent hospital admission as an exposure for a potential healthcare-associated case.
(7) Investigate and report future mucormycosis cases directly to the PA DOH for at least the next year.

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<th>4. What still needs to be done?</th>
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<td>Additional steps in the investigation include data analysis from the cohort and case-control studies. Rates of mucormycosis stratified by type of organ transplanted (e.g., lung, heart, liver) will be calculated. Environmental samples collected by the Epi-Aid team during the investigation are undergoing testing at the CDC laboratory (N.B., mucormycetes are slow-growing organisms that may take multiple weeks to culture and identify). A more comprehensive report of our findings will be written and appended to this preliminary Epi-2 report and submitted to the PA DOH.</td>
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<th>5. What are the impacts of this investigation thus far? How will you continue to track impacts?</th>
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<td>Solid organ transplantation resumed at Hospitals A and B on September 27th, 2015. Given the brief time elapsed since our investigation there are otherwise no measured impacts. However, continued tracking of implemented recommendations will be performed by the PA DOH and through surveillance for future cases.</td>
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