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# Nationwide tuberculosis outbreak in the USA linked to a bone graft product: an outbreak report

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## Summary

**Background** ***Mycobacterium tuberculosis*** **transmission through solid organ transplantation has been well described, but transmission through transplanted tissues is rare. We investigated a tuberculosis outbreak in the USA linked to a bone graft product containing live cells derived from a single deceased donor.**

**Methods In this outbreak report, we describe the management and severity of the outbreak and identify opportunities to improve tissue transplant safety in the USA. During early June, 2021, the US Centers for Disease Control and Prevention (CDC) worked with state and local health departments and health-care facilities to locate and sequester unused units from the recalled lot and notify, evaluate, and treat all identified product recipients. Investigators from CDC and the US Food and Drug Administration (FDA) reviewed donor screening and tissue processing. Unused product units from the recalled and other donor lots were tested for the presence of *M tuberculosis* using real-time PCR (rt PCR) assays and culture. *M tuberculosis* isolates from unused product and recipients were compared using phylogenetic analysis.**

**Findings The tissue donor (a man aged 80 years) had unrecognised risk factors, symptoms, and signs consistent with tuberculosis. Bone was procured from the deceased donor and processed into 154 units of bone allograft product containing live cells, which were distributed to 37 hospitals and ambulatory surgical centres in 20 US states between March 1 and April 2, 2021. From March 3 to June 1, 2021, 136 (88%) units were implanted into 113 recipients aged 24–87 years in 18 states (some individuals received multiple units). The remaining 18 units (12%) were located and sequestered. 87 (77%) of 113 identified product recipients had microbiological or imaging evidence of tuberculosis disease. Eight product recipients died 8–99 days after product implantation (three deaths were attributed to tuberculosis after recognition of the outbreak). All 105 living recipients started treatment for tuberculosis disease at a median of 69 days (IQR 56–81) after product implantation. *M tuberculosis* was detected in all eight sequestered unused units tested from the recalled donor lot, but not in lots from other donors. *M tuberculosis* isolates from unused product and recipients were more than 99·99% genetically identical.**

**Interpretation Donor-derived transmission of *M tuberculosis* via bone allograft resulted in substantial morbidity and mortality. All prospective tissue and organ donors should be routinely assessed for tuberculosis risk factors and clinical findings. When these are present, laboratory testing for *M tuberculosis* should be strongly considered.**

**Funding** None.



## Introduction

Donor-derived tuberculosis after solid organ transplantation has been well described in high-incidence and low-incidence countries and carries a high mortality risk.[1,2] However, *Mycobacterium tuberculosis* transmission through tissue grafts is rare. Case reports have shown transmission via bone,[3] heart valve,[4] and dura mater[5] grafts. Tuberculosis transmission can occur from donors with undetected tuberculosis disease or latent tuberculosis infection,[1] which is estimated to affect one quarter of the world's population[6] and 5% of the US population.[7] Despite this high prevalence, current regulations in the USA do not require organ or tissue donors to be assessed for tuberculosis or tuberculosis risk factors, and laboratory testing for *M tuberculosis* is not routinely performed.[8,9]

In the summer of 2021, we investigated an unprecedented outbreak of tuberculosis in the USA linked to a bone allograft product containing live cells derived from a single deceased donor. On May 25, 2021, a Delaware hospital notified public health authorities about an unusual cluster of tuberculosis cases in patients who had undergone spinal surgery, involving implantation of bone allograft material from a single product lot. On June 2, 2021, the manufacturer issued a voluntary nationwide recall of that product lot.[10] The same day, a different state health department notified the US Centers for Disease Control and Prevention (CDC) about another tuberculosis case in a surgical patient

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See Comment page 1522

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See Online for appendix

## Research in context

### Evidence before this study

Our preliminary report published in September, 2021, showed high attack rates of spinal and disseminated tuberculosis in bone allograft recipients at a single hospital. To identify previous reports of tuberculosis transmission through transplanted tissues, we searched PubMed for articles published between database inception and Nov 1, 2021, using the search terms "tuberculosis" and "transplant", "transplantation", "graft", or "allograft". We also reviewed regulatory and guidance documents from the US Food and Drug Administration, Centers for Medicare and Medicaid Services, American Association of Tissue Banks, and the Organ Transplantation and Procurement Network. We found three previous case reports of tuberculosis transmission through transplanted tissues and no current US regulations, guidelines, or professional standards that adequately address tuberculosis screening for tissue donors.

### Added value of this study

We provide a detailed description of the largest recorded tissue-derived tuberculosis outbreak, including multiple lines of evidence supporting donor-derived transmission; the incidence and severity of tuberculosis disease among all product recipients in the USA; and the rapid and effective response by public health authorities. We show that standard screening was unsuccessful at detecting infection in the donor and donated tissues, and we propose measures to improve safety of tissue and organ donation. Based on our investigation, the American Association of Tissue Banks issued new recommendations for preventing tissue-derived tuberculosis transmission.

### Implications of all the available evidence

All prospective tissue and organ donors should be routinely assessed for risk factors and clinical findings of tuberculosis. When these are present, laboratory testing for *Mycobacterium tuberculosis* should be strongly considered.

exposed to the same product lot. Initial investigations in Delaware have been described previously.[11] We describe nationwide efforts to sequester unused product, evaluate and treat product recipients, and identify opportunities to improve tissue transplant safety in the USA.

## Methods

### Study design

In this outbreak report, we describe the tuberculosis outbreak management, frequency and severity of tuberculosis among product recipients, procedures used to screen the tissue donor and donated tissues, and clinical and laboratory evidence for donor-derived transmission. To facilitate tracking of units from the recalled product lot, the product manufacturer immediately provided CDC with records of recipient health-care facilities and shipment dates. During early June, 2021, CDC worked with state and local health departments and health-care facilities to locate and sequester unused units from the recalled lot and notify and evaluate all identified recipients. This investigation was reviewed by CDC and conducted according to federal law and CDC policy (eg, 45 CFR part 46, 21 CFR part 56, 42 USC Section 241(d), 5 USC Section 552a, and 44 USC Section 3501). CDC determined this investigation constituted an emergency public health activity; thus, institutional board review and informed consent were not required.

### Donor and recipients

Information regarding the donor's medical history and social behaviour, including travel history, was collected by a donor specialist from a person considered knowledgeable using a standard donor risk assessment interview form.[12] CDC and US Food and Drug Administration (FDA) investigators worked with the tissue recovery firm and product manufacturer to review the donor's medical history, screening and testing records, and tissue recovery and processing procedures.

For all identified product recipients, investigators extracted demographic, clinical, laboratory, and imaging data from medical records using standardised case report forms. When data were missing from case report forms, equivalent data were obtained from provisional tuberculosis surveillance forms routinely submitted by state health departments to CDC.[13] Recipients were classified as having microbiological evidence of tuberculosis disease if acid-fast bacilli were detected by smear microscopy or *M tuberculosis* was detected by nucleic acid amplification testing or culture in a clinical specimen. Three CDC clinicians independently reviewed the available data from imaging reports and classified findings as consistent or inconsistent with tuberculosis disease; discrepancies were resolved by consensus. Recipients with positive mycobacterial testing or imaging consistent with tuberculosis disease were classified as having evidence of tuberculosis disease in the spine or paraspinal soft tissues or other surgical site, lungs, CNS, or other sites. For recipients who died, state health departments reported whether tuberculosis was the cause of death on the basis of death certificates, medical records, and an autopsy report.

### Procedures

Samples of unused product units from the recalled lot and other donor lots, processed at the same manufacturing facility within 12 weeks, were tested at

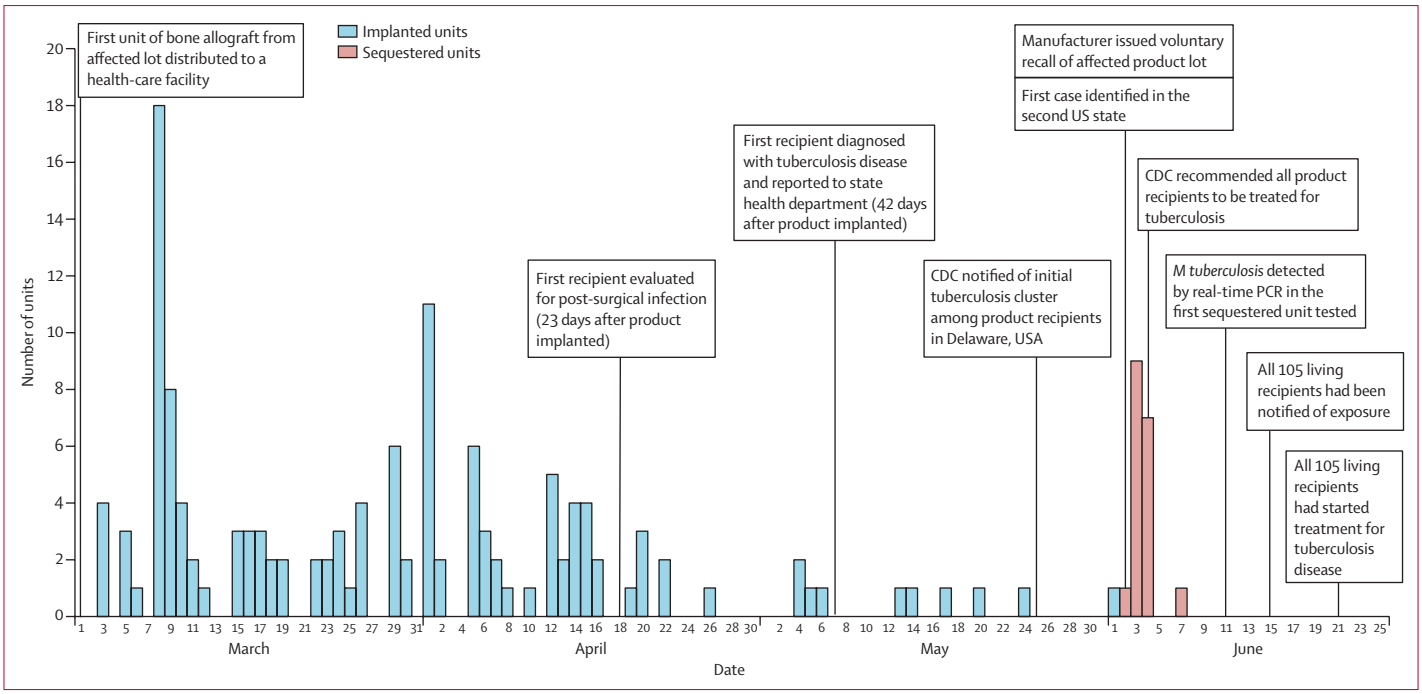


***Figure 1:*** **Timeline of use or sequestration of 154 bone allograft units containing *Mycobacterium tuberculosis* in 20 US states from March to June, 2021**
CDC=US Centers for Disease Control and Prevention.

the National Veterinary Services Laboratories (Ames, IA, USA) for the presence of *M tuberculosis* using real-time PCR (rt PCR) assays that amplified IS*1081* and IS*6110* insertion elements. *M tuberculosis* was cultured from unused products using BD BACTEC Mycobacterial Growth Indicator tubes (Becton Dickinson, Franklin Lakes, NJ, USA) and solid media. The National Tuberculosis Molecular Surveillance Center (Lansing, MI, USA) performed whole-genome sequencing and CDC performed phylogenetic analysis to determine the genetic relatedness of *M tuberculosis* isolates from unused product and product recipients. CDC performed molecular detection of drug resistance and growth-based drug susceptibility testing for an *M tuberculosis* isolate from the first unused product unit. State and local public health laboratories performed routine growth-based drug susceptibility testing for isolates from product recipients. Full methods are shown in the appendix (p 7).

### Statistical analysis

Deidentified data were stored in a secure REDCap database (version 12.0.8) hosted at CDC.[14] Descriptive statistics were calculated using SAS (version 9.4).

### Role of the funding source

There was no funding source for this investigation.

## Results

Bone was procured from a deceased donor and processed into 154 units of bone allograft product containing live cells, which were distributed to 37 hospitals and ambulatory surgical centres in 20 US states between March 1 and April 2, 2021. From March 3 to June 1, 2021, 136 (88%) units were implanted into 113 recipients in 18 states (figure 1; figure 2; some individuals received multiple units). After the manufacturer issued a voluntary recall of the affected product lot between June 2 and 7, 2021, the remaining 18 units (12%) were located and sequestered (eight were sent for *M tuberculosis* laboratory testing and ten were returned to the manufacturer). Seven (6%) of 113 product recipients died before outbreak detection and one (1%) died the day after being notified of exposure to the product. All 105 (93%) living recipients were notified of tuberculosis exposure by June 15, 2021. Eight (8%) of 105 living recipients began tuberculosis treatment before outbreak detection and the remaining 97 (92%) began tuberculosis treatment by June 21, 2021.

The tissue donor was a man aged 80 years who lived in the USA with previous residence in, and frequent travel to, a country with annual tuberculosis incidence greater than 20 cases per 100 000 population, a rate approximately 8·5 times higher than in the USA. The donor did not have a known history of latent tuberculosis infection or tuberculosis disease, exposure to tuberculosis, incarceration, homelessness, drug use, or excessive alcohol consumption. Risk factors for progression of tuberculosis disease included end-stage renal disease and type 2 diabetes. Other medical conditions were coronary artery disease, biventricular

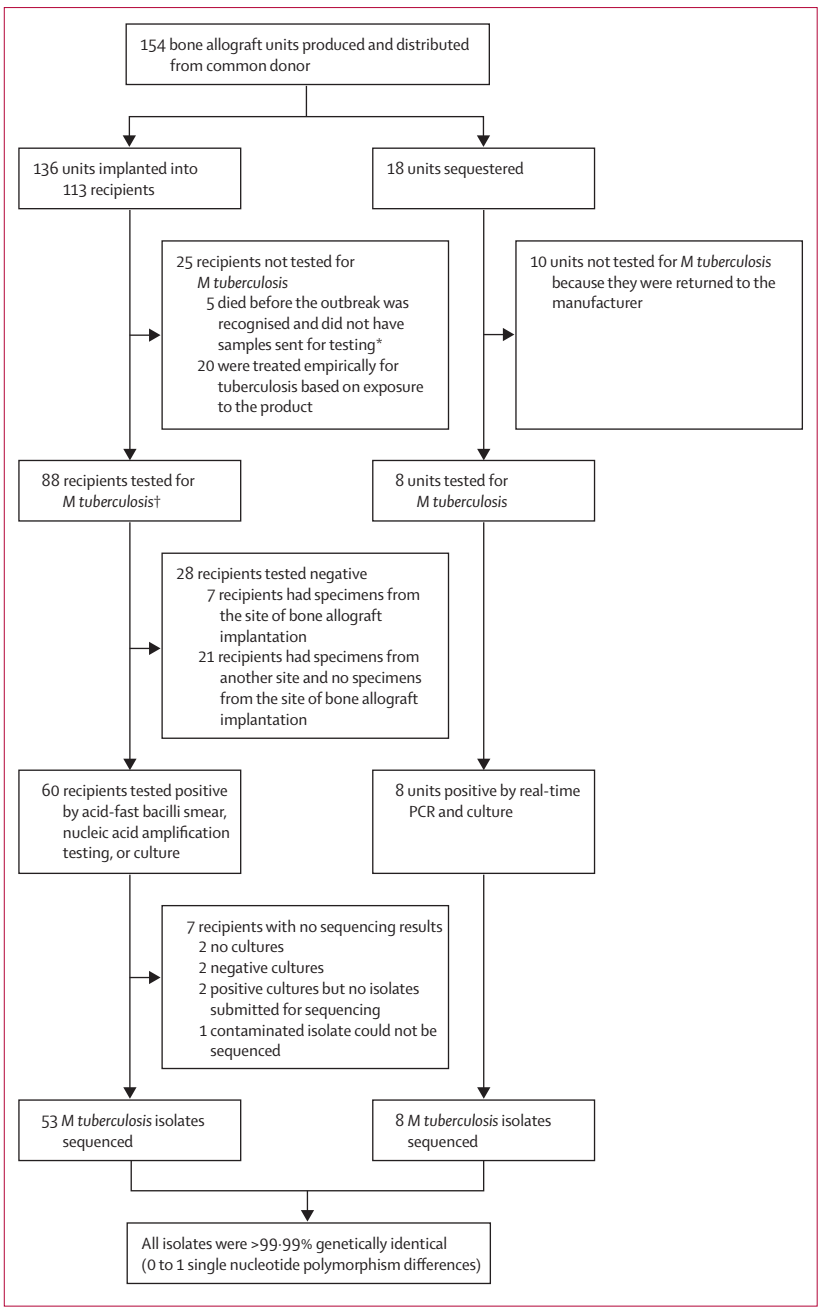


***Figure 2:* *Mycobacterium tuberculosis* testing of bone allograft recipients and sequestered units from the recalled product lot**
*Eight product recipients died in total (five were not tested and three were tested for *M tuberculosis*). †Includes the three deceased recipients who were tested.

heart failure, and sleep apnoea which required nocturnal supplemental oxygen.

The donor was admitted to hospital after 2–3 weeks of progressive dyspnoea, cough, orthopnoea, and lower extremity oedema after missing dialysis sessions. Initial laboratory evaluation revealed a normal white blood cell count with 89% neutrophils ($4·2\times10^9$/L), anaemia (haemoglobin 10·7 g/dL [6·64 mmol/L]), thrombocytopenia ($50\times10^9$/L), elevated procalcitonin (3·35 µg/L), and elevated ferritin (1416 µg/L). Initial chest radiography revealed patchy bilateral airspace opacities with a small pleural effusion. During hospital stay, the donor underwent dialysis and was treated for presumed community-acquired pneumonia. He subsequently developed bradycardia and cardiac arrest, and underwent extended cardiopulmonary resuscitation. After resuscitation, he developed persistent hypotension requiring vasopressors and had elevated white blood cell count ($14·6\times10^9$/L), lactic acid (7·8 mmol/L), procalcitonin (4·97 µg/L), liver aminotransferase, and bilirubin. Chest radiographs revealed evolving bilateral airspace opacities and bilateral pleural effusions. Abdominal ultrasound showed hepatosplenomegaly and ascites. Aerobic and anaerobic bacterial blood cultures drawn during initial evaluation and after resuscitation showed no growth. No mycobacterial testing was performed. 3 days after cardiac arrest, the donor was transitioned to comfort-focused care and died. Treating providers attributed the cause of death to cardiogenic shock and presumed hypoxic brain injury due to cardiac arrest.

The standard donor risk assessment interview noted signs and symptoms compatible with tuberculosis. However, medical records attributed the donor's cough and dyspnoea to heart failure and renal failure. Additionally, the donor's proxy attributed the 35 kg weight loss over 2 years to dietary changes. The proxy reported no knowledge of previous tuberculosis, positive testing for *M tuberculosis* infection, or household exposure to tuberculosis. Outbreak investigators identified that the donor had a negative tuberculin skin test performed at a dialysis centre 4 months before admission to hospital. At that time, he had completed a tuberculosis risk assessment questionnaire, answering no to all questions. Standard donor testing for hepatitis B and C, HIV, syphilis, and human T-lymphotropic virus was negative.

The long bones of the upper and lower extremities and pelvis were recovered from this donor; vertebrae were not recovered. Tendons, fascia lata, and skin were also recovered from this donor but were not implanted into patients. Recovered bones were manufactured into a product that included demineralised cortical bone and cancellous bone processed to retain live cells.[15] The manufacturer performed bioburden testing on samples collected during processing and from the final product to examine for bacteria and fungi, but not *M tuberculosis*.[15]

Baseline characteristics of product recipients are shown in table 1. The median age of recipients was 61 (IQR 52–71). 57 (50%) of 113 recipients were women and 91 (81%) were non-Hispanic White. Of 103 recipients with available data, only one (1%) was born in a country with tuberculosis incidence of 20 cases or greater per 100 000 population. 12 (11%) of 113 recipients were immunocompromised. 112 (99%) recipients had bone allograft implantation into the spine.

| | Identified product recipients (n=113) |
|---|---|
| Age, years | 61 (52–71) |
| Sex | |
| Female | 57/113 (50%) |
| Male | 56/113 (50%) |
| Race and ethnicity | |
| White, non-Hispanic | 91/112 (81%) |
| Black or African American, non-Hispanic | 17/112 (15%) |
| Hispanic or Latino | 2/112 (2%) |
| American Indian or Alaska Native, non-Hispanic | 1/112 (1%) |
| Multiple races, non-Hispanic | 1/112 (1%) |
| Country of birth | |
| USA | 98/103 (95%) |
| Another country with annual tuberculosis incidence <20 cases per 100 000 population | 4/103 (4%) |
| Country with annual tuberculosis incidence ≥20 cases per 100 000 population | 1/103 (1%) |
| Underlying conditions | |
| Obesity | 47/106 (44%) |
| Type 1 or 2 diabetes | 29/112 (26%) |
| Immunocompromising condition or medication* | 12/113 (11%) |
| Liver disease | 8/112 (7%) |
| End-stage renal disease | 2/112 (2%) |
| Site of bone allograft implantation | |
| Cervical spine | 42/113 (37%) |
| Cervical and thoracic spine | 6/113 (5%) |
| Thoracic and lumbosacral spine | 6/113 (5%) |
| Lumbosacral spine | 58/113 (51%) |
| First metatarsal | 1/113 (1%) |
| Volume of bone allograft implanted, mL | 5 (1–10) |

Data are n/N (%) or median (IQR). Denominators include recipients with available data for each variable. *Three patients had a history of solid organ transplantation, three received treatment for a malignancy or had a malignancy diagnosed in the previous 12 months before data collection, two received tumour necrosis factor α antagonists, one had HIV and was given antiretroviral therapy (CD4 T-lymphocyte count of 454 cells per mm$^3$), one received chronic corticosteroids, and two received other unspecified immunosuppressive medication.

***Table 1:*** **Baseline characteristics of patients who received a bone allograft product containing *Mycobacterium tuberculosis***

| | Identified product recipients (n=113) |
|---|---|
| **Clinical signs and symptoms** | |
| Surgical site* | 81/110 (74%) |
| Constitutional† | 74/110 (67%) |
| Neurological‡ | 43/110 (39%) |
| Pulmonary§ | 36/110 (33%) |
| Other¶ | 24/110 (22%) |
| None documented | 12/110 (11%) |
| **Evidence of tuberculosis disease** | |
| Positive acid-fast bacilli smear, nucleic acid amplification test, or culture‖ | 60/88 (68%) |
| Imaging consistent with tuberculosis disease** | 84/112 (75%) |
| Either | 87/113 (77%) |
| **Site of tuberculosis disease††** | |
| Surgical site | 83/113 (73%) |
| Spine or paraspinal soft tissues | 82/113 (73%) |
| Foot | 1/113 (1%) |
| Any other site | 28/113 (25%) |
| Lungs | 27/113 (24%) |
| CNS‡‡ | 3/113 (3%) |
| Blood | 3/113 (3%) |
| Bone marrow | 1/113 (1%) |
| Liver | 1/113 (1%) |
| **Complications** | |
| Hospital readmission related to bone graft implantation | 55/110 (50%) |
| Surgical drainage, debridement, or hardware removal | 48/111 (43%) |
| Death | 8/113 (7%) |
| Cause of death related to tuberculosis | 3/8 (38%) |
| Cause of death not related to tuberculosis | 3/8 (38%) |
| Cause of death unknown | 2/8 (25%) |

Data are n/N (%). Denominators include recipients with available data for at least one measure. *Including pain, erythema, wound dehiscence, and wound drainage. †Including fever, chills, night sweats, weight loss, fatigue, and loss of appetite. ‡Including paresthesia, upper or lower extremity weakness, bowel or bladder dysfunction, confusion, altered mental status, and headache. §Including cough, shortness of breath, and sputum production. ¶Including dizziness, dysphagia, odynophagia, chest pain, nausea, vomiting, diarrhoea, and joint pain. ‖88 recipients had microbiological results available from at least one specimen (63 recipients with surgical site, 58 with pulmonary, five with cerebrospinal fluid, and seven with other specimens; appendix pp 8–9). **112 recipients had available imaging results from at least one site (106 recipients with surgical site imaging, 110 with pulmonary imaging, and three with CNS imaging; appendix pp 8–9). ††Includes recipients with microbiological or imaging evidence of tuberculosis disease. ‡‡One additional recipient had clinically diagnosed tuberculous meningitis based on cerebrospinal fluid cell counts, protein, and glucose, but no microbiological or imaging evidence of tuberculosis.

***Table 2:*** **Clinical findings in patients who received a bone allograft product containing *Mycobacterium tuberculosis***

Table 2 describes clinical findings in identified product recipients at a median of 161 days (IQR 148–177) after product implantation. Among 110 recipients with available symptom data, 98 (89%) reported new clinical signs or symptoms after product implantation. The most common symptoms were at the surgical site (81 [74%]), followed by constitutional (74 [67%]), neurological (43 [39%]), and pulmonary (36 [33%]) symptoms.

87 (77%) of 113 identified product recipients had microbiological or imaging evidence of tuberculosis disease (table 2; appendix pp 8–9). 83 (73%) recipients had disease at the surgical site and 28 (25%) had dissemination to other sites. Median time from product implantation to first microbiological or imaging evidence of tuberculosis was 65 days (IQR 49–78). Among 88 recipients who had specimens tested for *M tuberculosis*, 60 (68%) were positive by smear microscopy, nucleic acid amplification testing, or culture (table 2; appendix pp 8–9). Surgical site imaging findings were available for 106 recipients; 80 (75%) had

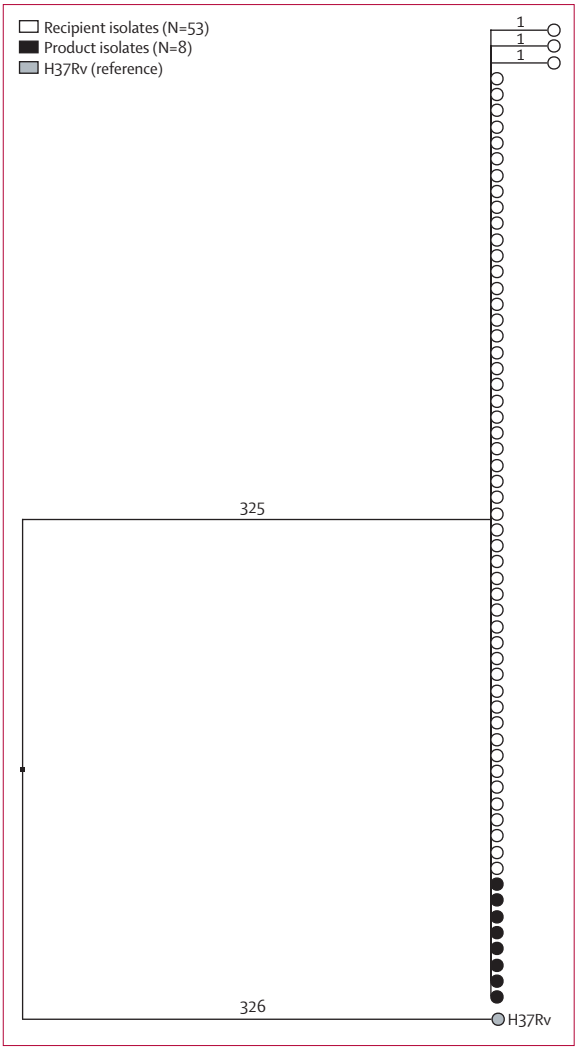


***Figure 3:*** **Phylogenetic tree of *Mycobacterium tuberculosis* isolates from bone allograft recipients and sequestered units**
Constructed with BioNumerics (version 7.6) using the neighbor-joining method. *M tuberculosis* strain H37Rv was used as the outgroup and the phylogenetic tree was rooted at the midpoint of the longest branch. The horizontal branch lengths represent genetic divergence on a logarithmic scale, and the number of single nucleotide polymorphisms is shown on each branch.

at least one finding consistent with tuberculosis (69 [65%] with abscesses or fluid collections, 36 [34%] with osteomyelitis, and 18 [17%] with discitis; appendix p 8). Among 110 recipients with available pulmonary imaging, 23 (21%) had findings consistent with tuberculosis (including 13 [12%] with miliary lesions, 19 [17%] with multifocal nodular lesions, and three [3%] with cavitary lesions; appendix p 8). CT or MRI of the brain was available for seven recipients, and CT or MRI of the spinal cord was available for 101. Three had imaging abnormalities consistent with CNS tuberculosis (two had brain tuberculomas and one had leptomeningeal enhancement of the cervical spine; appendix p 8).

55 (50%) of 110 recipients with available data were readmitted to hospital for product-related complications. 48 (43%) of 111 recipients underwent additional surgical procedures to treat tuberculosis-related complications (including 25 [22%] who had the allograft and associated hardware removed). Eight (7%) of 113 product recipients died 8–99 days after product implantation. After recognition of the outbreak, state health officials attributed three deaths to tuberculosis and three to unrelated causes; insufficient data were available to determine the cause of the remaining two deaths. All 105 living recipients started treatment for tuberculosis disease at a median of 69 days (IQR 56–81) after product implantation.

*M tuberculosis* was detected in all eight sequestered units from the recalled donor lot (figure 2). Liquid culture detected *M tuberculosis* at a median of 14·6 days (IQR 14·2–16·3) after inoculation, indicating a high mycobacterial load.[16] *M tuberculosis* rt-PCR and cultures were negative for all 11 tested units from other donor lots. *M tuberculosis* isolates from 53 product recipients and eight unused product units were sequenced and shared a unique genotype, which has not been previously identified in the USA. Isolates from 50 product recipients and eight sequestered units were genetically identical; three recipient isolates differed from the others by only a single nucleotide polymorphism (>99·99% identical; figure 3).

Growth-based drug susceptibility test results were available for 40 recipients. All 40 *M tuberculosis* isolates were susceptible to first-line medication (rifampicin, isoniazid, pyrazinamide, and ethambutol). No resistance to first-line or second-line medication was found with molecular or growth-based testing for an isolate from the first sequestered product unit.

In November, 2021, culture-confirmed tuberculosis with an isolate more than 99·99% identical to those from the recalled product units and recipients was reported in one additional person who had undergone bone allograft implantation in April, 2021. This patient's surgery occurred at a health-care facility with an inventory of the recalled lot and lots from other donors. Records indicated that the implanted product was not from the recalled lot. Investigation of this case was ongoing as of July, 2022.

## Discussion

This study found strong evidence of donor-derived transmission of *M tuberculosis* through the use of a bone allograft product containing live cells, resulting in spinal and disseminated tuberculosis in most (77%) product recipients residing in 15 US states. Rapid collaborative action by public health agencies, health-care facilities, and the product manufacturer enabled sequestration of 18 unused product units within 5 days of the recall and initiation of tuberculosis treatment by all 105 identified living recipients within 4 weeks of outbreak detection, which prevented morbidity. Nonetheless, half of the identified recipients required hospital readmission,

43% underwent repeat surgeries for tuberculosis-related complications, and at least three died from tuberculosis-related causes. Standard screening practices during tissue donation were unsuccessful at identifying donor infection and additional measures are needed to enhance recipient safety.

Although most product recipients were immunocompetent, tuberculosis developed rapidly and disseminated past the site of allograft implantation in 25% of recipients, probably because of several factors. First, the product contained a high mycobacterial load. In human and animal studies of pulmonary tuberculosis, the inhaled quantity of *M tuberculosis* has been shown to predict disease progression.[17] Second, mycobacteria were inoculated directly into skeletal sites, bypassing immune defences in the respiratory system.[18] Third, postoperative hyperaemia and vascular permeability might have facilitated dissemination of mycobacteria to other body sites.[19] Fourth, product contents (eg, live cells[20] and bone morphogenetic proteins[21]) could have supported mycobacterial growth. Regardless of the underlying mechanisms, the high attack rate and severe complications justified treating all identified product recipients for tuberculosis disease—even those few without apparent signs or symptoms. For many patients in this outbreak, optimal treatment will require ongoing collaboration between medical and surgical specialists, close monitoring, and possibly longer courses of therapy.

Close genetic similarity of *M tuberculosis* isolates between product recipients and sequestered product units confirms that the product lot was the source of this tuberculosis outbreak. The high mycobacterial load in all tested bone allograft material suggests that this tissue donor had undiagnosed disseminated tuberculosis disease with bone marrow involvement at death. A retrospective review of records identified epidemiological and clinical risk factors for tuberculosis infection and disease progression, and non-specific clinical findings compatible with disseminated tuberculosis. The donor's tuberculin skin test result 4 months before death might have been a false-negative, which can occur due to impaired T-lymphocyte function in individuals with end-stage renal[22] and tuberculosis disease.[23] Errors in test interpretation could have also occured.[24]

Based on the findings from this report, actions to reduce the risk of future transmission should be considered. First, because *M tuberculosis* can infect diverse cell types throughout the body,[20] all prospective organ and tissue donors should be routinely screened for a previous diagnosis or positive test for tuberculosis infection or disease; risk factors for tuberculosis infection and disease progression; and clinical signs and symptoms of tuberculosis using medical history, physical examination, and chest imaging. In the USA, key epidemiological risk factors for tuberculosis infection include previous exposure to tuberculosis; birth, residence, or travel in a country with a high incidence of tuberculosis; incarceration; homelessness; and residence or work in a congregate setting (eg, correctional facility, shelter for people experiencing homelessness, or a long-term care facility).[25] Key clinical risk factors for tuberculosis infection and disease progression include injection and non-injection drug use, excessive alcohol consumption, and conditions and medication that can impair immune function (eg, HIV infection, advanced kidney disease, or chronic corticosteroid use).[25]

Second, for solid organ donors with a history or findings compatible with tuberculosis disease or latent tuberculosis infection, mycobacterial testing of clinical specimens should be performed (including smear microscopy, nucleic acid amplification testing, and culture). A 2012 consensus conference statement recommended such testing for organ donors at risk.[26] Testing with an interferon-γ release assay could also be considered for donors with tuberculosis risk factors. However, false-negative or indeterminate results might occur in nearly 19% of culture-confirmed tuberculosis cases,[23] and the performance of interferon-γ release assays has not been validated in critically ill or deceased people. Nevertheless, positive results could enable actions to mitigate the risk of *M tuberculosis* transmission, such as exclusion from donation or prophylactic treatment of organ transplant recipients.[26]

Third, for tissue donors with risk factors or findings compatible with tuberculosis disease or latent tuberculosis infection, direct testing of donated tissues for *M tuberculosis* should be strongly considered. Bone allograft products containing live cells are commonly stored frozen and have expiration dates months or years after manufacturing. Storing tissue products for 6–8 weeks before distribution, pending mycobacterial culture results, could allow detection of *M tuberculosis*. Although culture remains the most sensitive test for *M tuberculosis,* nucleic acid amplification testing could provide more timely results. Currently, the only commercially available *M tuberculosis* nucleic acid amplification testing in the USA is FDA-approved for use with sputum specimens only.[23] However, laboratories could validate laboratory-developed nucleic acid amplification testing for use with other specimen types. In this report, rt-PCR assays detected *M tuberculosis* in all eight tested samples from the recalled lot showing the potential use of nucleic acid amplification testing for tissues. Based on our findings, the American Association of Tissue Banks issued a new recommendation that PCR testing might be considered for tissues obtained from donors with tuberculosis risk factors or minimally processed tissues at highest risk for transmitting *M tuberculosis* (eg, fresh grafts, live cells, stem cells, or any tissue with viable cells).[27]

Fourth, surgeons should weigh the risk of tissue-derived infection when deciding whether to use tissue-based products, particularly those containing live

cells. Informed consent for prospective recipients of tissue-based products should include a discussion of this risk.[28]

Finally, standardised mechanisms to ensure tissue traceability and adverse event reporting should be established. Previous investigations have documented challenges in tracing tissue products from donors to recipients in the USA.[29,30] Here, product tracing was only accomplished through voluntary and resource-intensive efforts, which included cooperation from the product manufacturer and distributor; collaboration between federal, state, and local health officials; and voluntary product tracking by the affected health-care facilities. However, identification of tuberculosis in a patient who received a bone allograft from a different donor highlights ongoing limitations in the ability to trace tissues from donor to recipient. Efforts to improve traceability of tissues are warranted.

This report has limitations. Because not all product recipients had mycobacterial testing or imaging, the presented counts of recipients with evidence of tuberculosis overall and at each anatomical site should be considered as lower bound estimates. The evaluation of exposed contacts is incomplete, so the full extent of this outbreak remains to be determined.

In summary, *M tuberculosis* transmission via bone allograft resulted in a widespread outbreak of spinal and disseminated tuberculosis with substantial morbidity and mortality. To improve tissue and organ safety, all prospective tissue and donors should be routinely assessed for tuberculosis risk factors and clinical findings. When these are present, laboratory testing could reduce the risk of *M tuberculosis* transmission through tissue and organ transplantation.

#### Contributors

MD detected, investigated, and reported the initial cluster of cases. NGS, ACH-R, PA, TDF, SPA, RJF, RL, WWW, MD-F, MD, EH, KW, SAB, BC, JBG, RJS, JMW, and MBH collected and interpreted epidemiological and clinical data. KAL, TCT, LSC, and AMS provided expertise and input in tuberculosis diagnostics and performed laboratory and molecular analyses. NGS, TDF, SPA, MD-F, EH, KW, SBM, PL, RJS, JMW, and MBH provided expertise and input in tuberculosis control. ACH-R, RL, WWW, MD, IB, and JBG provided expertise and input in infection control. PA, RJF, SAB, BC, and SVB provided expertise and input in tissue safety. SVB, IB, JBG, SBM, PL, JMW, and MBH provided leadership and guidance. TDF, SPA, NGS, and ACH-R have accessed and verified all the data in the study, performed statistical analyses, and created the tables and figures. NGS and ACH-R wrote the original draft. All authors reviewed, revised, and approved the manuscript, including all of the data presented, and accept responsibility to submit the manuscript for publication.

#### Declaration of interests

We declare no competing interests.

#### Data sharing

Individual participant data will not be made available.

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