BRIEF REPORT

Multistate Outbreak of Melioidosis Associated with Imported Aromatherapy Spray

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SUMMARY

Melioidosis, caused by the bacterium *Burkholderia pseudomallei*, is an uncommon infection that is typically associated with exposure to soil and water in tropical and subtropical environments. It is rarely diagnosed in the continental United States. Patients with melioidosis in the United States commonly report travel to regions where melioidosis is endemic. We report a cluster of four non–travel-associated cases of melioidosis in Georgia, Kansas, Minnesota, and Texas. These cases were caused by the same strain of *B. pseudomallei* that was linked to an aromatherapy spray product imported from a melioidosis-endemic area.

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Melioidosis is caused by infection with *Burkholderia pseudomallei*, which naturally occurs in soil and water in many tropical and subtropical regions.[1-3] Exposure to this bacterium typically occurs through inhalation, ingestion, or the percutaneous route. Melioidosis can manifest as a wide array of clinical syndromes with variable severity, including skin abscesses in the absence of fever, pneumonia, generalized sepsis with or without multiple organ abscesses, genitourinary infection, and encephalomyelitis.[1,3]

Melioidosis is rare in the United States. The approximately dozen cases reported to the Centers for Disease Control and Prevention (CDC) each year are predominantly associated with travel to melioidosis-endemic areas.[4,5] However, the occasional cases in patients who have not traveled to such areas suggest domestic exposure.[4,6-11] Analyses of isolates obtained from these patients have indicated that South or Southeast Asia is the probable origin and suggest exposure to imports contaminated with *B. pseudomallei*.[6,9-11] For example, a clinical isolate obtained from a patient in 2019 was a clonal match to isolates obtained from the patient's aquarium.[9] Although melioidosis is not considered to be zoonotic, it has been reported in pet iguanas, nonhuman primates, and a dog imported into the United

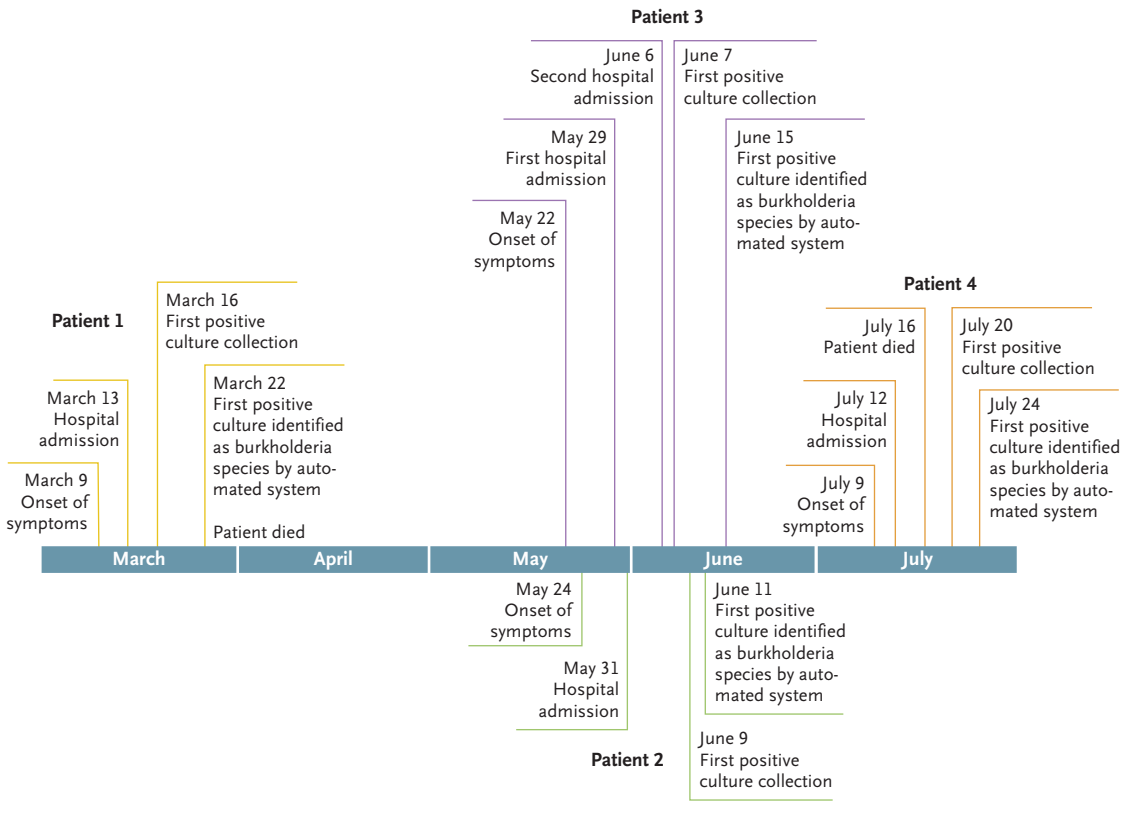


Figure 1. Timeline of Four Cases of Melioidosis between March and July 2021.

Shown are the dates of symptom onset, hospital admission, positive cultures (the collection date and the date of initial identification by automated systems that resulted in consideration of melioidosis), and the patient's death, if applicable. The date of symptom onset is not necessarily specific to a diagnosis of melioidosis because Patients 1, 2, and 4 had coinfections. The date of symptom onset in Patient 3 was estimated on the basis of a family report noted in the medical record and was not necessarily specific to a diagnosis of melioidosis.

States; thus, animals from melioidosis-endemic areas may present a risk of exposure.[12-15]

Genetic analysis of isolates obtained from two patients in the southern United States who had not recently traveled to melioidosis-endemic areas showed that these isolates were related to isolates from the Western Hemisphere. These findings provided evidence supporting the hypothesis that *B. pseudomallei* may be endemic in the southern United States.[2,8] In addition, reports of melioidosis associated with contaminated wound-irrigation fluids and hand detergent indicate the hazard of contaminated products.[16,17]

Here, we report a cluster of four cases of melioidosis that occurred throughout the United States over a period of a few months. Isolates obtained from these four patients were clonal and matched an isolate of *B. pseudomallei* obtained from a bottle of room spray (Better Homes and Gardens brand), labeled as a "highly fragranced essential oil and semi-precious stone infused room spray" with a "lavender and chamomile" scent, that had been imported from India to the United States.

CASE REPORTS

Patient 1, a 53-year-old woman, presented to an emergency department in Kansas on March 13, 2021, with a 4- to 5-day history of shortness of breath, cough, malaise, and weakness (Fig. 1). Her medical history was notable for chronic obstructive pulmonary disease (COPD), cirrhosis due to hepatitis C, coronary artery disease, hypo-

thyroidism, polysubstance abuse (current tobacco use, a positive amphetamine drug screen, and a history of alcohol and cocaine use), and psoriatic arthritis. Interviews with the patient's family members revealed that she did not have a history of international travel.

Computed tomography (CT) of the patient's chest showed subsegmental pulmonary emboli and focal consolidation in the right upper lobe. On admission, her laboratory values were unremarkable except for anemia (hematocrit, 24.7%). Empirical antibiotics (i.e., ceftriaxone and azithromycin) were initiated to treat community-acquired pneumonia and an *Escherichia coli* urinary tract infection that were present at admission. She also received glucocorticoids for COPD exacerbation. On hospital day 4, encephalopathy, hypotension, and respiratory distress developed, prompting her transfer to the intensive care unit (ICU), and the antibiotic regimen was broadened to include vancomycin and cefepime. Blood cultures obtained before the transfer to the ICU grew a gram-negative rod, and the antibiotics were switched to meropenem and levofloxacin. The gram-negative rod was later identified with the use of a Vitek 2 instrument as *B. pseudomallei* (KS2021a isolate). On hospital day 6, septic shock developed, and she received vasopressors and mechanical ventilation. Despite aggressive care, her clinical status continued to decline, and she died on hospital day 9. A postmortem examination was not performed.

Patient 2 was a 4-year-old girl from Texas. On May 31, 2021, she presented to her pediatrician with a 3-day history of fever associated with decreased activity and appetite; this fever was preceded by vomiting for 1 day. She had no clinically significant medical history, and interviews with her parents revealed that she had never traveled outside the United States. Her physical examination was unremarkable except for a temperature of 38.1°C. She received a diagnosis of viral gastroenteritis.

Two days later, she was taken to an urgent care clinic because of continued fever (39.5°C). A chest radiograph was normal, and the white-cell count was 17,700 per cubic millimeter. A urinary tract infection was diagnosed on the basis of a urinalysis, and she was discharged home with amoxicillin–clavulanic acid. Blood cultures showed no growth, and a urine culture grew *E. coli*.

After an initial improvement in her condition, the patient returned to the emergency department 2 days later with intermittent fevers, recurrence of vomiting, and progressive lethargy. She was febrile (38.3°C), tachycardic, and tachypneic, and her white-cell count was 16,000 per cubic millimeter. A respiratory panel was positive for human rhinovirus and enterovirus. She was admitted to the pediatric ICU with a diagnosis of septic shock and meningoencephalitis, and ceftriaxone was initiated. Her trachea was intubated after an episode of oxygen desaturation to 40% following emesis with copious secretions. A course of methylprednisolone was administered early in the course of hospitalization, after the results of magnetic resonance imaging (MRI) aroused concerns regarding acute disseminated encephalomyelitis. Over the course of the patient's stay in the pediatric ICU, her respiratory and neurologic status continued to decline. Given a concern regarding resistant bacterial infection, the antibiotic regimen was broadened to include meropenem and vancomycin.

The diagnosis of melioidosis was confirmed when a lower respiratory culture grew *B. pseudomallei* (TX2021a isolate), which was initially misidentified as *B. thailandensis* on a MALDI-TOF (matrix-assisted laser desorption ionization–time of flight) mass spectrometer. The patient received intravenous meropenem, followed by ceftazidime, for a total of 8 weeks, as well as trimethoprim–sulfamethoxazole, which was then continued as eradication therapy that was planned for an additional 6 months. Three months after discharge, the patient remained wheelchair-bound and nonverbal.

Patient 3, a 53-year-old man, presented to an emergency department in Minnesota on May 29, 2021, after family members found him with altered mental status and weakness. His medical history included alcohol dependence and tobacco use. Interviews with the patient's family members revealed that he did not have a history of international travel. Findings on MRI of the brain were consistent with Wernicke's encephalopathy, and he was admitted to the hospital for treatment of acute metabolic encephalopathy. Hip pain was noted during hospitalization, and images of the pelvis obtained on lumbar MRI showed mild degenerative changes that were considered to be the source of his hip pain. After

6 days, he was discharged to a transitional care facility.

On June 6, the patient was transferred from that facility to the emergency department with fever and declining mental status. His temperature was 40.0°C, and his oxygen saturation was 90% while breathing ambient air. Findings on chest CT were consistent with pneumonia, and meropenem was initiated for possible hospital-acquired or aspiration pneumonia. However, meropenem was later switched to ceftazidime because of the appearance of new-onset rash. Blood cultures grew a gram-negative rod. The patient became afebrile and was weaned off oxygen, but on hospital day 6, the fever returned with worsening right hip pain. MRI of the hip showed an acute inflammatory process that included myositis, possibly a septic hip, and osteomyelitis of the right pelvis.

Culture of the joint aspirate grew a gram-negative rod. The blood culture findings were initially misidentified as *B. thailandensis* on a MALDI-TOF mass spectrometer and as *Sphingomonas paucimobilis* on the Vitek 2 instrument. *B. pseudomallei* (MN2021a isolate) was later identified on cultures of blood and aspirate obtained from the right hip joint. The patient was discharged to a transitional care facility on June 23, 2021. He completed 8 weeks of intravenous ceftazidime, with a plan to receive trimethoprim–sulfamethoxazole for eradication therapy. After discharge, his confusion did not decrease, and he had evidence of osteonecrosis of the infected hip joint.

Patient 4, a 5-year-old boy, presented to an emergency department in Georgia on July 12, 2021, with a 3-day history of weakness, tongue swelling, sore throat, fever, nausea, and vomiting. He did not have a clinically significant medical history, and interviews with his parents revealed that he had never traveled outside the United States. At presentation, he was febrile (38.9°C), tachycardic, and intermittently tachypneic. His white-cell count was elevated at 137,000 per cubic millimeter. A polymerase-chain-reaction assay was positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Findings on initial chest radiography were normal.

The patient was admitted to the hospital for observation and rehydration. Overnight, his oxygen saturation decreased and he was transferred to a pediatric ICU because of concerns regarding impending respiratory failure. A chest radiograph obtained after the transfer showed bilateral opacities with effusions in the lower lobes of both lungs. Remdesivir and dexamethasone were initiated for treatment of coronavirus disease 2019 (Covid-19), and vancomycin and ceftriaxone were initiated given the possibility of superimposed bacterial infection; vancomycin was later switched to linezolid. The patient remained febrile and had declining respiratory status. On day 3 of hospitalization, weakness developed in the right arm. On hospital day 4, the patient's pupils were dilated and nonreactive, and a CT scan showed a large cerebral infarct involving the left cerebral cortex and midbrain. The patient's cardiopulmonary status progressively deteriorated despite full resuscitation measures. He became neurologically unresponsive and died on hospital day 4.

Autopsy revealed lung abscesses and areas of softening and hemorrhage of the cortical white matter, basal ganglia, and brain stem, and a lung swab grew *B. pseudomallei* (GA2021a isolate), which was identified with a Vitek 2 instrument. Histopathological findings showed suppurative necrotizing pneumonia along with hepatic and brain microabscesses, findings consistent with disseminated melioidosis. Immunohistochemical analysis showed *B. pseudomallei* in the lungs, liver, spleen, and brain, as well as SARS-CoV-2 in the lungs and upper-airway tissues (Fig. 2).

LABORATORY TESTING AND RESULTS

We tested many items that the patients had been exposed to, and *B. pseudomallei* was isolated from an aromatherapy room spray obtained from the home of Patient 4. The results of subsequent whole-genome sequencing analysis indicated that the isolate from the spray bottle and those from the four patients were all the same strain, which we have named ATS2021 (i.e., aromatherapy spray 2021). This finding indicates that the spray or a component of the spray was the source of exposure. Strain ATS2021 also clustered with samples of *B. pseudomallei* from South Asia that are consistent with the origin of the spray — India (Fig. 3). Additional information and treatment recommendations are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

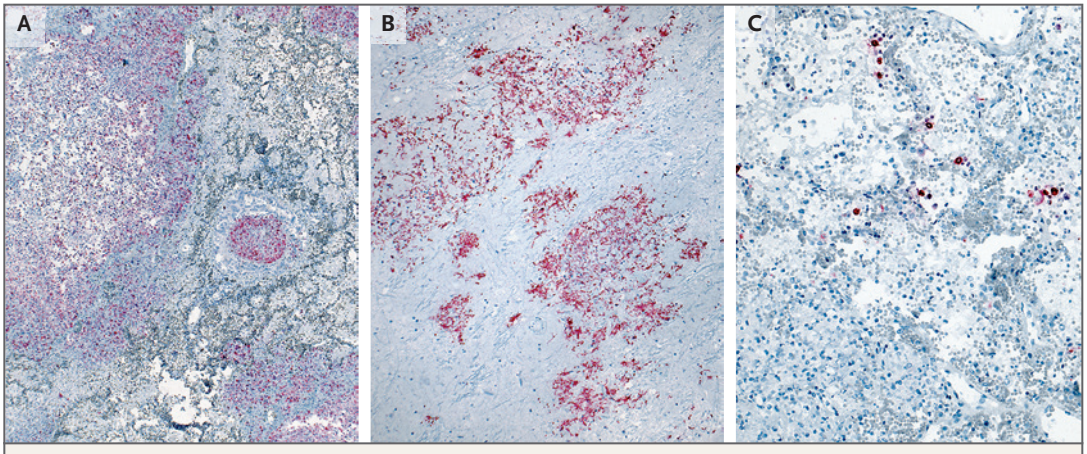


Figure 2. Coinfection Detected on Immunohistochemical Analysis of Tissues at Autopsy in Patient 4.

Panel A shows extensive immunolabeling of *Burkholderia pseudomallei* in the pneumonic lung, and Panel B shows extensive immunolabeling of *B. pseudomallei* within and around microabscesses in the brain. Panel C shows scattered immunolabeling of severe acute respiratory syndrome coronavirus 2 within intraalveolar cells in the lung.

DISCUSSION

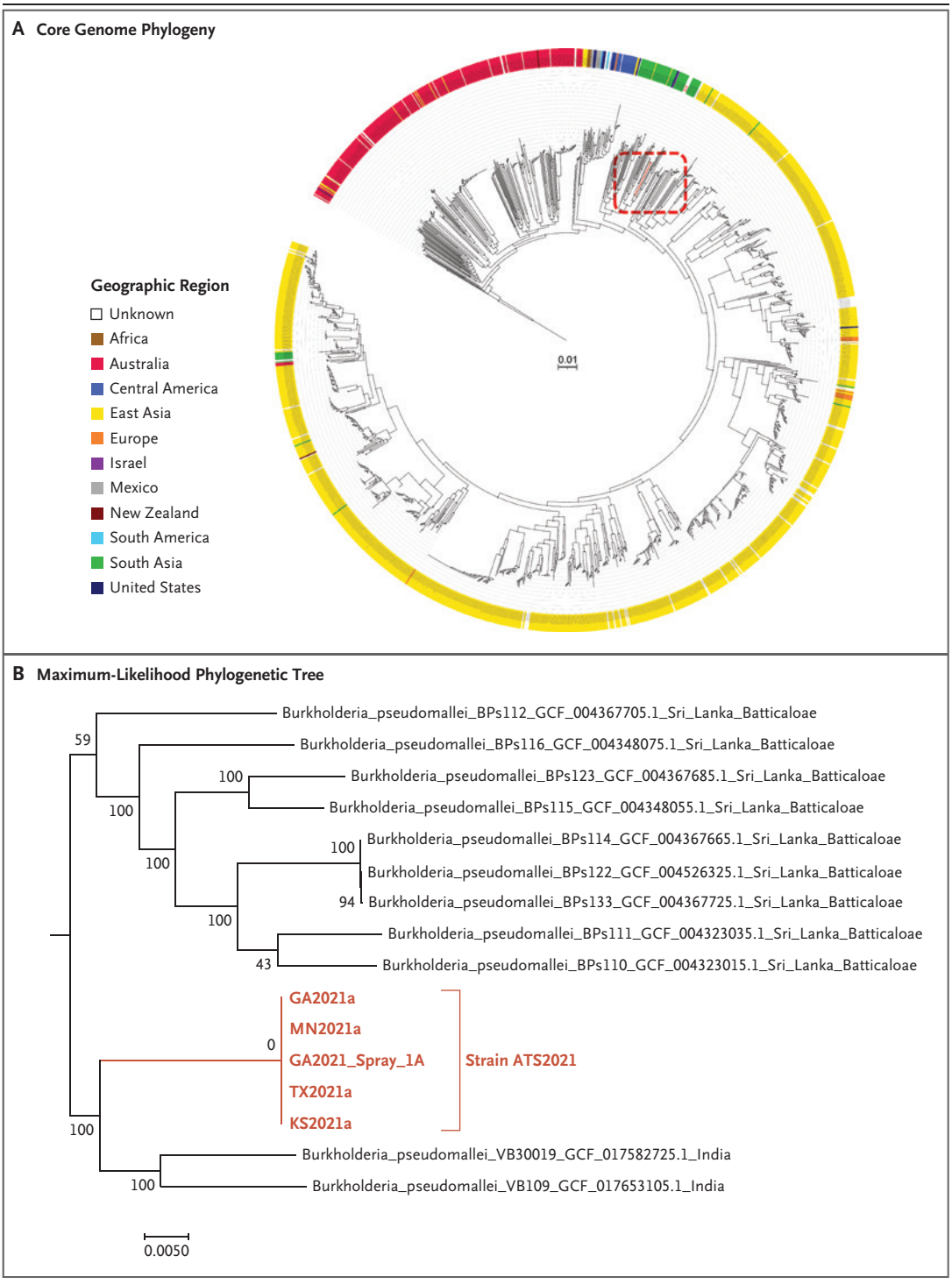
Melioidosis was detected in four U.S. residents who did not have a history of travel to melioidosis-endemic areas but who apparently were exposed to an aromatherapy room spray or a component of the room spray that had been imported from India. Only the two adults had a medical history or conditions that were recognized as risk factors for melioidosis (i.e., COPD, liver disease, and alcohol use in Patient 1 and excessive alcohol use in Patient 3). Melioidosis may not have been considered initially in these patients because they had not traveled to areas where melioidosis is endemic.

All four patients were hospitalized early during their clinical course; however, initial cultures did not reveal *B. pseudomallei* infection. The two adults eventually had positive blood cultures that confirmed melioidosis pneumonia; Patient 1 had progression to fatal septic shock, and Patient 3 survived despite his coexisting conditions and the development of melioidosis-related septic arthritis and osteomyelitis. Severe neurologic melioidosis developed in both children; Patient 2 had a prolonged pediatric ICU stay, with a subsequent protracted and ongoing neurologic recovery. Patient 4 quickly died from disseminated melioidosis that was concomitant with SARS-CoV-2 infection.

All the patients except Patient 3 had received glucocorticoid therapy for different indications before they received a diagnosis of melioidosis. The effect of systemic glucocorticoids on their immune systems could have contributed to the severity of disease. Patient 4 had SARS-CoV-2 coinfection that probably contributed to the severity of his illness. The CDC investigated a previous fatal coinfection of Covid-19 and melioidosis in which the SARS-CoV-2 infection is thought to have reactivated a latent *B. pseudomallei* infection.[18]

Melioidosis is an emerging infectious disease in the United States. Whole-genome sequencing from two previous patients with no recent travel history to melioidosis-endemic areas showed *B. pseudomallei* strains that were most closely related to other strains from the Americas.[8,11] Melioidosis has also been detected in persons who have not traveled to endemic areas and whose bacterial isolates appear to be of South or Southeast Asian origin, with infection postulated to result from contact with contaminated imported products or animals.[6,9-11]

Culture of *B. pseudomallei* from any specimen is diagnostic for the disease. The recommended specimens for culture are guided by the clinical syndrome and include blood, sputum, urine, pus from skin and internal abscesses, joint aspirate, and cerebrospinal fluid. Throat swabs and rectal swabs inoculated into selective mediums increase diagnostic yield. When melioidosis is suspected,



it is advised that the laboratory be informed that cultures may grow *B. pseudomallei* and that staff strictly follow appropriate safety precautions to avoid exposure.[1,3,19]

With the use of identification methods such as MALDI-TOF mass spectrometry and 16S ribosomal RNA gene sequencing and instruments such as Vitek 2 that are used in clinical labora-

Figure 3 (facing page). Phylogenomic Comparisons of *B. pseudomallei* Genomes with Isolates Obtained from the Four Patients and from a Contaminated Aromatherapy Spray Bottle.

The isolates obtained from the four patients (KS2021a, TX2021a, MN2021a, and GA2021a) and an isolate obtained from a contaminated aromatherapy spray bottle (GA2021_Spray_1A) contained strain ATS2021. Panel A shows the core single-nucleotide polymorphism phylogeny of 1696 genomes in which the new isolates were initially placed. Geographic origins were selected from the BioSample database of the National Center for Biotechnology Information, and the specific geographic regions listed were based on definitions from the 2021 *World Factbook* of the Central Intelligence Agency (https://www.cia.gov/the-world-factbook/). Samples of unknown geographic origin are white. The red branch inside the dashed red square denotes the outbreak strains, surrounded by isolates predominantly from South Asia. Panel B shows the high-resolution clade with the closest isolates to the outbreak strain from maximum-likelihood analysis in Parsnp (Harvest, version 1.3) rendered with the use of MEGA X software (https://www.megasoftware.net/).

tories, *B. pseudomallei* may be misidentified as another bacterium. Health care providers are encouraged to reevaluate patients with isolates identified by automated systems as burkholderia species (specifically *B. cepacia* and *B. thailandensis*), *Chromobacterium violaceum*, *Ochrobactrum anthropi*, and possibly aeromonas species, acinetobacter species, and pseudomonas species in order to assess for possible infection with *B. pseudomallei*.[3,20,21] If *B. pseudomallei* is identified or suspected, confirmatory testing should be performed. *B. pseudomallei* is a tier 1 "select agent" under the Federal Select Agent Program and must be reported to either the CDC or the Animal and Plant Health Inspection Service of the U.S. Department of Agriculture according to federal regulations.[3,22]

These cases highlight the risk of melioidosis associated with exposure to imported products from areas where the bacterium is endemic. Health care providers should consider melioidosis in patients with a compatible illness, even if they do not have a history of travel to melioidosis-endemic areas. In addition, patients who have acute respiratory or neurologic symptoms that do not have a response to initial treatment may be candidates for closer assessment for melioidosis.

The conclusions, findings, and opinions expressed by the authors do not necessarily reflect the official position of the U.S. Department of Health and Human Services, the Public Health Service, the Centers for Disease Control and Prevention (CDC), or the authors' affiliated institutions. Use of trade names is for identification only and does not imply endorsement by any of the groups named above.

This work is dedicated to and in memory of Sherif R. Zaki, M.D., Ph.D., the founder and leader of the Infectious Diseases Pathology Branch of the CDC.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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