Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 72 / No. 52-53
January 5, 2024

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

Jonathan M. Wortham, MD[1]; Maryam B. Haddad, PhD[1]; Rebekah J. Stewart, MSN, MPH[1]; Pallavi Annambhotla, DrPH[2]; Sridhar V. Basavaraju, MD[2]; Scott A. Nabity, MD[1,3]; Isabel S. Griffin, PhD[2]; Emily McDonald, MD[2]; Elizabeth M. Beshearse, PhD[2]; Marissa K. Grossman, PhD[2,4]; Kimberly R. Schildknecht, MPH[1,4]; Helene M. Calvet, MD[5]; Chris E. Keh, MD[3]; Jeffrey M. Percak, MD[6]; Myron Coloma[7]; Tambi Shaw, MPH[3]; Peter J. Davidson, PhD[8]; Shona R. Smith, MPH[8]; Robert P. Dickson, MD[8,9]; Daniel R. Kaul, MD[9]; Annett R. Gonzalez, MSN[10]; Saroj Rai, PhD[11]; Gretchen Rodriguez, MPH[11]; Sandra Morris, MPH[11]; Lisa Y. Armitige, MD, PhD[12]; Jessica Stapleton, MPH[13]; Michael Lacassagne, MPH[13]; Laura R. Young, MPH[14]; Kiley Ariail, MPH[15]; Heidi Behm, MPH[15]; Hannah T. Jordan, MD[16]; Magdalene Spencer, MSc[16]; Diana M. Nilsen, MD[16]; Brenda Montoya Denison, MPH[17]; Marcos Burgos, MD[17]; Juliet M. Leonard, MSN[18]; Erick Cortes, MPH[18]; Tyler C. Thacker, PhD[19]; Kimberly A. Lehman, DVM[19]; Adam J. Langer, DVM[1]; Lauren S. Cowan, PhD[1]; Angela M. Starks, PhD[1]; Philip A. LoBue, MD[1]

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.

INSIDE

Continuing Education examination available at https://www.cdc.gov/mmwr/mmwr_continuingEducation.html

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

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

The *MMWR* series of publications is published by the Office of Science, Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services, Atlanta, GA 30329-4027.

Suggested citation: [Author names; first three, then et al., if more than six.] [Report title]. MMWR Morb Mortal Wkly Rep 2024;73:[inclusive page numbers].

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.

Acknowledgments

Philip Robinson, Hoag Hospital; Patti Steger, Hoag Orthopedic Institute; Megan Foster, Munson Healthcare Cadillac Hospital; Elizabeth Recker, University of Michigan Health – West; Christy A. Scipione, Emily K. Stoneman, Laraine L. Washer, University of Michigan Health; Dean E. Smith, El Paso Spine Center; Enid LeBlanc, The Hospitals of Providence; Vivian Nguyen, Cecille Teope, Matthew Zahn, Orange County Health Care Services Agency; Antonio Bejarano, Tania Chiem, Megan Crumpler, Orange County Public Health Laboratory; Coroner Division of the Orange County Sheriff's Department; Romina Beltran, Debora Cartagena, Raymond Chinn, Ashley Cortez, Grace Kang, Ronabee Rullan-Tangonan, Lawrence Wang, Wilma Wooten, County of San Diego Health and Human Services Agency; Lisa Gooze, Che Waterman, San Mateo County Health; Zenda Berrada, Martin Cilnis, Camille Dollinger, Erin Epson, Idamae Kennedy, Janice Kim, Varvara Kozyreva, Hilary Metcalf, Yoran (Lana) Sato, Juliet Stoltey, Terry Weber, California Department of Public Health; Jennifer Morse, Mid-Michigan District Health Department and District Health Department #10; Kelly Block, Central Michigan District Health Department; Annette Marvin, Lisa McCormick, District Health Department #10; Loretta Hernandez, City of El Paso Department of Public Health; Amanda Decimo, Nicole Evert, Elizabeth Foy, Texas Department of State Health Services; Juzar Ali, Amy Wolfe, Louisiana State University Health Sciences Center; Crystal Zheng, Tulane University School of Medicine; Chris Brown, Candace DesHotel, Erica Washington, Louisiana Department of Health; Kendall Cook, Sumac Diaz, Shania Gupton, Elizabeth Vega, Melissa Williams, Virginia Department of Health; Laurie Forlano, Virginia Department of Health; Trevor Hostetler, Gloria Matthews, Washington County Health and Human Services; Lisa Chambliss, Patrick Luedtke, Heather Young, Lane County Health & Human Services; Christine Chuck, Dawn Cummins, Jeanne Sullivan Meissner, Brendan Oram, Lisa Trieu, New York City Department of Health and Mental Hygiene; Janet Glowicz, David Kuhar, Kiran Perkins, Joseph Perz, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, CDC; Julian A. Villalba, Sarah Reagan-Steiner, Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, CDC; Michele Neuburger, Division of Oral Health, National Center for Chronic Disease Prevention and Health Promotion, CDC; Leeanna Allen, Sandy Althomsons, Bruce Bradley, Gail Burns-Grant, Tracina Cropper, Justin Davis, Clint McDaniel, Neela Goswami, Andrea Lomeli, Shameer Poonja, Shanica Railey, Kala Marks Raz, Paul Regan, Frank Romano, Audilis Sanchez, Noah Schwartz, Julie Self, Sarah Talarico, Division of Tuberculosis Elimination, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, CDC; Cam-Van Huynh, Cassandra Schember, Paula Williams, Epidemic Intelligence Service, CDC.

Corresponding author: Jonathan M. Wortham, vij5@cdc.gov.

[1]Division of Tuberculosis Elimination, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, CDC; [2]Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, CDC; [3]California Department of Public Health; [4]Epidemic Intelligence Service, CDC; [5]Orange County Health Care Services Agency, Santa Ana, California; [6]County of San Diego Health and Human Services Agency, San Diego, California; [7]San Mateo County Health, San Mateo, California; [8]Michigan Department of Health and Human Services; [9]University of Michigan, Ann Arbor, Michigan; [10]City of El Paso Department of Public Health, El Paso, Texas; [11]Texas Department of State Health Services; [12]University of Texas at Tyler Health Science Center, Tyler, Texas; [13]Louisiana Department of Health; [14]Virginia Department of Health; [15]Oregon Public Health Division; [16]New York City Department of Health and Mental Hygiene, New York, New York; [17]New Mexico Department of Health; [18]New Jersey Department of Health; [19]National Veterinary Services Laboratories, Veterinary Services, Animal and Plant Health Inspection Service, U.S. Department of Agriculture, Ames, Iowa.

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. Saroj Rai reports uncompensated service as the Association of Immunization Managers' (AIM) liaison to CDC's Advisory Committee on Immunization Practices – Chikungunya Workgroup and on the Legacy Council for AIM; and retirement stocks at Novartis Pharmaceuticals. Jeffrey M. Percak reports travel support from the County of San Diego and from the California Tuberculosis Controller's Association for attendance at the California Tuberculosis Controller's Association fall meeting. Lisa Y. Armitige reports support from the Texas Department of State Health Services, consulting fees (paid to institution) from the Kansas Health Department, and honoraria (forwarded to institution) from the American Academy of HIV Medicine. No other potential conflicts of interest were disclosed.

References

1. Li R, Wilson WW, Schwartz NG, et al. Notes from the field: tuberculosis outbreak linked to a contaminated bone graft product used in spinal surgery—Delaware, March–June 2021. MMWR Morb Mortal Wkly Rep 2021;70:1261–3. PMID:34499629 https://doi.org/10.15585/mmwr.mm7036a4
2. Schwartz NG, Hernandez-Romieu AC, Annambhotla P, et al.; Bone Allograft Tuberculosis Investigators. Nationwide tuberculosis outbreak in the USA linked to a bone graft product: an outbreak report. Lancet Infect Dis 2022;22:1617–25. PMID:35934016 https://doi.org/10.1016/S1473-3099(22)00425-X

3. McVeigh LG, Zaazoue MA, Lane BC, Voorhies JM, Bradbury J. Management and outcomes of surgical site tuberculosis infection due to infected bone graft in spine surgery: a single-institution experience and 1-year postoperative follow-up. J Neurosurg Spine 2022;38:281–92. PMID:36272124 https://doi.org/10.3171/2022.7.SPINE22534
4. Ruan T, Naveed M, Vien H. Case report: tuberculosis recall on bone graft patient. N Am Spine Soc J 2023;15:100241. PMID:37483264 https://doi.org/10.1016/j.xnsj.2023.100241
5. Li R, Deutsch-Feldman M, Adams T, et al.; Bone Allograft Tuberculosis Investigators. Transmission of *Mycobacterium tuberculosis* to healthcare personnel resulting from contaminated bone graft material, United States, June 2021–August 2022. Clin Infect Dis 2023;76:1847–9. PMID:36660866 https://doi.org/10.1093/cid/ciad029
6. James JI. Tuberculosis transmitted by banked bone. J Bone Joint Surg Br 1953;35-B:578. PMID:13108919 https://doi.org/10.1302/0301-620X.35B4.578
7. American Association of Tissue Banks. Bulletin 22–2: recommendation issued to tissue banks regarding the risk of Mtb transmission. McLean, VA: American Association of Tissue Banks; 2022. https://www.aatb.org/bulletin-22-2
8. Food and Drug Administration. Important information for human cell, tissue and cellular and tissue-based product (HCT/P) establishments regarding tuberculosis outbreaks linked to a bone matrix product. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2023. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/important-information-human-cell-tissue-and-cellular-and-tissue-based-product-hctp-establishments-1
9. Tyrrell FC, Budnick GE, Elliott T, et al. Probability of negative *Mycobacterium tuberculosis* complex cultures based on time to detection of positive cultures: a multicenter evaluation of commercial-broth-based culture systems. J Clin Microbiol 2012;50:3275–82. PMID:22837326 https://doi.org/10.1128/JCM.01225-12
10. Marshall KE, Free RJ, Filardo TD, et al. Incomplete tissue product tracing during an investigation of a tissue-derived tuberculosis outbreak. Am J Transplant 2023. Epub September 15, 2023. PMID: 37717630 https://doi.org/10.1016/j.ajt.2023.09.005

Notes from the Field

Supply Interruptions of First- and Second-Line Oral Drugs to Treat Tuberculosis During the Previous 12 Months — California, January–March, 2023

Scott A. Nabity, MD[1,2]; Rocio Agraz-Lara, MSN[3,4]; Angelito Bravo, MD[4,5]; Robert Benjamin, MD[4,6]; Vanessa Fong, MPH[1,2]; C. Kin Lam, MS, MPH[1,2]; Chris Keh, MD[1]; Sundari Mase, MD[4,6,7]; Jennifer Flood, MD[1]

Tuberculosis (TB) drug supply disruptions are a recurring concern in the United States (*1*). Contributors to these disruptions include loss of manufacturers to the U.S. market, inefficient supply chains, and lack of active ingredients available for import.* The last severe U.S. TB drug shortage occurred in 2012, when isoniazid (INH) was temporarily unavailable for several months (*2*). INH and rifampin (RIF) are the cornerstones for treatment of drug-susceptible TB, and rifapentine (RPT), a long acting rifamycin, has been incorporated into shorter first-line regimens† to treat both latent TB infection (LTBI) (*3*) and TB disease§ (*4*). In recent years, the U.S. supply of several TB drugs has again been disrupted. The Food and Drug Administration has declared shortages of RPT (on March 25, 2020), RIF (on December 22, 2021), and INH (on May 17, 2023).¶ Approximately one fifth of all U.S. TB cases are reported from California (*5*). TB drug procurement is decentralized among the state's 61 local TB programs,** mirroring the decentralization among U.S. states and territories. The California Department of Public Health and the California TB Controllers Association assessed the impact of the shortage on California's TB programs.

Investigation and Outcomes

A web-based Research Electronic Data Capture (REDCap) survey (version 13.1.30; Vanderbilt University) was distributed to TB controllers and program managers of all 61 California TB programs†† to assess delays in availability§§ and unavailability of oral first- and second-line TB drugs during the preceding 12 months. On a priority scale of 1 (lowest) to 10 (highest), programs ranked the importance of addressing TB drug instability relative to other TB control priorities. Respondents were encouraged to confer with program, clinic, and pharmacy colleagues to obtain a single, comprehensive response for the TB program in each local health jurisdiction. Programs were categorized according to their average annual number of TB cases during 2016–2021 as high (15 or more cases) or low (fewer than 15 cases). This activity was reviewed by CDC and the California Department of Public Health, deemed not research, and conducted consistent with CDC policy.¶¶

Overall, 54 (89%) programs responded, including all categorized as high case-count programs. The mean priority level assigned to ensuring a stable supply of TB drugs was 8.6 (95% CI = 8.1–9.2) among all programs and 9.4 (95% CI = 8.8–9.9) among high case-count programs. Among the 50 programs in California reporting at least one TB case during 2016–2021, 32 (64%) experienced a delay in availability or unavailability of any oral first-line TB drug (Table). First-line oral TB drug supply interruptions led to delayed initiations or temporary pauses in treatment of TB disease or LTBI (37% for all programs and 55% for high case-count programs) and permanent changes in the choice of drugs to treat TB disease or LTBI and the duration of treatment (33% for all programs and 65% for high case-count programs). TB drug supply interruptions led to a negative patient outcome for 6% of all TB programs: two TB programs reported at least one case of prolonged treatment and a third program reported at least one adverse drug event.

Conclusions and Actions

Ensuring drug availability is a high priority for TB programs. This survey in California identified a high frequency of TB drug interruptions in 2022, which led to delayed treatment initiations and permanent regimen changes and restricted implementation of short-course regimens for both LTBI and TB disease. Programs also reported preventable negative patient outcomes

* https://www.hsgac.senate.gov/wp-content/uploads/2023-06-06-HSGAC-Majority-Draft-Drug-Shortages-Report.-FINAL-CORRECTED.pdf

† Oral first-line TB drugs include RIF, RPT, INH, rifabutin, pyrazinamide, and ethambutol. Oral second-line TB drugs included cycloserine, ethionamide, levofloxacin, linezolid, moxifloxacin, para-aminosalicylate, and pretomanid. Bedaquiline and clofazimine were not included in this survey because they have unique procurement processes.

§ These short course regimens include a 3-month regimen of weekly INH and RPT for LTBI treatment (3HP) and a 4-month regimen of INH, RPT, moxifloxacin, and pyrazinamide for drug-sensitive TB disease (4HPMZ).

¶ https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm (Accessed August 30, 2023).

** The 61 local TB programs in California have diverse infrastructures and TB incidences (average annual TB case counts during 2016–2021 ranged from zero to 508 cases).

†† The survey was available for completion from January 29 to March 17, 2023.

§§ TB drug delays were defined as short-lived interruptions in acquiring a drug, lasting a few weeks or less, and not broadly affecting programmatic or clinical practice. TB drug unavailability was defined as an interruption in the supply of a drug lasting more than a few weeks and potentially requiring a change in programmatic or clinical practice.

¶¶ 45 C.F.R. part 46.102(l)(2), 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.

TABLE. Frequency and effects of the unavailability of oral first- and second-line tuberculosis drugs during the previous 12 months — California, January–March 2023

Effects on program	no./No. (%)	
	High case-count programs*	All programs
Delay†		
Rifampin	15/20 (75.0)	**25/50 (50.0)**
Rifapentine	16/20 (80.0)	**25/50 (50.0)**
Rifabutin	1/20 (5.0)	**5/50 (10.0)**
Isoniazid	5/20 (25.0)	**8/50 (16.0)**
Pyrazinamide	5/20 (25.0)	**8/50 (16.0)**
Ethambutol	3/20 (15.0)	**3/50 (5.0)**
Any second-line TB drug§	5/20 (25.0)	**8/50 (16.0)**
Unavailability†		
Rifampin	6/20 (30.0)	**11/50 (22.0)**
Rifapentine	14/20 (70.0)	**20/50 (40.0)**
Rifabutin	0/20 (—)	**2/50 (4.0)**
Isoniazid	4/20 (20.0)	**4/50 (8.0)**
Pyrazinamide	0/20 (—)	**2/50 (4.0)**
Ethambutol	3/20 (14.0)	**2/50 (4.0)**
Any second-line TB drug§	1/20 (5.0)	**2/50 (4.0)**
Delayed initiation or paused treatment	11/20 (55.0)	**20/54 (37.0)**
TB disease only	2/11 (18.2)	**5/20 (25.0)**
LTBI only	8/11 (72.7)	**11/20 (55.0)**
Both TB disease and LTBI	1/11 (9.1)	**4/20 (20.0)**
Permanently changed regimen	13/20 (65.0)	**18/54 (33.3)**
TB disease only	2/13 (15.4)	**2/18 (11.1)**
LTBI only	11/13 (84.6)	**15/18 (83.3)**
Both TB disease and LTBI	0/13 (—)	**1/18 (5.6)**
Recorded a negative patient outcome¶	2/20 (10.0)	**3/54 (5.6)**
Not using 3HP due to rifapentine unavailability**	11/12 (91.7)	**13/24 (54.2)**
Not using 4HPMZ due to rifapentine unavailability**	5/13 (38.5)	**5/31 (16.1)**

Abbreviations: LTBI = latent tuberculosis infection; TB = tuberculosis; 3HP = 3-month regimen of weekly isoniazid and rifapentine for LTBI treatment; 4HPMZ = 4-month regimen of isoniazid, rifapentine, moxifloxacin, and pyrazinamide for drug-sensitive TB disease.

* High case-count programs are those reporting 15 or more TB cases during 2016–2021.

† Denominator includes only those programs reporting one or more TB case during 2016–2021.

§ Oral second-line TB drugs included cycloserine, ethionamide, levofloxacin, linezolid, moxifloxacin, para-aminosalicylate, and pretomanid. Bedaquiline and clofazimine were not included in this survey because they have unique procurement processes.

¶ One program recorded a negative patient outcome for LTBI only, and two reported negative patient outcomes for both TB disease and LTBI (two programs reported at least one case with prolonged treatment and one program reported at least one adverse drug event).

** Denominator restricted to programs not using the stated regimen.

caused by drug delays or unavailability. Limitations of this analysis included a retrospective study design, possibility of recall bias, and variability in respondents' interpretation of the definitions of access delays and unavailability of TB drugs. To meet the standards of practice for TB disease and LTBI, and to continue progress toward TB elimination, California has established a centralized buffer supply of several TB drugs. Securing a more stable TB drug supply might avert some of the unfavorable clinical and programmatic effects of TB treatment interruptions.

Acknowledgments

Survey respondents at the local TB programs.

Corresponding author: Scott A. Nabity, scott.nabity@cdph.ca.gov.

[1]Tuberculosis Control Branch, California Department of Public Health, Richmond, California; [2]Division of Tuberculosis Elimination, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, CDC; [3]San Francisco Department of Public Health, San Francisco, California; [4]California Tuberculosis Controllers Association, San Francisco, California; [5]Orange County Health Care Agency, Santa Ana, California; [6]Sonoma County Department of Health Services, Santa Rosa, California; [7]Division of Global Migration and Health, National Center for Emerging and Zoonotic Infectious Diseases, CDC.

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflicts of interest were disclosed.

References

1. CDC. Interruptions in supplies of second-line antituberculosis drugs—United States, 2005–2012. MMWR Morb Mortal Wkly Rep 2013;62:23–6. PMID:23325352
2. CDC. Impact of a shortage of first-line antituberculosis medication on tuberculosis control—United States, 2012–2013. MMWR Morb Mortal Wkly Rep 2013;62:398–400. PMID:23698604
3. Sterling TR, Njie G, Zenner D, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recomm Rep 2020;69(No. RR-1):1–11. PMID:32053584 https://doi.org/10.15585/mmwr.rr6901a1
4. Carr W, Kurbatova E, Starks A, Goswami N, Allen L, Winston C. Interim guidance: 4-month rifapentine moxifloxacin regimen for the treatment of drug-susceptible pulmonary tuberculosis—United States, 2022. MMWR Morb Mortal Wkly Rep 2022;71:285–9. PMID:35202353 https://doi.org/10.15585/mmwr.mm7108a1
5. Schildknecht KR, Pratt RH, Feng PI, Price SF, Self JL. Tuberculosis—United States, 2022. MMWR Morb Mortal Wkly Rep 2023;72:297–303. PMID:36952282 https://doi.org/10.15585/mmwr.mm7212a1

Notes from the Field

Seizures, Hyperthermia, and Myocardial Injury in Three Young Adults Who Consumed Bromazolam Disguised as Alprazolam — Chicago, Illinois, February 2023

Paul F. Ehlers, MD[1,2]; Amy Deitche[2]; Leslie M. Wise, PhD[3]; Sarah L. Patrick, PhD[3]; Alfreda Holloway-Beth, PhD[4]; Ross Ellison[5]; Jordan Trecki, PhD[6]; Roy Gerona, PhD[5]; Michael S. Wahl, MD[1,2]

Bromazolam is a "designer" triazolobenzodiazepine synthesized in 1976 but never approved for therapeutic use (*1*). Since its first detection in Sweden in 2016, a significant increase has persisted in both the toxicologic identification of bromazolam in combination with fentanyl and its identification in counterfeit benzodiazepine preparations (*2*). The number of law enforcement seizures in the United States that involved bromazolam increased from no more than three per year during 2016–2018 to 2,142 in 2022, and 2,913 in 2023.* In Illinois, bromazolam-involved† deaths increased from 10 in 2021 to 51 in 2022.§ Although human studies with clinical data are limited, animal models suggest bromazolam acts predominantly as a sedative, similar to other benzodiazepines, and to date, no signal for hyperthermia, myocardial injury, or seizures attributable to bromazolam intoxication exists (*3*). Although mostly detected alongside fentanyl or other opioids (88%–100% of tested samples),¶ consumption of bromazolam can be life-threatening even in the absence of other drugs. This report discusses a cluster of three young adult patients who were treated at local emergency departments for hyperthermia, seizures, and myocardial injury after consuming bromazolam disguised as alprazolam. This activity was reviewed by CDC, deemed not research, and was conducted consistent with applicable federal law and CDC policy.**

Case Series

On February 1, 2023, in a southern suburb of Chicago, three previously healthy young adults, two men aged 25 years (patients A and B) and a woman aged 20 years (patient C), ingested pressed tablets of bromazolam that they reported they believed to be alprazolam, a drug prescribed for anxiety and panic disorders, but which is misused recreationally because its effects include disinhibition and euphoria. They were found unresponsive by patient A's mother approximately 8 hours later. All three received naloxone from emergency medical services without response and were unresponsive on arrival at local emergency departments.†† Patient A was hypertensive (blood pressure measurement = 152/100 mm Hg), tachycardic (heart rate 124/minute), and hyperthermic (temperature = 101.7°F [38.7°C]); pupils were dilated but reactive, and he experienced multiple generalized seizures. He was intubated to maintain airway control. Patient B was hyperthermic (temperature = 100.4°F [38.0°C]) and was intubated because of unresponsiveness and multiple generalized seizures. Patient C was obtunded with focal seizures and was intubated. All three had myocardial injury as demonstrated by elevated troponin levels. Urine drug screen for all three patients was positive for benzodiazepines. None of the patients received flumazenil, a benzodiazepine overdose antidote that can precipitate benzodiazepine withdrawal and cause seizures or tachyarrhythmias (*4*). All were admitted to an intensive care unit, and the Illinois Poison Center was contacted for assistance in evaluation and management (Table).

Patient A required intubation until hospital day 5 because of depressed mental status. After extubation, he had moderate aphasia and dysphagia, and was discharged on hospital day 11 with persistent neurologic deficits. Patient B was extubated on hospital day 1 and discharged on day 4 with mild hearing difficulty, but otherwise neurologically intact. Patient C progressed to status epilepticus despite administration of multiple antiepileptic medications (lorazepam, propofol, levetiracetam, and valproic acid), and persistent coma. She was transferred to a second hospital on day 11 and was subsequently lost to follow-up. Testing of serum (the preferred body fluid) or plasma samples from all three patients by the Drug Enforcement Administration's Toxicology Testing Program (DEA TOX)§§ confirmed the presence of bromazolam (range = 31.1–207 ng/mL), without the presence of fentanyl or any other opioid.

* The National Forensic Laboratory Information System (NFLIS) is an important resource in monitoring illicit drug trafficking, including the diversion of legally manufactured pharmaceuticals into illegal markets. NFLIS-Drug is a comprehensive information system that includes data from forensic laboratories that handle approximately 98% of an estimated 1.5 million distinct annual federal, state, and local drug analysis cases. NFLIS-Drug includes drug chemistry results from completed analyses only. Query date was December 14, 2023; data for 2023 are still being reported. https://www.nflis.deadiversion.usdoj.gov/

† A case was categorized as bromazolam-involved if bromazolam was listed as a contributing cause of death on the death certificate in the Illinois Vital Records system.

§ https://dph.illinois.gov/data-statistics/vital-statistics.html

¶ Per surveillance from the Center for Forensic Science and Education, and the DEA TOX 2022 Annual Report. https://www.cfsre.org/images/content/reports/public_alerts/Public-Alert_Bromazolam_NPS-Discovery_061522.pdf

** 45 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.

†† Patients A and B were transported to the same facility; patient C was transported to a separate facility.

§§ The Drug Enforcement Agency has contracted with the University of California San Francisco to analyze biologic samples from patients who overdose on suspected novel psychoactive substances as part of the DEA TOX program. https://www.deadiversion.usdoj.gov/dea_tox/annual_reports/2022_Annual_Report.pdf

TABLE. Characteristics, circumstances, and co-occurring substances among bromazolam overdose patients — Chicago, Illinois, February 2023

Characteristic	Patient A	Patient B	Patient C
Age, yrs; sex	25; Male	25; Male	20; Female
Blood pressure, mm Hg	152/100	Unknown	132/109
Bromazolam level, ng/mL (plasma or serum) by LCMS	207 (plasma)	70.5 (plasma)	31.1 (serum)
Heart rate per min	124	Unknown	118
In-hospital neurologic recovery (HD)	Yes (HD 5)	Yes (HD 1)	No
Myocardial injury (peak troponin, ng/L)	Yes (154)	Yes (239)	Yes (430)
Neurologic deficits at discharge	Moderate aphasia	Hearing loss	Unknown
Other LCMS findings using plasma (level, ng/mL)	8-aminoclonazolam (0.2)*	Aripiprazole (NQ), methamphetamine (0.5),† midazolam (NQ)	None
Rhabdomyolysis (finding)	Yes (CK 4067/Cr 1.41)	No	No
Seizures	Multiple	Multiple	Refractory status epilepticus
Temperature	101.7°F (38.7°C)	100.4°F (38.0°C)	98.8°F (37.1°C)
Urine drug screen result	BZD	AMP, BZD, THC	BZD

Abbreviations: AMP = amphetamine; BZD = benzodiazepine; CK = creatinine kinase; Cr = creatinine; HD = hospital day; LCMS = liquid chromatography–mass spectrometry; NQ = not quantified; THC = delta-9 tetrahydrocannabinol.

* 8-aminoclonazolam is the primary metabolite of the designer BZD clonazolam, which is the 1,4-triazolo derivative of clonazepam. 0.2 ng/mL is under the lower limit of quantification (0.4 ng/mL) but above the lower limit of detection (0.1 ng/mL).

† Above the lower limit of detection (0.4 ng/mL) but below the lower limit of quantification (6.0 ng/mL).

Preliminary Conclusions and Actions

Bromazolam has been misrepresented[¶¶] as a benzodiazepine approved by the Food and Drug Administration. The constellation of signs and symptoms in this case series is unexpected for a benzodiazepine overdose, which might 1) be a product of anoxic brain injury attributable to prolonged obtundation, 2) represent additional features of bromazolam in overdose or withdrawal, or 3) be due to an additional intoxicant not detected on liquid chromatography–mass spectrometry. Since 2021, 114 cases analyzed via DEA TOX had specimens that were positive for bromazolam, with mean blood levels reported as 44.8 ng/mL. Bromazolam has also been detected in drivers arrested for driving under the influence, in whom it produced a largely sedative toxidrome (*5*).

It is essential that physicians, medical examiners, toxicology laboratories, public health officials, and emergency responders be aware of the increased presence of bromazolam both in polydrug ingestions and in substance use disorder patients who report the use of benzodiazepines. Clinically, this knowledge can inform prognosis (two out of three patients in this cluster had confirmed recovery to near independence) and could indicate the need for aggressive seizure control. From a public health perspective, the constellation of findings reported should prompt close involvement with public health officials and regional poison centers, given the more severe findings in these reported cases compared with those expected from routine benzodiazepine overdoses. Clinicians, responders, and health officials should also consider bromazolam in cases of patients requiring treatment for seizures, myocardial injury, or hyperthermia after illicit drug use, as occurred in these case reports. Bromazolam intoxication should also be suspected in patients with a sedative toxidrome who do not respond adequately to naloxone reversal. In cases of suspected bromazolam exposure, clinicians should call their poison center for additional guidance. Testing for bromazolam is not routinely available but can be arranged through a variety of send-out reference laboratories.[***]

¶¶ Bromazolam, sold as alprazolam, submitted anonymously as sample ID 16949 analyzed by DrugsData, an independent laboratory testing. https://drugsdata.org/view.php?id = 16949

*** Send-out reference laboratories offer a wide variety of specialized testing that is typically not available at primary hospital laboratories. Examples include NMS Labs and Quest Diagnostics, among others, in addition to the DEA TOX program.

Corresponding author: Paul Ehlers, paul.ehlers@cookcountyhhs.org.

[1]Toxikon Consortium, Chicago, Illinois; [2]Illinois Poison Center; [3]Division of Emerging Health Issues, Office of Health Promotion, Illinois Department of Public Health, Springfield, Illinois; [4]Epidemiology Unit, Cook County Department of Public Health, Chicago, Illinois; [5]Clinical Toxicology and Environmental Biomonitoring Lab, University of California San Francisco, San Francisco, California; [6]Drug and Chemical Evaluation Section, Diversion Control Division, Drug Enforcement Administration, Arlington, Virginia.

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflicts of interest were disclosed.

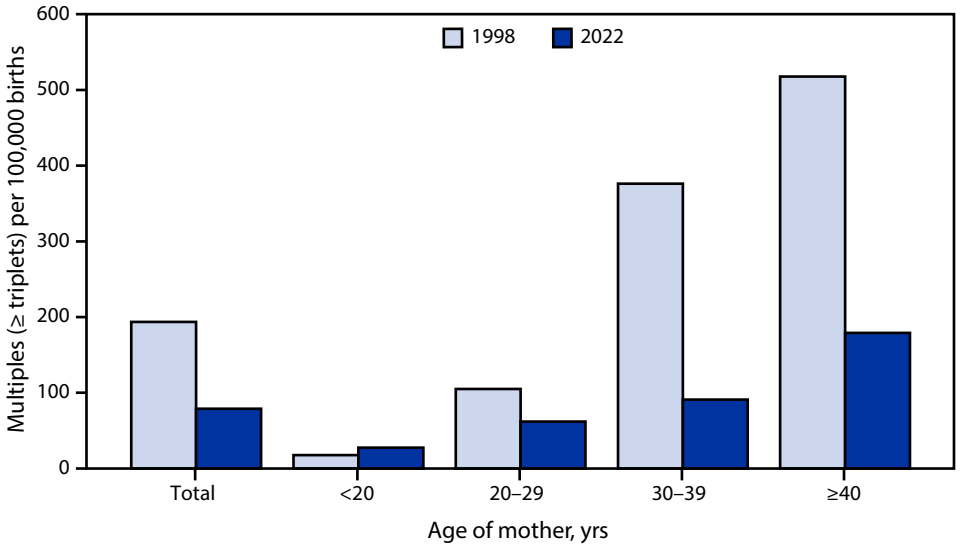
References

1. Manchester KR, Lomas EC, Waters L, Dempsey FC, Maskell PD. The emergence of new psychoactive substance (NPS) benzodiazepines: a review. Drug Test Anal 2018;10:37–53. PMID:28471096 https://doi.org/10.1002/dta.2211
2. Mérette SAM, Thériault S, Piramide LEC, Davis MD, Shapiro AM. Bromazolam blood concentrations in postmortem cases—a British Columbia perspective. J Anal Toxicol 2023;47:385–92. PMID:36715069 https://doi.org/10.1093/jat/bkad005
3. Hester JB Jr, Von Voigtlander P. 6-Aryl-4H-s-triazolo[4,3-a][1,4]benzodiazepines. Influence of 1-substitution on pharmacological activity. J Med Chem 1979;22:1390–8. PMID:42799 https://doi.org/10.1021/jm00197a021
4. Penninga EI, Graudal N, Ladekarl MB, Jürgens G. Adverse events associated with flumazenil treatment for the management of suspected benzodiazepine intoxication—a systematic review with meta-analyses of randomised trials. Basic Clin Pharmacol Toxicol 2016;118:37–44. PMID:26096314 https://doi.org/10.1111/bcpt.12434
5. Papsun DM, Chan-Hosokawa A, Lamb ME, Logan B. Increasing prevalence of designer benzodiazepines in impaired driving: a 5-year analysis from 2017 to 2021. J Anal Toxicol 2023;47:668–79. PMID:37338191 https://doi.org/10.1093/jat/bkad036

QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Rate of Triplet and Higher-Order Multiple Births,*,† by Age of Mother — National Vital Statistics System, United States, 1998 and 2022



* Per 100,000 births.
† Triplet and higher-order multiple births are births in triplet, quadruplet, quintuplet, and higher-order deliveries.

The triplet and higher-order multiple birth rate declined from an all-time high of 193.5 per 100,000 total births in 1998 to 78.9 in 2022. From 1998 to 2022, triplet and higher-order birth rates increased among mothers aged <20 years (from 17.6 to 27.5) but declined among mothers aged ≥20 years. In both 1998 and 2022, triplet and higher-order multiple birth rates were lowest among mothers aged <20 years and highest among mothers aged ≥40 years (517.6 in 1998 and 179.0 in 2022) but differences across the age groups narrowed from 1998 to 2022.

Source: National Center for Health Statistics, National Vital Statistics System, Natality Data, 1998 and 2022. https://www.cdc.gov/nchs/nvss/births.htm

Reported by: Joyce A. Martin, MPH, jcm9@cdc.gov.

For more information on this topic, CDC recommends the following link: https://www.cdc.gov/art/key-findings/multiple-births.html

The *Morbidity and Mortality Weekly Report (MMWR)* Series is prepared by the Centers for Disease Control and Prevention (CDC) and is available free of charge in electronic format. To receive an electronic copy each week, visit *MMWR* at *https://www.cdc.gov/mmwr/index.html*.

Readers who have difficulty accessing this PDF file may access the HTML file at https://www.cdc.gov/mmwr/index2023.html. Address all inquiries about the *MMWR* Series to Editor-in-Chief, *MMWR* Series, Mailstop V25-5, CDC, 1600 Clifton Rd., N.E., Atlanta, GA 30329-4027 or to mmwrq@cdc.gov.

ISSN: 0149-2195 (Print)