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Original Article

Incomplete tissue product tracing during an investigation of a tissue-derived tuberculosis outbreak

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ABSTRACT

In the United States, there is currently no system to track donated human tissue products to individual recipients. This posed a challenge during an investigation of a nationwide tuberculosis outbreak that occurred when bone allograft contaminated with *Mycobacterium tuberculosis* (Lot A) was implanted into 113 patients in 18 US states, including 2 patients at 1 health care facility in Colorado. A third patient at the same facility developed spinal tuberculosis with an isolate genetically identical to the Lot A outbreak strain. However, health care records indicated this patient had received bone allograft from a different donor (Lot B). We investigated the source of this newly identified infection, including the possibilities of Lot B donor infection, product switch or contamination during manufacturing,

Abbreviations: AATB, American Association of Tissue Banks; ACBTSA, Advisory Committee on Blood and Tissue Safety and Availability; CDC, Centers for Disease Control and Prevention; CDPHE, Colorado Department of Public Health and Environment; FDA, Food and Drug Administration; IGRA, interferon-gamma release assay; ISBT, International Society of Blood Transfusion; rt-PCR, real-time polymerase chain reaction.

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product switch at the health care facility, person-to-person transmission, and laboratory error. The findings included gaps in tissue traceability at the health care facility, creating the possibility for a product switch at the point of care despite detailed tissue-tracking policies. Nationally, 6 (3.9%) of 155 Lot B units could not be traced to final disposition. This investigation highlights the critical need to improve tissue-tracking systems to ensure unbroken traceability, facilitating investigations of recipient adverse events and enabling timely public health responses to prevent morbidity and mortality.

1. Introduction

Approximately 3.2 million human tissue allografts are distributed annually by tissue establishments in the United States.[1] Although rare, the use of these tissues can result in donor-to-recipient infectious disease transmission.[2] In contrast to blood transfusion or solid organ transplantation, where 1 or a small number of products from an individual donor are available for use in recipients, >100 tissue allografts can be manufactured from a single donor.[3,4] Therefore, when a suspected infectious disease transmission event involves a tissue product, identifying the potentially large number of recipients can be challenging.

Additional factors complicate tissue product tracing from donors to recipients in the United States. First, unlike blood products and solid organs, tissue allografts have no standard system of coding and nomenclature.[3-5] Product names can be proprietary and are assigned at the discretion of tissue manufacturers.[3-5] Federal regulations require tissue establishments to ensure the following: (1) assign a distinct identification code to tissue products, (2) track each product from the donor to the receiving health care facility, and (3) inform receiving facilities of the tracking system they use.[6,7] However, health care facilities are not required to track tissue receipt, storage, or use for individual recipients, and there is wide variability in facility-level tissue-tracking practices.[3] Although professional organizations and accrediting bodies, such as the American Association of Tissue Banks (AATB) and the Joint Commission, require additional standards for member facilities, participation is voluntary, resulting in monitoring and enforcement challenges.[8,9] Further, although tissue establishments are required to investigate any adverse reaction involving a communicable disease related to the use of a cell/tissue product and, when certain conditions are met, report it to the US Food and Drug Administration (FDA), recognition and notification by health care providers is inconsistent and often delayed.[3] These tissue tracking and adverse event reporting challenges have resulted in the inability to trace the disposition of tissue products during disease transmission investigations, increasing the risk of patient harm.[10-13]

During May-August 2021, the Centers for Disease Control and Prevention (CDC), FDA, and state and local health departments investigated a nationwide outbreak of tuberculosis caused by contamination of a bone allograft product.[14,15] The allograft implicated in this outbreak was manufactured to retain live cells. Overall, 154 units of a single product lot (Lot A) contaminated with *Mycobacterium tuberculosis* were distributed to 37 health care facilities in 20 US states and surgically implanted into 113 recipients in 18 states, causing significant morbidity and mortality. *M. tuberculosis* isolates from recipients and unused units from Lot A were genetically identical. [15] In collaboration with the product manufacturer, distributor, and health care facilities, public health officials traced and accounted for every identified unit of Lot A. This success contrasted with previous investigations involving contaminated tissue products, where tracing to final disposition of all individual units was not possible.[5,10-13]

One of the 37 health care facilities nationwide that had received units from Lot A, a health care facility in Colorado (Facility A), received 3 units. These 3 units were documented as being implanted into 2 patients (ie, 1 patient received 2 units) in April and May 2021, before the *M. tuberculosis* contamination was discovered. However, in November 2021, a third patient, recorded as having undergone spinal surgery with a different lot (Lot B) of the same product at Facility A in May 2021, was newly diagnosed with tuberculosis. The new patient's isolate was subsequently found to be genetically identical to isolates from both Lot A and Lot A recipients who developed tuberculosis in other states.

In partnership with the health care facility, the Colorado Department of Public Health and Environment (CDPHE) and CDC investigated to determine the source of the new *M. tuberculosis* infection, identify any other patients potentially at risk, and, if necessary, recommend approaches to improve tissue safety. Five hypotheses for the source of *M. tuberculosis* infection were considered: (1) the Lot B tissue donor also had unrecognized tuberculosis infection; (2) a product switch or cross-contamination with Lot A occurred during manufacturing; (3) a product switch with Lot A occurred at Facility A; (4) person-to-person transmission or indirect transmission via surgical equipment occurred at Facility A; or (5) a laboratory error or cross-contamination occurred during handling at a clinical laboratory.

2. Methods

2.1. Donor investigation

Medical and social behavioral records for the Lot B donor were provided by the bone allograft manufacturer and were reviewed by CDPHE and CDC investigators to assess for tuberculosis risk factors and signs or symptoms of tuberculosis disease.

2.2. Laboratory testing

Unused units from Lot B were evaluated at the National Veterinary Services Laboratories for the presence of *M. tuberculosis* complex using real-time polymerase chain reaction (rt-PCR) assays that amplified the IS*1081* insertion element.[15] *M. tuberculosis* culture was attempted from unused products using BACTEC Mycobacterial Growth Indicator Tubes (Becton Dickinson) and solid media.[15]

2.3. Nationwide Lot B product tracing to final disposition and case finding

The product manufacturer provided CDC with shipment records documenting which health care facilities had received units from Lot B as well as information gleaned from their review of returned implant cards, which accompany each distributed unit and are requested to be voluntarily returned to the manufacturer following each unit's use. During November-December 2021, CDC, state and local health departments, and health care facilities located and sequestered unused units from Lot B. Health care facilities identified patients who had received bone allograft products from Lot B and reviewed medical records to identify whether there existed any postsurgical complications that might be consistent with tuberculosis. Patients with signs or symptoms consistent with possible postsurgical tuberculosis were referred to local health departments for additional evaluation.

2.4. Manufacturer investigation

The tissue manufacturer provided investigators with manufacturing records, including processing and packaging dates, processing locations, and a list of personnel involved in the manufacturing and packaging of Lot A and Lot B products, as well as general product handling, packaging, and labeling procedures. Records were reviewed to determine if Lot B contamination or mislabeling could have occurred during manufacturing and to assess the integrity of handling, packaging, and labeling procedures during tissue processing and manufacturing.

2.5. Facility A investigation

CDPHE conducted a case investigation through medical record review and 2 onsite assessments at Facility A to determine the following: (1) examine product handling and movements from the time tissue products enter the facility to the time they are implanted into patients, and (2) assess potential modes of nosocomial transmission. Tissue-tracking documentation and implant cards for all recipients of Lot A or Lot B bone allograft products at Facility A were reviewed, and investigators observed a surgical procedure during which bone allograft products were used. Facility A's operating room staff and sterile processing staff were interviewed to identify potential gaps in the facility's tissue product retrieval process during surgery. Sterile processing of surgical instruments was assessed to determine if local transmission could have occurred via contaminated instruments. Where potential nosocomial transmission routes were identified, patients who might have been exposed were offered interferon-gamma release assay (IGRA) testing to assess for tuberculosis infection.

2.6. Laboratory handling assessment

To assess the potential for laboratory cross-contamination, the CDC determined which laboratories processed clinical specimens and mycobacterial isolates from Facility A patients and Lot A recipients in other states. CDC reviewed the dates of specimen collection and mycobacterial testing to determine whether any specimens or isolates were processed in the same laboratory on the same date.

2.7. Investigation oversight

This outbreak investigation led by CDPHE was conducted consistent with applicable federal and state regulations and policies. Institutional Review Board approval was not required as this was considered an outbreak investigation and did not require human subjects' review.

3. Results

3.1. Donor investigation

A review of the medical and social behavior history of the donor for Lot B did not reveal any recognized risk factors for tuberculosis or signs or symptoms consistent with tuberculosis disease. Born in the United States with no documented history of latent tuberculosis infection or tuberculosis disease, exposure to tuberculosis, incarceration, substance use, Human Immunodeficiency Virus, or other immunocompromizing conditions, the donor did have shortness of breath, but no documented cough, weight loss, fever, or night sweats. Death was attributed to a saddle pulmonary embolism identified during autopsy. No organs were transplanted from this donor.

3.2. Laboratory testing

Five sequestered units from Lot B were tested. Four of the 5 rt-PCR results were negative; the fifth yielded an invalid result and could not be retested. Mycobacterial cultures of all 5 units were negative after 8 weeks of incubation.

3.3. Nationwide Lot B product tracing to final disposition and case finding

During March-June 2021, 155 units of bone allograft product from Lot B were distributed to 44 health care facilities in 24 US states, including 18 facilities that had also received units from Lot A (Fig. 1). Ultimately, 149 (96%) units were successfully traced to final disposition. Of the units with known disposition, 130 had been implanted into 124 patients, 14 had either been discarded or returned to the manufacturer, and 5 were unused, sequestered, and sent for *M. tuberculosis* testing. The status and final disposition of 6 units remain unknown despite efforts by

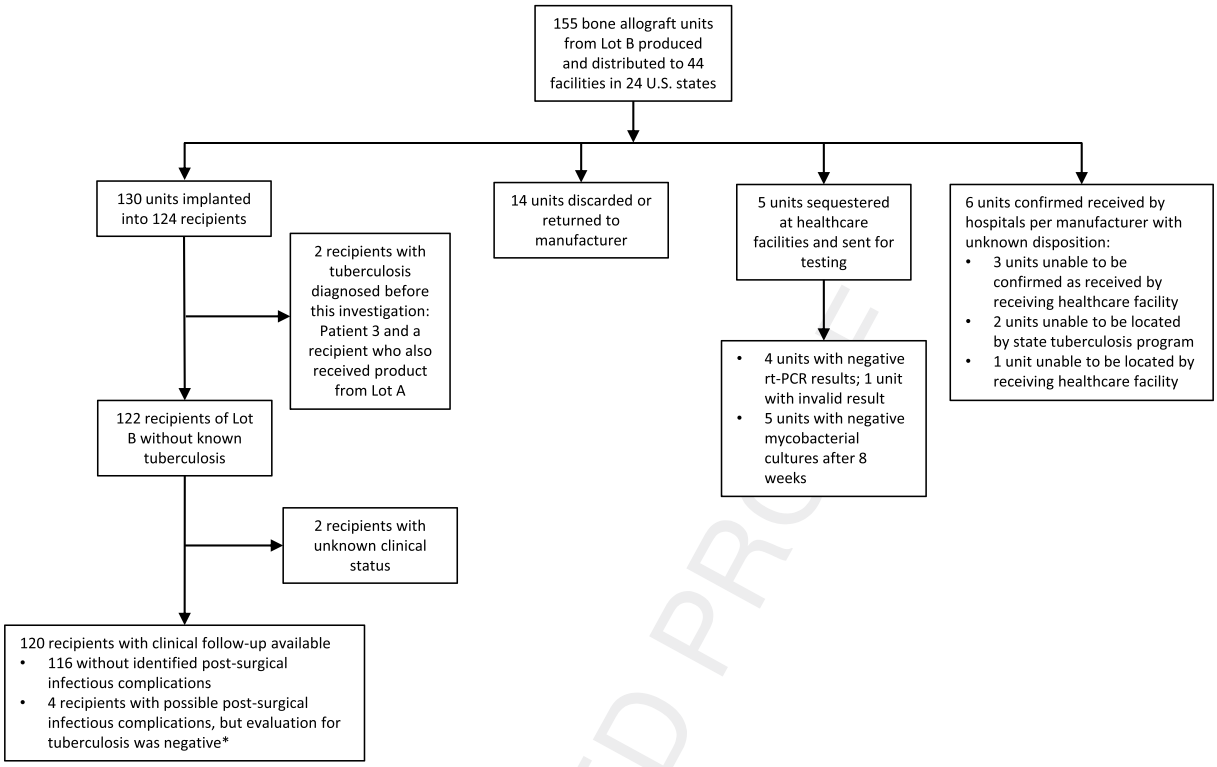

Figure 1. Distribution and status of 155 units of bone allograft product from Lot B. AFB, acid-fast bacilli; IGRA, interferon-gamma release assay; rt-PCR, real-time polymerase chain reaction.

federal, state, and local health officials. In total, 4 units from Lot B were distributed to Facility A between April 12, 2021, and April 30, 2021.

A review of implant cards revealed that 1 Lot B unit was implanted at a different facility than the one to which it had been shipped. It was determined the unit was transported, from the health care facility to which the manufacturer had originally shipped it, to a different health care facility by an unknown individual (possibly a surgeon or distributor representative).

Among the 124 Lot B product recipients, 2 had known spinal tuberculosis at the start of this investigation (Fig. 1). One was the index patient in Colorado that triggered the investigation. The second patient had also received a unit of Lot A (ie, units from both lots in the same surgery) and was being treated for tuberculosis disease. Of the remaining 122 Lot B recipients, clinical follow-up related to possible postsurgical infectious complications was available for 120. Three recipients were identified with chronic pulmonary or constitutional symptoms. These patients were evaluated at local health departments and lacked evidence of tuberculosis; all 3 had negative IGRA test results and normal chest imaging, and 2 had sputum evaluations performed which were negative for *M. tuberculosis* by culture. One additional recipient developed a paraspinal seroma. Evaluation of the fluid aspirate was negative for *M. tuberculosis* by acid-fast bacilli smear and culture.

3.4. Manufacturer investigation

During manufacturing, each unit of tissue allograft is placed in a vial, sealed in a plastic pouch, and placed in a product box. The product box also contains the manufacturer's instructions for use and additional labels for use in patient medical records and is sealed with a barcoded label on the outside of the box.

All tissue donations from both the Lot A donor and the Lot B donor were processed by a single manufacturer. The processing and packaging records provided by the tissue manufacturer indicated no temporal overlap had occurred in the processing of Lots A and B at the manufacturer. Lot B processing was completed during a single day, and final packaging was completed during a subsequent single day. The manufacturer completed the final packaging of Lot B 3 days prior to the start of Lot A processing. Although the room used for processing both lots was the same, there was no crossover in the personnel involved in processing.

3.5. Facility A investigation

3.5.1. Cases

Three patients underwent surgery with implantation of at least 1 unit of Lot A or Lot B product at Facility A (Patients 1-3 in order of detection, Table, Fig. 2). Patient 1 was documented as Q4 receiving Lot A in April 2021, developed clinical signs and symptoms of spinal tuberculosis without evidence of pulmonary disease, as evidenced by a significant increase in back pain and fluid collection at the surgical site, and was treated with 4-drug therapy for 12 months. Patient 2 was documented as receiving Lot A in May 2021 and did not develop signs or symptoms of tuberculosis but was treated with 4-drug therapy empirically due to the high attack rate associated with receipt of the contaminated Lot A product.[15] Patient 3, documented as receiving Lot B

Table
Characteristics of product recipients at Facility A.

Surgery date	Day 0	Day 21	Day 33
Patient No.	Patient 1	Patient 3	Patient 2
History of tuberculosis disease, prior tuberculosis exposure, or tuberculosis risk factors	No	No	No
Documentation of implanted lot	Lot A	Lot B	Lot A
Surgical instrument overlap	Yes, Patient 3	Yes, Patient 1	No
Postsurgical course	Experienced fevers, night sweats, and fatigue. MRI revealed a lumbar spine fluid collection consistent with infection.	CT revealed a flank and abdominal fluid collection tracking anteriorly from lumbar spine along the surgical tract.	Asymptomatic. Chest x-ray revealed no radiographic signs consistent with postsurgical infection.
Overlap in healthcare facility during postsurgical course	No	No	No
Tuberculosis testing			
Interferon-gamma release assay or tuberculin skin test	Not performed	Not performed	IGRA negative
Mycobacterial testing	Not performed	Detected in PCR and culture	Not performed

Abbreviations: CT, computed tomography; IGRA, interferon-gamma release assay; MRI, magnetic resonance imaging; PCR, polymerase chain reaction.

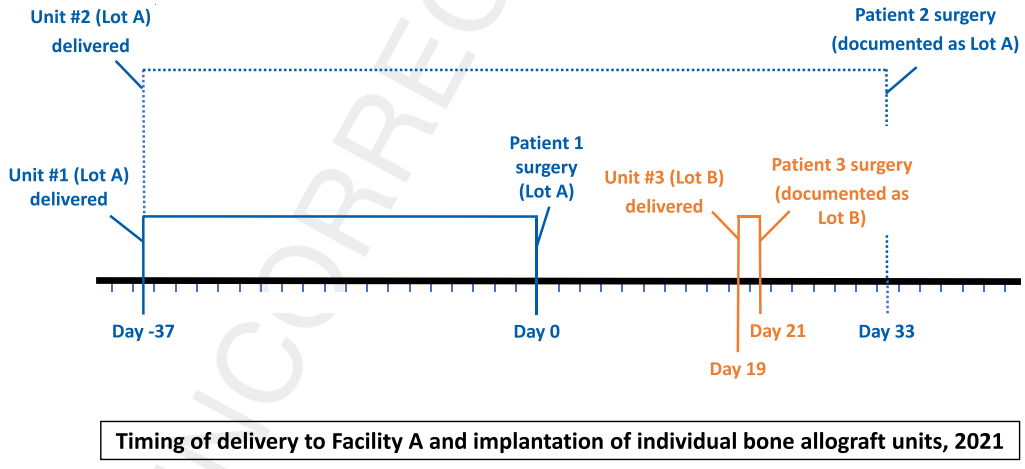

Figure 2. Timeline of delivery of 2 Lot A units and 1 Lot B unit to Facility A and subsequent surgical implantation into Patients 1-3.

in May 2021, underwent surgery 21 days after Patient 1 and 12 days before Patient 2. Patient 3 developed a paraspinal flank abscess and culture-positive spinal tuberculosis without evidence of pulmonary disease and was treated with 4-drug therapy for 12 months. There was no overlap in hospitalizations after Patients 1 and 3 developed symptoms.

3.5.2. Product handling

Lots A and B of the tissue product arrived at Facility A consistent with the packaging process reported by the manufacturer—the product vial was sealed inside a plastic pouch, packaged inside a product box, and shipped to the facility inside a foam cooler. While the product box contains an affixed barcode for the facility to scan upon receipt, the plastic pouch and product vial within the box did not contain affixed barcodes for the facility to scan upon implantation. Facility A used a commercial tissue-tracking software program to document tissue products' receipt and implantation. The facility maintained product tracking records by scanning the barcode on the cooler and sealed product box upon receipt, storage, and retrieval for implantation. Sealed tissue product boxes were stored with a single paper implant card to record the patient's medical record label and information related

to retrieving staff, package verification, and surgery details for that particular vial of product. The product was linked to a patient chart when the product box barcode and medical record label were both scanned in the retrieval process during surgery. A review of the tracking records indicated that Lot A was implanted into Patients 1 and 2, and Lot B was implanted into Patient 3.

Managerial staff at Facility A reported their tissue product retrieval protocol indicated that only a single tissue product at a time could be retrieved and brought into an operating room at the request of the surgeon, although additional boxes could later be requested. During staff interviews, responses to whether a retrieved and subsequently unused tissue product could be returned to the freezer were inconsistent. Several staff members reported that products that were retrieved would never be returned to the tissue freezer if unused and unopened. Other staff members, however, reported that unopened product boxes could be returned to the freezer at the surgeon's discretion if within a specified timeframe. All staff reported that opened product boxes would not be returned to the freezer.

3.5.3. Infection control

Patients 1 and 3 (who both developed symptomatic tuberculosis) were not hospitalized simultaneously. Gaps in instrument cleaning prior to steam sterilization were observed (eg, debris found in cannulated instruments that had already undergone sterilization) and were remedied appropriately in collaboration with CDPHE. Facility A recommended tuberculosis testing to 5 patients who had received surgical procedures with the same instrument set in the 2 weeks between Patients 1 and 3. Two of the 5 patients pursued IGRA laboratory testing for tuberculosis infection, and both were negative.

3.6. Laboratory handling assessment

Both Facility A's clinical laboratory and the reference mycobacteriology laboratory only handled the newly identified patient's specimen; neither handled any other specimens associated with the outbreak.

4. Discussion

This investigation demonstrates challenges in tracking tissue products from donors to recipients, which impede the prevention of and response to donor-derived infections. We investigated 5 hypotheses for how the patient documented to have received a product from Lot B (Patient 3) developed tuberculosis. While we were unable to determine definitively how Patient 3 developed tuberculosis, we did not find evidence of contamination or a product switch at the manufacturer or cross-contamination at a laboratory, and we were able to exclude Lot B donor infection and person-to-person transmission. Multiple findings support our conclusion that the donor for Lot B did not have tuberculosis and that Patient 3 likely received Lot A rather than Lot B: (1) the clinical *M. tuberculosis* isolate was genetically identical to isolates from Lot A; (2) the Lot B tissue donor did not have risk factors, signs, or symptoms of tuberculosis; (3) tested units from Lot B did not have evidence of *M. tuberculosis* contamination; and (4) no other recipients of Lot B developed tuberculosis. While we did not conclusively demonstrate a product switch at Facility A, simultaneous storage of allograft Lots A and B at Facility A maintains this as a plausible hypothesis. Additionally, the lack of a barcode label on the product vial and the absence of an effective tissue-tracking process made it difficult to confirm whether patients received the products they were documented to have received.

The investigation highlights gaps in tissue tracking in the United States that continue to pose risks to patient safety. As was evident here, an inability to track tissue products quickly and easily from donor to recipient can result in morbidity and mortality. A patient (Patient 2) appears to have been incorrectly assigned exposure to Lot A, leading to unnecessary tuberculosis treatment for several months, while another patient (Patient 3) received the contaminated product and developed potentially preventable tuberculosis disease. Despite extensive efforts by public health officials, at least 6 (3.9%) of 155 product units from Lot B could not be traced to final disposition. Furthermore, 1 of the Lot B units appears to have been personally transported by an unknown individual to a different surgical facility than the one to which it was documented as being delivered. These findings are consistent with previous studies that have reported an inability to trace all tissue products from a common donor to final disposition.[5,10-13] The gap in tissue-tracking requirements for hospitals also stands in contrast to the systems for solid organs and blood and blood components in the United States. Universal naming conventions and tracking requirements for solid organs and blood components contribute to an unbroken chain of traceability from donors to recipients.[3,16-22] The lack of a requirement to track tissue products once they arrive at the health care facility allows for a gap in the chain of traceability of tissue products at this final stage.[3,6-21] Efforts to enhance the traceability of tissues after receipt by the health care facility are critical to improve patient safety and ensure appropriate interventions reach patients in the setting of disease transmission events.

Limitations in tissue tracking in the United States have been the subject of previous policy discussions. In 2015, the Advisory Committee on Blood and Tissue Safety and Availability (ACBTSA), which advises the Secretary of the US Department of Health and Human Services, convened to discuss approaches to enhancing tissue tracking and traceability.[21] The resulting recommendations addressed many of the issues discussed in this present study and remain relevant today. Recommendations included the following: (1) using the International Society of Blood Transfusion (ISBT) 128 codes as a universal tissue identification standard, (2) establishing a single database for all organ and tissue donation, and (3) establishing oversight to cover all health care settings engaged in tissue transplantation to support bidirectional traceability and tissue surveillance.[21] To date, these recommendations have not been implemented on a national level.

The recommendations made by the ACBTSA provide a useful framework for improving tissue safety. A standardized coding system would improve the ability to track tissue products and identify individual recipients in events of suspected infectious

disease transmission through tissue products.[3,5,11,22] One system, ISBT 128, has been proposed as a universal nomenclature system for all human tissue products by various bodies, including the World Health Organization. Several organizations, including the Department of Veterans Affairs, blood collection establishments, eye banks, and the National Marrow Donor Program have individually adopted ISBT 128.[5,21,23] Additionally, including such identification codes (eg, as barcodes) on individual product vials could prevent future misidentification of implanted units.

Despite the absence of requirements pertaining to tissue tracking extending to health care facilities, some voluntary standards used by accrediting bodies cover the management of tissue products. The Joint Commission requires accredited facilities to comply with several standards related to handling tissue products.[9] These include maintaining written procedures for the "acquisition, receipt, storage, and issuance of tissues," documenting receipt of tissue products, ensuring package integrity and requisite storage temperatures are met, documenting and maintaining records on the donor or tissue supplier, and final product disposition, and, when a potential adverse event occurs, investigating the event and notifying the tissue supplier as well as any potential recipients.[9] Similarly, AATB publishes standards that include a section for Tissue Dispensing Services; however, no hospitals are accredited by AATB for that function.[8]

In addition to tracking procedures, health care facilities should implement procedures to properly identify, investigate, and report tissue recipient adverse events. Although the FDA's MedWatch reporting[24] provides the opportunity for health care providers to voluntarily report adverse events involving tissue products, there is no national requirement to report.[3] A national system would include efforts to monitor tissue recipients for the development of adverse events and to report these events to tissue establishments. Such a system is particularly relevant to products containing live cells, which carry a higher risk of infectious disease transmission.[14,15,21] Systems for reporting adverse events involving recipients of organ transplantation and blood product transfusion have mitigated disease transmission among co-recipients, helped identify emerging threats to organ transplantation and blood safety, and led to the adoption of additional safety measures to protect recipients.[25-27]

Governmental and nongovernmental partners in the United States continue to collaborate to identify and address gaps associated with tissue product tracking as well as with reporting suspected tissue recipient adverse events. To enhance patient safety, systems and procedures to ensure unbroken traceability within health care facilities and to facilitate reporting recipient adverse events to tissue establishments are critically needed.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

Declaration of Interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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