CDC Tissue Safety Investigations: Lessons Learned and Opportunities for Improvements

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The problem…

- In the United States, current tissue tracking, and safety measures are inadequate
  - Gap in traceability for tissues from donor to recipient by end users
    - Exacerbated by lack of common nomenclature, coding, & labeling
  - No requirement for adverse event monitoring or reporting by consignees/end users
  - Imminent and ongoing risk of patient harm, particularly among those who receive products containing live cells

Notable Tissue-Transmitted Infections Investigated by Public Health Authorities: United States, 1979–2023

- Rabies – Corneas 1979
- Creutzfeldt-Jakob Disease – Dura Mater 1987 (2001, 2007-2008)
- HIV – Bone allograft (1988, 1992)
- *Ochrobactrum anthropi* Meningitis – Pericardial Tissue 1996
- *Candida albicans* endocarditis – Aortic Valve 1998
- Septic Arthritis – ACL Tendons 2000
- Hepatitis C – Tendon+ Bone 2000-2002
- *Streptococcus pyogenes* – Tendon 2003
- *Clostridium* – Musculoskeletal Tissue 2004
- Rabies – Vascular tissue 2005
- *Elizabethkingia meningoseptica* – Musculoskeletal Tissue 2006
- Hepatitis C virus – Cardiopulmonary Patch 2011
- *Mycoplasma hominis* – Amniotic Tissue Product 2015
- *Mycobacterium tuberculosis* – Bone Graft 2021 & 2023

Difficulty Tracking Tissues during Investigations

- **1991, HIV**: Could not confirm disposition of 6 products
- **2000-2002, Hepatitis C virus**: 5 recipients not tested
- **2001, *Clostridium spp.***: Incomplete tissue processing information
- **2008, Creutzfeldt-Jakob disease**: 2 recipients lost to follow-up
- **2011, Hepatitis C virus** : Could not locate all tissues and delayed communication resulted in preventable transmission
- **2015, *Mycoplasma hominis***: Could not locate all tissues

The challenge of tissue tracking and safety

- 58,000 tissue donors annually*
  - ~3,300,000 allografts distributed
  - ~2,500,000 tissues are implanted
    - Including minimally processed tissues such as fresh grafts, live cells, stem cells, and any tissue with viable cells
- Minimally processed tissues may present an elevated infectious risk

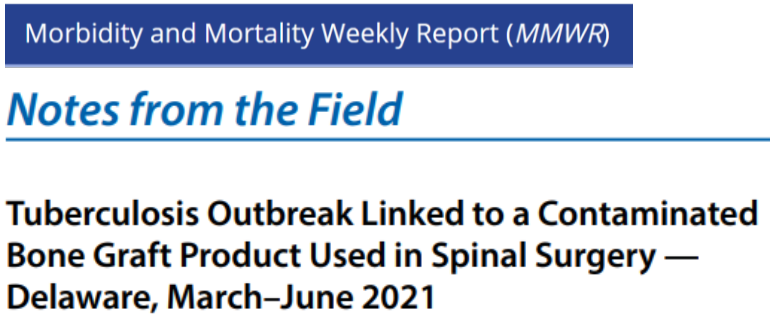
* www.aatb.org

Efforts to Improve Tissue Safety

- 2005 - CDC/FDA/HRSA Organ and Tissue Safety Workshop Priorities
- 2009 - Public Health Service Biovigilance Gap Assessment
- 2015 - Advisory Committee on Blood and Tissues Safety and Availability Recommendations

Multi-State Tuberculosis Transmission — 2021

Initial events

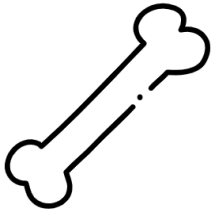


May 31 Nationwide call for cases on CDC's Epidemic Information Exchange (*Epi-X*)

June 2 Manufacturer issues voluntary recall

Different state notifies CDC about another case

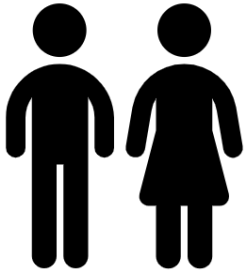
Rapid action to sequester unused product and evaluate recipients



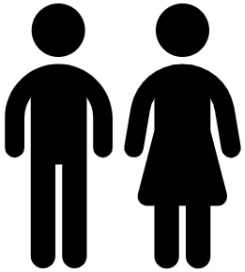
Bone recovered from deceased donor

154 units of bone allograft produced and distributed to 37 facilities in 20 U.S. states

18 units sequestered and sent for testing or returned to manufacturer



136 units implanted into **113 patients**



105 patients alive and started TB treatment by June 10

10 patients died

Investigation methods

- Abstracted medical records from 113 identified product recipients
- Reviewed donor screening and tissue processing
- Laboratory testing:
  - *Mycobacterium tuberculosis* PCR + culture for unused product from recalled lot and other products processed at same facility
  - Whole-genome sequencing + phylogenetic analysis
  - Molecular Detection of Drug Resistance (MDDR)
  - Growth-based drug susceptibility testing (DST)

We found high attack rates of surgical site and disseminated TB among identified product recipients

Total identified product recipients

(N=113)

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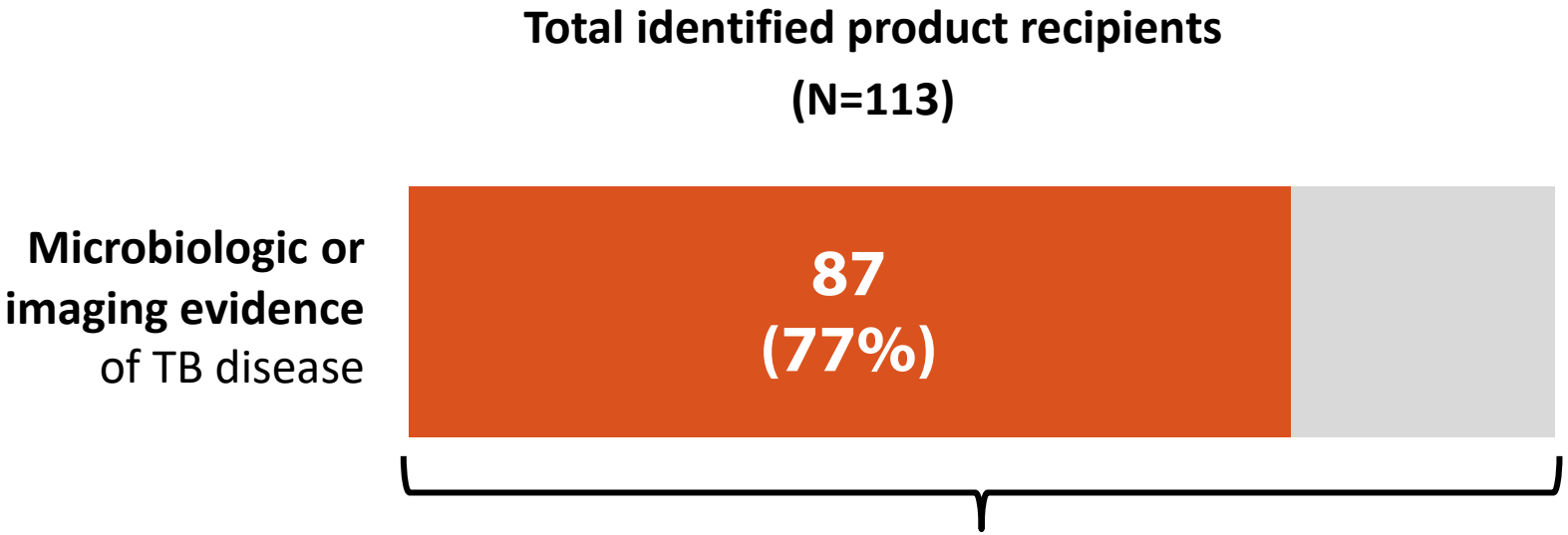
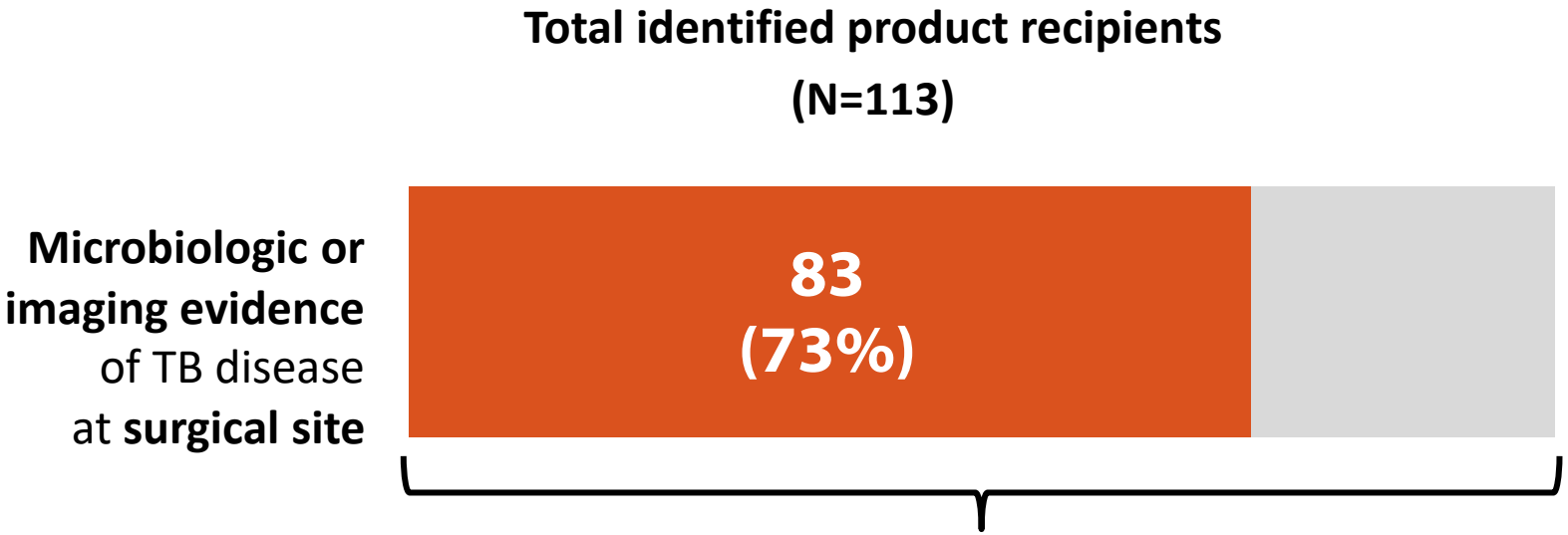


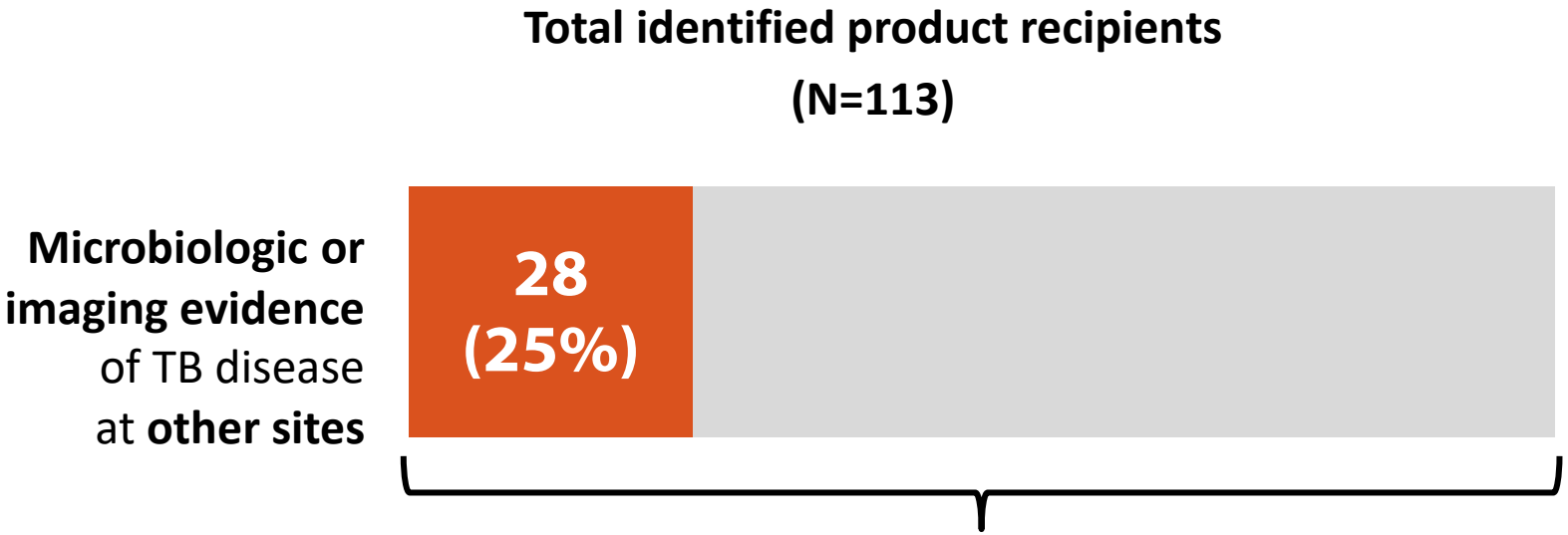
Data as of 10/20/2021

Surgical site TB among identified product recipients



Data as of 10/20/2021

Disseminated TB among identified product recipients



Data as of 10/20/2021

Donor medical history

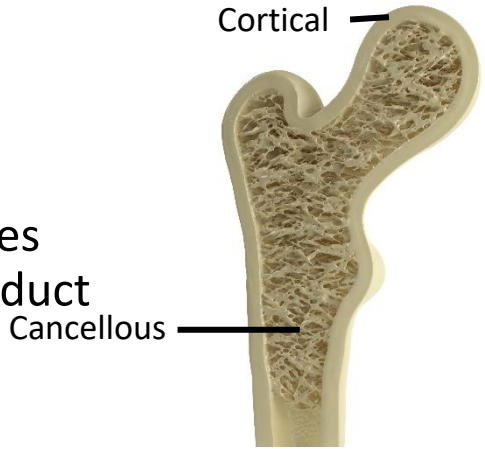
- 80-year-old man with several risk factors for TB:
  - Prior residence in and frequent travel to a country with endemic TB
  - End-stage renal disease (ESRD); started dialysis 6 months before death
  - Diabetes mellitus type II requiring insulin
- Other medical history:
  - Coronary artery disease
  - Biventricular heart failure
  - Sleep apnea requiring nocturnal supplemental oxygen

Donor screening

- Uniform Donor Risk Assessment Interview with proxy:
  - No reported history of TB, positive TB skin or blood test, or household exposure to TB in previous 12 months
  - Cough and dyspnea: attributed to ESRD, congestive heart failure
  - 70- to 80-pound weight loss in prior 2 years: attributed to dietary changes
- Donor eligibility form:
  - Assessed not to be at high risk for sepsis
- Negative tuberculin skin test 4 months before death
  - Note: false-negative TST results are not uncommon in patients with ESRD
- Negative standard donor testing for hepatitis B and C, HIV, syphilis, human T-lymphotropic virus (HTLV)

Tissue procurement and processing

- No organs procured
- Tissues procured:
  - Bones
  - Skin, fascia lata, tendons (not used)
- Bone tissue processed at a single facility:
  - Cortical bone demineralized
  - Cancellous bone processed to retain live cells
  - Bioburden testing followed industry standards:
    - Bacterial + fungal testing performed on samples collected during processing and from final product
    - Mycobacterial testing not performed



Testing of unused bone allograft products

- *M. tuberculosis* detected by PCR and culture in all 8 tested bone allograft units from the recalled lot
  - *M. tuberculosis* isolates from recipients and unused product >99.99% identical genetically
- *M. tuberculosis* NOT detected in 11 bone allograft products from other donors processed at same facility during 12-week period

We thought all recipients of this product were identified and put on treatment… but

- Remember there is no standardized donor to recipient tissue tracking system in the United States

November 2021: CDC was alerted by a State TB controller of another patient who was positive for spinal TB at Facility A

- Facility A cared for 2 patients involved in the national outbreak
- Facility A received 2 units of **Lot A** from the manufacturer and implanted them in 2 patients **(Patients 1 and 2)** during April–May 2021
- These two patients were identified after notification of the national investigation, and were started on treatment in June 2021

A third patient with TB was identified at Facility A

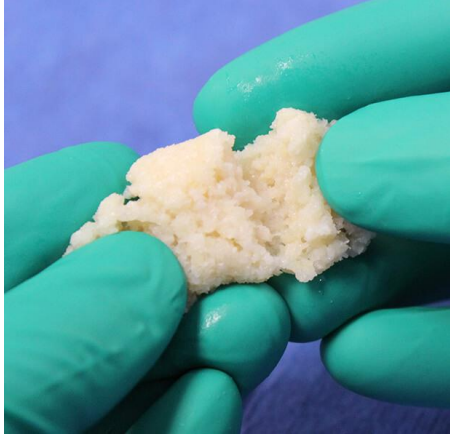
- In November 2021, a new patient (**Patient 3**) was identified with spinal TB at Facility A
  - **Patient 3** received bone allograft product from same manufacturer but from a different donor (Lot B)
  - A CDC/state health department investigation determined that an unrecognized product swap likely occurred at this facility
- Another national traceback for Lot B was performed
  - Testing of 5 unused products was negative by TB PCR and culture
  - 122 products were prepared from this donor
    - **5/122 (4%) products could not be tracked to final disposition**

But there’s more (unfortunately)…2023 TB again

Fri, July 7, 2023: Initial notification to CDC

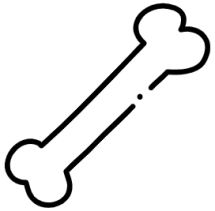
- State A notified CDC of a patient who underwent spinal fusion surgery in May 2023 and developed TB meningitis
  - Woman in her 50s with no known social, epidemiologic, or clinical risk factors for TB
    - Initially developed symptoms ~5 weeks post surgery
    - **NAT+** for *M. tuberculosis* complex
      no rpoB mutations consistent with RIF resistance identified
    - Received ViBone allograft product
    - Autopsy: multiple specimens **Acid Fast Bacilli+, NAT+** for *M. tuberculosis*

Viable Bone Matrix Material from Elutia Inc (formerly Aziyo Biologics)



- Different donor, product, and lot from those in 2021 outbreak, same manufacturer (previous product was **FiberCel**)
- Bone tissue allograft comprised of cancellous bone particles with preserved cells and demineralized cortical bone particles derived from deceased donor
- Used primarily in spinal fusion surgeries (**ViBone** product) and dental procedures (**alloOss** product)

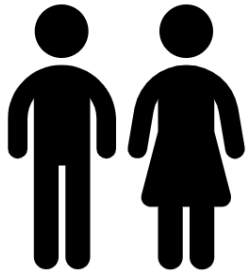
Rapid action to sequester unused product and evaluate recipients



Bone and tissue recovered from deceased donor

114 units of bone allograft produced

50 units distributed to **13 facilities** in **7 states**



49 units implanted into **36 patients**

64 units not distributed

5 units sent for testing

36 patients underwent procedures using at least one unit from the product lot

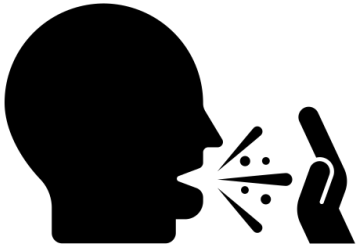
Dental (n = 6)
Spinal (n = 30)

27 tested positive for TB infection

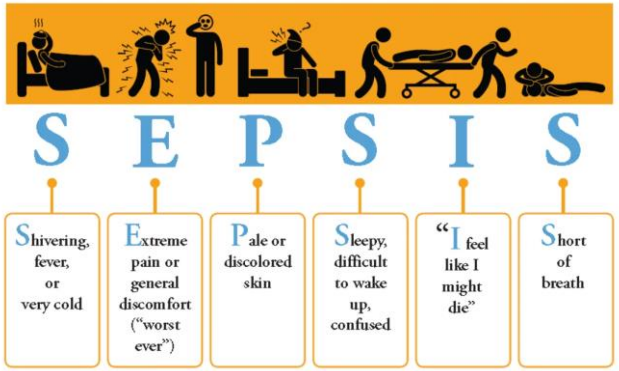
5 had laboratory-confirmed TB disease

2 patients died from TB disease

The donor had symptoms consistent with TB disease



2–3 weeks



Lessons learned by CDC

1. Basic data related to tissue safety (e.g. how much tissue is used?) are lacking

- Difficult to identify risk without a denominator

2. Although traceability is not an issue with other medical products of human origin including solid organs and blood, there is no standardized donor to recipient tissue tracking system in the United States

- The problem is not limited to *M. tuberculosis*
- Risk mitigation steps for *M. tuberculosis* may be useful, but do not solve larger traceability challenges

3. When an infectious disease transmission occurs via tissues, CDC cannot reliably trace 100% of tissue products from donor-recipient-donor in all situations

- Patients who receive contaminated products may not be identified or receive life-saving interventions

Lessons learned by CDC

4. Currently, there are no requirements for adverse event monitoring of patients or reporting of potential disease transmission events by consignees/end users (e.g., hospitals or physicians)

- Tissue-transmitted infections are likely under-recognized and under-reported

5. Patients (and often providers) are generally unaware that tissues can transmit infections

- There is no required informed consent of patients receiving tissue products (unlike solid organs or blood products)

2024 Advisory Committee on Blood and Tissues Safety and Availability (ACBTSA) Recommendations

1. Tissue Source
2. Tissue Processing
3. Tissue end-user/consignee receipt and use
4. Tissue recipient adverse events/reactions

https://www.hhs.gov/sites/default/files/acbtsa-gap-analysis-tissue-biovigilance-subcommittee-report.pdf

These problems are not new or newly identified

- Previously discussed by the ACBTSA (2015)
  - No coordinated action occurred after these meeting recommendations
- Ongoing risk of patient harm, particularly among those who receive tissue products containing live cells
- CDC is planning some tissue-safety focused efforts
  - Survey, communications, partnership engagement

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HRSA

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For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

10 recipients died after product implantation

- At least 3 deaths caused by TB
  - 2 additional deaths had TB as a possible cause of death (insufficient data)
- 5 deaths attributed to causes unrelated to TB

Data as of 04/19/2022