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Second Nationwide Tuberculosis Outbreak Caused by Bone Allografts Containing Live Cells — United States, 2023

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Abstract

During July 7–11, 2023, CDC received reports of two patients in different states with a tuberculosis (TB) diagnosis following spinal surgical procedures that used bone allografts containing live cells from the same deceased donor. An outbreak associated with a similar product manufactured by the same tissue establishment (i.e., manufacturer) occurred in 2021. Because of concern that these cases represented a second outbreak, CDC and the Food and Drug Administration worked with the tissue establishment to determine that this product was obtained from a donor different from the one implicated in the 2021 outbreak and learned that the bone allograft product was distributed to 13 health care facilities in seven states. Notifications to all seven states occurred on July 12. As of December 20, 2023, five of 36 surgical bone allograft recipients received laboratory-confirmed TB disease diagnoses; two patients died of TB. Whole-genome sequencing demonstrated close genetic relatedness between positive *Mycobacterium tuberculosis* cultures from surgical recipients and unused product. Although the bone product had tested negative by nucleic acid amplification testing before distribution, *M. tuberculosis* culture of unused product was not performed until after the outbreak was recognized. The public health response prevented up to 53 additional surgical procedures using allografts from that donor; additional measures to protect patients from tissue-transmitted *M. tuberculosis* are urgently needed.

Introduction

On July 7, 2023, a state health department notified CDC that an otherwise healthy adult experienced symptoms of meningitis 5 weeks after spinal fusion surgery that incorporated a bone allograft product containing live cells; *Mycobacterium tuberculosis* was identified in the cerebrospinal fluid. On July 11, a different state health department notified CDC of a patient with a persistent surgical site infection after a laminectomy that appeared to have used a similar product; drainage from the surgical site tested positive for acid-fast bacilli, and a nucleic acid amplification test confirmed the presence of *M. tuberculosis*. When reporting these cases to their respective public health authorities, the clinicians caring for these two patients independently noted similarities to the 2021 outbreak (*1*–*4*) and asked that CDC investigate.

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Investigation and Results

Initial Identification

After receiving the first case report, CDC notified the Food and Drug Administration (FDA) and requested that the tissue establishment* quarantine (i.e., store and prohibit use of) any remaining tissue from this donor (i.e., same product lot). On July 11, the tissue establishment quarantined the 53 units that had not yet been distributed and provided a list of all health care facilities that had purchased tissue units from that lot. Eight hospitals and five dental offices in seven states (California, Louisiana, Michigan, New York, Oregon, Texas, and Virginia) received a total of 50 bone allograft units from this product lot during February 27–June 20, 2023.

Public Health Response

On July 12 (within hours of confirming that the two patients in both states had received units from the same product lot), CDC notified the seven affected state health departments, sharing with each a list of health care facilities in their states that had received units of the bone allograft. As during the previous outbreak, CDC recommended that any unused units be quarantined, recipients be evaluated and started on multidrug treatment for TB disease regardless of signs and symptoms (*1*–*4*), and health care facilities implement TB-specific infection prevention and control measures during follow-up encounters with these patients (*5*). These outbreak response activities were reviewed by CDC, deemed not research, and conducted consistent with federal law and CDC policy.†

The deceased donor was a U.S.-born person whose donor risk assessment interview with next of kin documented no TB risk factors. A radiograph of the donor's chest before death demonstrated pulmonary infiltrates and a right upper lobe nodule; pneumonia and sepsis were documented as the causes of death.

By July 14 (1 week after receipt of the first case report by CDC), health departments had worked with affected hospitals and dental facilities to confirm that 36 patients had undergone procedures using at least one unit from the product lot under investigation. Unused units were sent to the National Veterinary Services Laboratories§ for nucleic acid amplification and culture-based testing for *M. tuberculosis*.

As of December 20, 2023, five of the 36 recipients had received a diagnosis of laboratory-confirmed TB disease, including four that were culture-confirmed. The two patients initially reported to CDC in July 2023 both subsequently died with TB as the cause of death. At least 10 other recipients had clinical signs or

*A tissue establishment is defined as an entity that manufactures human cells, tissues, and cellular and tissue-based products and is regulated under 21 C.F.R. part 1271, 42 U.S.C. Sect. 216, 243, 263(a), 264, 265(c), 271. https://www.fda.gov/vaccines-blood-biologics/biologics-establishment-registration/tissue-establishment-registration

†5 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

§https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/lab-info-services/sa_about_nvsl/ct_about_nvsl

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symptoms compatible with TB disease. Among the 34 recipients with test results for *M. tuberculosis* infection reported, 27 (79%) had positive interferon-gamma release assay results. Whole-genome sequencing from culture-confirmed cases among recipients in four different states, along with positive *M. tuberculosis* cultures from the unused product, demonstrated an extremely close relationship with 0–1 single nucleotide polymorphism difference between *M. tuberculosis* genomes, confirming the bone allograft as the transmission source.

Discussion

Significance and Interpretation of Findings

This second nationwide TB outbreak in 2023 was detected when clinicians in two states recognized similarities to the 2021 outbreak and reported their concerns to their respective health departments, thereby initiating a rapid public health response that prevented as many as 53 additional surgical procedures with the implicated bone allograft material. Before the 2021 TB outbreak, which involved 113 recipients in 18 states, bone allograft–related *M. tuberculosis* transmission had last been reported in the United Kingdom in 1953 (*1*–*6*).

After the 2021 outbreak, tissue establishments considered whether to perform nucleic acid amplification testing for *M. tuberculosis* in tissues that retain live cells before distribution (*7*). The tissue establishment involved in both investigations voluntarily implemented such testing for bone allografts but did not detect the *M. tuberculosis* contamination of this second product lot.[¶] Although extremely useful for diagnosing TB disease, nucleic acid amplification tests are less sensitive than are the slower culture-based tests for identifying *M. tuberculosis* (*2*). Therefore, more comprehensive laboratory evaluations for *M. tuberculosis* in donor tissues could include culture-based testing, which can take up to 8 weeks (56 days) for final confirmation. In this outbreak, *M. tuberculosis* was not identified from liquid cultures of the donor specimen until day 40 after inoculation.

Because false-negative culture results can occur, laboratory testing alone will not eliminate the risk of transmitting *M. tuberculosis* or other infectious agents through tissue products. Careful review of donor information with exclusion of those who do not meet current requirements (i.e., the donor is ineligible) is also critical. Both donors in the 2021 and 2023 outbreaks had evidence of sepsis during terminal hospitalization, but no TB testing was documented. Persons with evidence of sepsis should be determined to be ineligible for tissue donation (*8*). The second donor also had pneumonia and radiographic findings consistent with, but not specific for, TB disease.

Low *M. tuberculosis* concentrations in the bone allograft material might explain the negative nucleic acid amplification test results before distribution and why the positive culture from quarantined product did not occur within the 14–21-day period during which *M. tuberculosis* is typically isolated from culture (*9*). Low-level contamination could also help explain the apparently lower rate of symptomatic TB disease among recipients in this 2023 outbreak compared with the 2021 outbreak (*2*–*5*). In addition, prompt treatment might have interrupted the disease process and prevented morbidity. Identification of this outbreak likely facilitated initiation of multidrug treatment for some recipients before they might have otherwise become symptomatic. Nevertheless, five persons developed laboratory-confirmed TB disease, including two persons who died of TB after surgical implantation of this contaminated product.

Implications for Public Health Practice

The tissue transplant industry is growing, with approximately 58,000 donors providing tissue allografts for 2.5 million transplants in the United States each year.[**] Additional interventions are necessary to address gaps in transplant tissue safety in the United States. Informed consent, including discussion of infectious disease risks and alternative treatment options, is needed before patients receive tissue allografts, particularly those containing live cells, which carry a higher risk for disease transmission (*2*,*10*). Health care facilities should also implement tissue-tracking protocols similar to those required for solid organs and blood products (*10*). Routine postimplant monitoring should be conducted on all tissue allograft recipients, because prompt and systematic reporting of adverse events enables rapid implementation of mitigation measures among other recipients (*10*).

This outbreak serves as another reminder that TB has not been eliminated from the United States, where up to 13 million persons of all ages are living with untreated and often undiagnosed latent TB infection (LTBI).[††] Diagnosing LTBI and TB disease is challenging because diagnostic tests have imperfect sensitivity. In addition, LTBI is asymptomatic, and nonspecific TB disease signs and symptoms overlap with many other disease processes. Because tissue allografts containing live cells are stored frozen and have expiration dates months or even years after manufacture, ample time exists for both culture-based testing and additional scrutiny of donor medical records. To reduce the risk for *M. tuberculosis* transmission through tissue allografts, culture-based testing of donor tissues before product distribution should be strongly considered, and current recommendations stipulating rejection of donors with sepsis[§§] should be followed.

[¶] https://investors.aziyo.com/news-releases/news-release-details/aziyo-biologics-announces-voluntary-recall-viable-bone-matrix

[**] https://donatelife.net/donation/organs/tissue-donation/

[††] https://www.cdc.gov/tb/statistics/ltbi.htm

[§§] https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/tissue-guidances

Summary

What is already known about this topic?

Tuberculosis (TB) outbreaks associated with tissue transplantation are rare; one outbreak involving 113 patients occurred after surgical implantation of contaminated bone allografts in 2021.

What is added by this report?

Noting similarities to the 2021 outbreak, clinicians diagnosed and promptly reported two TB cases among bone allograft recipients. These case reports initiated an investigation that confirmed a bone allograft–related outbreak affecting 36 recipients. Removal of the product from further distribution prevented implantation of the implicated allografts in up to 53 additional persons.

What are the implications for public health practice?

This second outbreak of bone allograft–related TB in recent years underscores the urgent need to implement improved donor screening and culture-based testing to prevent tissue-derived *Mycobacterium tuberculosis* transmission.

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