Bloodstream Infections With a Novel Nontuberculous *Mycobacterium* Involving 52 Outpatient Oncology Clinic Patients——Arkansas, 2018

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Background. In July 2018, the Arkansas Department of Health (ADH) was notified by hospital A of 3 patients with bloodstream infections (BSIs) with a rapidly growing nontuberculous *Mycobacterium* (NTM) species; on 5 September 2018, 6 additional BSIs were reported. All were among oncology patients at clinic A. We investigated to identify sources and to prevent further infections.

Methods. ADH performed an onsite investigation at clinic A on 7 September 2018 and reviewed patient charts, obtained environmental samples, and cultured isolates. The isolates were sequenced (whole genome, 16S, *rpoB*) by the Centers for Disease Control and Prevention to determine species identity and relatedness.

Results. By 31 December 2018, 52 of 151 (34%) oncology patients with chemotherapy ports accessed at clinic A during 22 March–12 September 2018 had NTM BSIs. Infected patients received significantly more saline flushes than uninfected patients ($P < .001$) during the risk period. NTM grew from 6 unused saline flushes compounded by clinic A. The identified species was novel and designated *Mycobacterium FVL 201832*. Isolates from patients and saline flushes were highly related by whole-genome sequencing, indicating a common source. Clinic A changed to prefilled saline flushes on 12 September as recommended.

Conclusions. *Mycobacterium FVL 201832* caused BSIs in oncology clinic patients. Laboratory data allowed investigators to rapidly link infections to contaminated saline flushes; cooperation between multiple institutions resulted in timely outbreak resolution. New state policies being considered because of this outbreak include adding extrapulmonary NTM to ADH's reportable disease list and providing more oversight to outpatient oncology clinics.

Keywords. nontuberculous mycobacteria; healthcare-associated infections; outbreak investigation.

In recent years, outpatient management of cancers has become increasingly more common [1]. Infections are a substantial contributor to morbidity and mortality among patients with cancer, despite overall improvements in survival [2–4]. Immunosuppressive chemotherapy drugs, effects of the underlying cancer, and long-term indwelling central venous lines (CVLs) all contribute to the risk for infections among oncology patients.

Sterile drug compounding, defined by the United States Pharmacopeia (USP) General Chapter 797 as "combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug or bulk drug substance to create a sterile medication" [5], is also known to be associated with risks. The US Food and Drug Administration (FDA) has regulatory oversight of compounding facilities, though many outpatient cancer clinics compound medications for patients without registering with the FDA and many states do not have the resources for day-to-day oversight of these facilities [6, 7]. Since 2011, the Centers for Disease Control and Prevention (CDC) has provided guidance on the basics of outpatient oncology clinic infection control and prevention that includes information on medication handling and preparation [8].

In July 2018, an office of the Arkansas Department of Health (ADH) not associated with outbreak response was notified by hospital A of 3 patients with 1 or more blood cultures that tested positive for an organism initially identified as *Mycobacterium parafortuitum* [9], a nontuberculous *Mycobacterium* (NTM). No investigation was initiated until 5 September 2018, when 6 additional patients who tested positive for NTM were reported to ADH's Healthcare-Associated Infections office. All had received treatment at clinic A, a private, freestanding, outpatient oncology clinic. ADH, CDC, hospital A, and clinic A investigated the cluster of NTM bloodstream infections to determine the source and provide recommendations to stop transmission.

METHODS

Epidemiologic Investigation

Definition of Exposure

ADH visited hospital A and clinic A on 7 September 2018. Clinic A allowed ADH to collect environmental and product samples for culture and observe staff practices; they also provided access to electronic medical records (EMRs), *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes billed for visits, and paper chemotherapy port access logs. Twenty-three clinic-compounded flushes for use with patient chemotherapy ports were collected by investigators; 5 were cultured at the hospital A microbiology laboratory. Hospital A also provided ADH access to their EMRs for review.

The first positive blood culture result with NTM was obtained on 20 May 2018; 1 patient had persistent positive blood cultures for approximately 6 weeks. We defined patients with chemotherapy ports accessed beginning 22 March 2018 to be at risk for exposure. ADH provided clinic A and hospital A with a list of all exposed patients based on review of chemotherapy port access logs from clinic A; we inferred that each port access for blood draw was followed by a flush since flush use was not specifically documented, and the log was the best available source for estimating these exposures.

Notification and Screening of Exposed Patients

Clinic A providers notified all exposed patients by phone and then by mailed letter on 20 September 2018 and scheduled asymptomatic exposed patients for blood cultures in their facility as quickly as feasible for patients through the month of October. They contracted directly with a private reference laboratory (laboratory A) to process and perform the cultures.

With input from CDC, hospital A, and laboratory A, ADH defined a confirmed outbreak case as a positive blood culture showing beaded and branching gram-variable rods that excreted orange pigment identified as NTM in any clinic A patient, with or without clinical symptoms, who had received ≥1 flush during 22 March–12 September 2018.

Bacterial Isolates

Isolates were initially reported as *M. parafortuitum* by 16S ribosomal RNA (rRNA) sequencing at a commercial reference laboratory. Patient isolates and chemotherapy ports removed from patients were sent to CDC for further analysis and identification. To confirm species identity, isolates taken from Middlebrook 7H11 plates (Remel, Lenexa, Kansas) were subjected to matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry using a modified version of the manufacturer's Standard Operating Procedure Mycobacteria Extraction (MycoEX; Bruker Daltonics, Billerica, Massachusetts) protocol. Spectra were analyzed using MALDI-TOF Biotyper Compass software and Mycobacteria Library version 4.0 (Bruker Daltonics), supplemented by

CDC's MicrobeNet (CDC, Atlanta, Georgia) library. The manufacturer-recommended cutoff scores for species-level identification is ≥2.00, 1.700–1.999 for genus-level identification, and <1.700 as unreliable for identification. Sanger DNA sequencing of the full-length 16S rRNA [10, 11] and region V of the *rpoB* gene [12] were also performed after MALDI-TOF failed to provide a definitive identification. Resulting sequences were compared with sequences in GenBank, using basic local alignment search tool.

Whole-genome Sequencing

Whole-genome sequencing (WGS) was performed to assist in identification and characterization and determine relatedness. DNA was extracted from a representative of subset isolates using a Promega Maxwell 16 Cell Low Elution Volume DNA Purification Kit and Maxwell 16 MDx Instrument (Promega, Madison, Wisconsin). WGS was performed using an Illumina MiSeq System (Illumina, San Diego, California) with a 2 × 250 paired-end run after DNA shearing to 600 bp using the Covaris ME220 Focused ultrasonicator (Covaris, Woburn, Massachusetts), and genomic library preparation using the NuGEN Ovation Ultralow System V2 assay kit (NuGEN, San Carlos, California) and the PerkinElmer Zephyr G3 NGS Workstation (Perkin Elmer, Waltham, Massachusetts).

Bioinformatic Analyses

Isolates were analyzed using CDC's Division of Healthcare Quality and Promotion QuAISAR pipeline for quality analyses, genome assembly, and species identification by average nucleotide identity using PYANI (ANIm) [13]. For phylogenetic analyses, SNVPhyl was used [14]. The assembly of isolate 2018-32-35-02 was randomly selected as reference for phylogenetic analyses.

Statistical Methods

A database was created to consolidate patient data originating from clinic A, hospital A, and laboratory A. Race was not documented consistently in clinic A charts, so the ADH abstractor inferred race from patient pictures if present and the data were otherwise missing. Unadjusted associations were used to compare characteristics among exposed patients with positive vs negative blood cultures, and among patients with positive blood cultures who were symptomatic vs asymptomatic, using χ^2 test, Fisher exact test, unpaired *t* test, Wilcoxon rank-sum test, and Mann-Whitney *U* test. Nonparametric analyses were used where cell sizes were <5 and distributions warranted. An α level of .05 determined statistical significance for all analyses. Multiple logistic regression was used to assess unadjusted and adjusted associations between patient characteristics and case status. Because there were numerous potential explanatory variables, we used backward stepwise variable selection with the Akaike information criterion as the

standard for model construction. All analyses were performed using R version 3.5.1.

Both the CDC and the University of Arkansas for the Medical Sciences (UAMS) institutional review board (IRB) reviewed this study and determined it to be nonresearch (UAMS IRB 228974).

RESULTS

Epidemiologic Investigation

Descriptive Demographics of Cultured Patients

In total, 151 clinic A patients were exposed. Blood cultures were collected from 131 patients, 7 patients died, and 13 declined or could not be contacted. Patients' chemotherapy ports were accessed and flushes administered in 2 locations of clinic A: the blood-draw area and the infusion area. As of 31 December 2018, 52 (34%) patients with chemotherapy ports accessed in the blood-draw area during 22 March–12 September 2018 tested positive for NTM bloodstream infections (Table 1). Among these, 23 patients were cultured because they had symptoms of fever, rigors, or general malaise (Figure 1). Additionally, 29 patients were asymptomatic but had ≥1 positive cultures by active screening. All patients were notified by their healthcare provider at either hospital A or clinic A of their culture status; patients with positive blood cultures were scheduled for port removal and treated with multidrug antimycobacterial therapy for 2–6 weeks, depending on severity of illness and underlying medical problems.

Risk Factors Among Cases

There were significantly more women than men with positive blood cultures ($P = .02$, χ^2 test) (Table 1). Among the positive culture group, 16 patients had metastatic cancer. No *ICD-10* codes or laboratory results for neutropenia, leukopenia, or lymphopenia were available in clinic A's EMR. There was no significant difference in distribution of age, race, or underlying cancer diagnoses between the positive and negative culture groups. Three patients with positive cultures and advanced cancer died. Infected patients had received a median of 4.5 (range, 1–17) flushes during the risk period (22 March–12 September 2018), significantly more than the culture-negative group ($P < .001$, Wilcoxon rank-sum test).

Risk Factors Among Symptomatic Cases

Within the positive culture group, we compared symptomatic vs asymptomatic patients (Table 2). The symptomatic group received significantly more flushes than the asymptomatic group. There was no significant difference by age, sex, race, or underlying cancer diagnosis between the groups.

Table 1. Descriptive Demographics of Exposed Patients, With Comparisons of Those With Positive and Negative Blood Cultures

Characteristic	Overall[a,b]	Positive Culture (n = 52)	Negative Culture (n = 79)	P Value
Infection prevalence among exposed, no./No. (%)	52/151 (34)	…	…	
Prevalence of symptoms among positive cultures, No. (%)	…	23 (44)	…	
Age, y, mean (SD)	64.6 (11.1)	64.1 (12.9)	64.2 (10.2)	.95
Sex, male, No. (%)	56 (43)	15 (29)	41 (51)	.02
Race/Ethnicity, No. (%)				
White	67 (51)	30 (58)	37 (47)	.37
Black	39 (30)	14 (27)	25 (32)	
Other	25 (19)	8 (15)	17 (22)	
Underlying cancer diagnosis, No.				
Breast	20	7	13	.80
Colorectal	17	7	10	1
Lung	21	7	14	.63
Prostate	3	2	1	.56
Gynecologic	9	4	5	.74
Ovarian[c]	6	3	3	1
Other	63	22	41	
Metastatic, any type[d]	49	16	33	.28
No. of flushes received during risk period, median (range)	3 (1–17)	4.5 (1–17)	3 (1–12)	< .001
Male	6 (1–17)[e]	6 (1–17)[f]	4 (1–12)[g]	
Female	4 (1–16)[e]	4 (1–16)[f]	2 (1–10)[g]	

Abbreviation: SD, standard deviation.

[a]Denominator for Overall column is 131 unless otherwise noted.

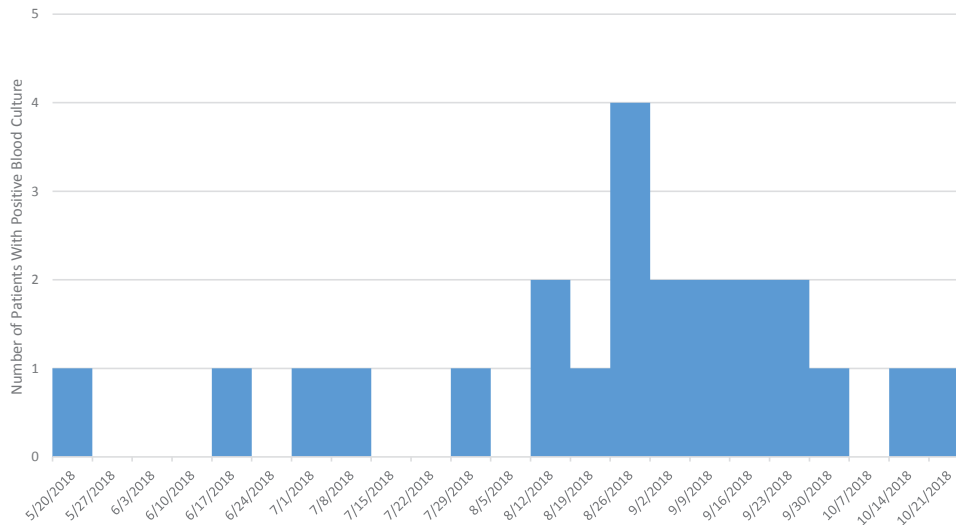[b]Some patients in the negative culture group had >1 cancer diagnosis, so denominator is >131.

[c]Ovarian cancers are also counted in the "Gynecologic" group.

[d]Metastatic cancers may be included in the other categories listed.

[e]*P* = .04.

[f]*P* = .54.

[g]*P* = .37.

Figure 1. Number of patients presenting symptomatically with positive blood culture for *Mycobacterium FVL 201832* by date, May–October 2018. Epidemic curve of 23 symptomatic cases by date (shown as month/day/year) of first positive blood culture.

Incubation Period

For each patient with ≥1 positive cultures, we aligned all clinic encounters in which a flush exposure was inferred, onset date of symptoms (if applicable), and date of first positive blood culture (Figure 2). Patients who had received only 1 flush were identified in April (n = 3), May (n = 2), June (n = 1), July (n = 1), August (n = 4), and September (n = 1), indicating flush contamination over an extended period; the remaining 40 patients had >1 flush before positive culture results. Because flushes were not enumerated, we estimated that there was 1 flush used per visit. The incubation period between the last flush received and positive blood culture was a median of 23 days (range, 0–171 days); median time between when the first flush was received during the risk period and positive blood culture was 107.5 days (range, 1–190 days). Among 12 patients who received a single flush during the risk period, the median incubation period was 122.5 days (range, 11–171 days). Three patients who had positive cultures in July were treated for their infections and then had ≥1 flushes later during the risk period. Follow-up cultures from all 3 patients after the risk period were negative.

Observations at Clinic A and Patient Follow-up

Onsite investigation identified staff compounding 10-mL saline flushes by drawing from intravenous fluid (IVF) bags near sinks, storage of partially used saline bags without dates in cabinets with food and other supplies, and no dates or lot number tracking on syringes after they were compounded and stored for an indefinite period in plastic drawers. The clinic reported that this had always been their standard practice.

Clinic A changed to commercially produced sealed flushes on 12 September and no further positive cases were identified in patients of clinic A who received flushes outside of the initially established risk period. Four of 5 clinic-made saline flushes sent to the hospital A microbiology laboratory were positive for the same NTM within 72 hours of culture. Additionally, 9 patients were identified whose ports were accessed for chemotherapy administration during the risk period, but in the infusion area of the clinic. All were asymptomatic and none tested positive for NTM by blood culture.

Table 2. Descriptive Demographics of Patients With Positive Blood Culture, With Comparisons of Symptomatic and Asymptomatic Patients

Characteristic	Symptomatic (n = 23)	Asymptomatic (n = 29)	P Value
Age, y, mean (SD)	63.7 (12.8)	64.4 (13.2)	.85
Sex, male, No. (%)	9 (43)	6 (26)	.22
Race/Ethnicity, No. (%)			
White	13 (57)	17 (59)	.92
Black	6 (26)	8 (28)	
Other	4 (17)	4 (14)	
Underlying cancer diagnosis, No.			
Breast	3	4	1
Colorectal	3	4	1
Lung	4	3	.63
Prostate	1	1	1
Gynecologic	2	2	1
Ovarian[a]	2	1	.58
Other	10	15	
Metastatic, any type[b]	8	15	.80
No. of flushes received during risk period, median (range)	6 (1–17)	2 (1–12)	< .001

Abbreviation: SD, standard deviation.

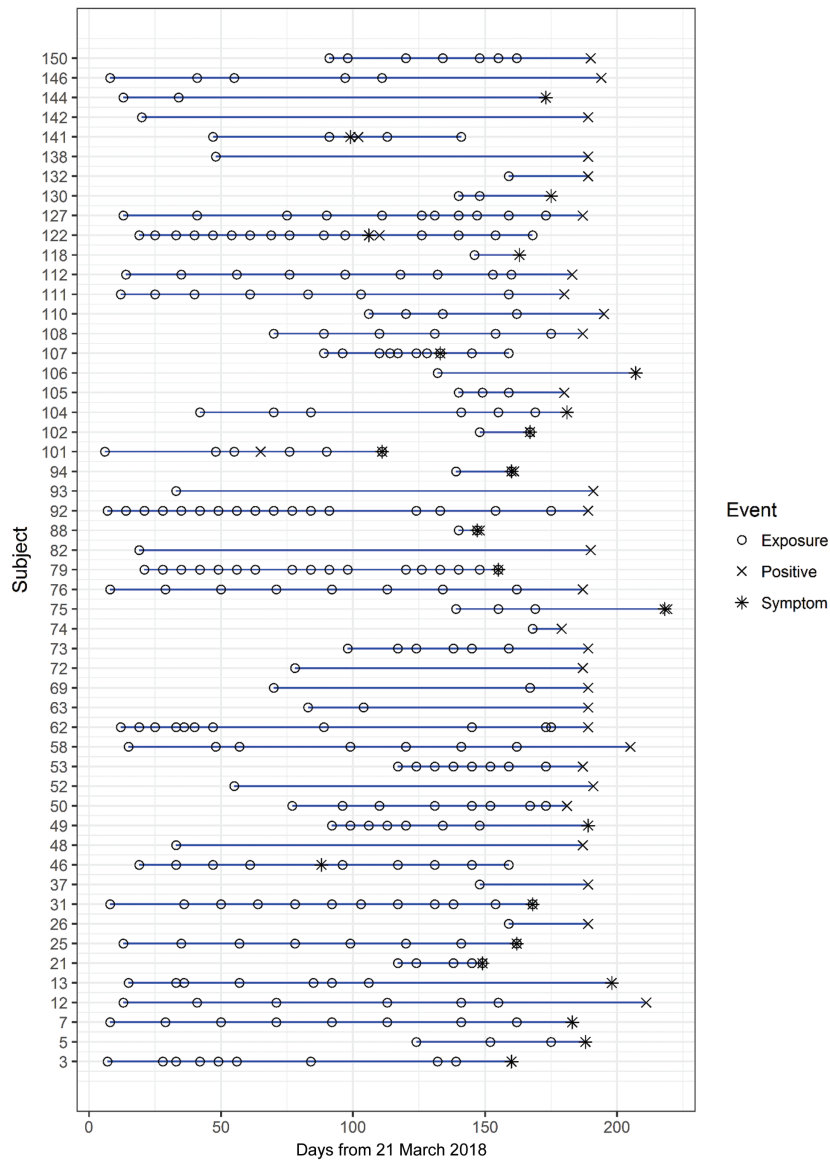[a]Ovarian cancers are also counted in the "Gynecologic" group.

[b]Metastatic cancers may be included in the other categories listed.

Figure 2. Dates of exposures, onset of symptoms, and positive cultures in the affected 52 patients.

Bacterial Isolates

The organism grew from 6 of 7 flushes from the blood-draw area, 0 of 16 flushes from the infusion area, and 9 of 9 patient ports sent for culture after removal. All environmental samples collected from clinic A, which included saline from a partially used IVF bag, materials used in accessing ports, swab samples from water taps and surfaces in the blood-draw and infusion areas, and bulk water samples were culture negative for the NTM. We examined the source, timing, and type of positive cultures for all 52 patients, and summarized the findings in Supplementary Table 1.

NTM species initially identified as *M. parafortuitum* grew smooth, orange colonies on Middlebrook 7H11 agar at 35°C after 3 days (Supplementary Figure 1). Species confirmation using MALDI-TOF was attempted, but failed to yield reliable identification with an average score of 1.35. The low score, but good spectral quality, indicated the absence of this particular species in current MALDI-TOF databases. Library entries using reference isolates of this aberrant NTM were generated, then added to CDC's MicrobeNet database, which subsequently facilitated its identification by MALDI-TOF. The isolates were found to be most closely related to species within the *Mycobacterium fortuitum* group and *M. parafortuitum* [15] by16S rRNA gene sequencing (98.9%). The isolates were only remotely related to any validated species by *rpoB* gene sequencing, with *Mycobacterium grossiae* [16] being the most closely related (93.2%). The 16S rRNA and *rpoB* gene sequences for the type strain are also accessible through CDC's MicrobeNet. The NTM

Figure 3. Phylogenetic tree from SNVPhyl. Scale is average substitutions per site.

species was determined by CDC to be novel based on 16S and *rpoB* sequencing results and was designated *Mycobacterium FVL 201832.*

WGS and Bioinformatics Analysis

Fourteen isolates (6 chemotherapy ports, 5 peripheral veins, and 3 flushes) underwent WGS. Average nucleotide identity results, using the National Center for Biotechnology Information (NCBI) reference genomes from >20 species of NTM were 85% or less, confirming that *Mycobacterium FVL 201832* does not belong to any recognized species in NCBI (see accession numbers for sequence data in the Notes).

For phylogenetic analyses, 13 isolates were nearly identical (0–2 single-nucleotide polymorphisms [SNPs] across a 90% core genome). Isolate 14 was also highly related (9 or 10 SNPs from the other isolates across a 90% core genome) (Supplementary Table 2; Figure 3). Together, these data provide evidence of a common source (Figure 3).

Patient Risk Factors

In unadjusted logistic regression, only female sex was significantly associated with having a positive blood culture (Table 3). When adjusting for covariates, female sex and increasing number of flushes received were significantly associated with infection; no specific cancer diagnosis was significantly associated with infection, and direct measures of immunosuppression were not available for analysis.

DISCUSSION

Novel *Mycobacterium FVL 201832* caused a cluster of bloodstream infections linked to saline flushes compounded in clinic A. Patient and flush culture results allowed investigators to rapidly link these infections to contaminated flushes within 1 week of the initial site visit.

There are multiple potential risks to compounding saline flushes in outpatient settings, including batch preparation, contamination due to environmental exposures (ie, near a sink), and accessing an IVF bag intended as single use multiple times. Per the FDA's Compounding Report from 2017, "Compounding drugs under insanitary conditions creates a significant risk of contamination that could lead to widespread patient harm, especially when the compounder engages in large-scale, nonpatient specific compounding and distribution" [7]. An outbreak of *Enterobacter cloacae* and *Klebsiella oxytoca* in Chicago in 2004 [17], a cluster of *Tsukamurella* species infections in 2011–2012 in West Virginia [18], and a cluster of *Exophilia dermatitidis* fungal bloodstream infections in New York State in 2016 [19] were each associated with clinic-compounded flushes in outpatient oncology clinics. Additionally, NTM are known to grow in tap water and form biofilms in pipes, making this the most likely source of contamination in the outbreak [20]. Clinics that compound flushes outside of a pharmacy, or without a pharmacist present, are still held to the USP 797 standard for sterile compounding; if there is a need to compound drugs, such as a shortage of prefilled saline flushes,

Table 3. Unadjusted and Adjusted Odds Ratios for Risk Factors Associated With Positive Blood Culture for *Mycobacterium FVL 201832*

Risk Factor	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age	0.99 (.97–1.03)	…
No. of flushes received	1.09 (.99–1.20)	1.12 (1.02–1.25)
Metastatic cancer diagnosis	0.62 (.29–1.29)	…
Male sex	0.38 (.17–.78)	0.31 (.13–.66)
Non-white race	0.74 (.24–2.16)	…
White race	1.45 (.65–3.31)	…

Abbreviations: CI, confidence interval; OR, odds ratio.

clinics may utilize the services of a registered outsourcing facility to support their needs to reduce the risks of contamination [5].

This investigation stimulated broader outreach and an evaluation of practices and policies in Arkansas. As a first step, all outpatient clinics in the state that reported treating >1 oncology patient were sent communications containing CDC's outpatient oncology clinic infection prevention recommendations [10]. Additionally, infection control assessment and response (ICAR) visits for assistance with assessing facilities' infection prevention policies and readiness were offered to each clinic. Outreach began during the spring of 2019 and will likely continue through 2020. In the United States, each state has different requirements and authority in regulating healthcare facilities. In Arkansas, ADH has no authority to regulate outpatient clinics; this duty rests with the state medical board, since all outpatient facilities operate under the jurisdiction of their medical director's medical license only. Because approximately 200 clinics in the state report caring for oncology patients and limited resources within ADH are available, one possibility being considered for enhanced guidance would require clinics to affiliate with an infection control provider to oversee their policies and procedures. As an outbreak investigation follow-up, an ICAR visit was performed at clinic A using CDC's ICAR tool for outpatient settings to assist the facility with strengthening its overall infection control practices.

The Council of State and Territorial Epidemiologists case definition for extrapulmonary NTM infections was established in 2017 [21], but adoption is at the discretion of each state. By making NTM reportable using this case definition, jurisdictions may improve the ability to identify clusters of cases and intervene in a timely manner. ADH is considering adding extrapulmonary NTM infections to the state reportable disease list.

There are several limitations to this study. Although we were able to use billing data to confirm underlying cancer diagnoses, we were unable to ascertain comorbidities among the patient population, including lymphopenia, neutropenia, and diabetes, or cumulative chemotherapy dose exposure, because of difficulties extracting data from clinic A's EMR and limitations of staffing available during the course of the investigation. The presence of a CVL, including chemotherapy ports, are known to be a risk factor for NTM bloodstream infections; immunosuppression from medications like chemotherapy and specific cytokine defects, including interferon-γ and interleukin 12, also make patients more susceptible [22–24]. Additionally, race was not documented in the EMR for most patients, but many records included patient photographs. When race was not documented but a picture was included, race was inferred from the appearance of the photograph by 1 investigator, but 19% of charts had no race documentation or photograph, limiting interpretation of race data. Finally, there were at least 2 patients with contaminant gram-positive rods or other organisms that were quickly referred for chemotherapy port removal before complete identification. This caused some misclassification of case counts during the outbreak, but after results were available they were excluded from analyses.

This investigation of a novel pathogen highlights the adverse effects possible of compounding in the outpatient setting. Fifty-two patients required unplanned surgical procedures to remove infected ports, disrupting their cancer treatment and, for many, requiring hospitalization for initial treatment of the infection. This outbreak also serves as a reminder that guidelines for compounding practices must be emphasized and that education for providers (including outpatient oncology centers) should be ongoing to prevent contamination of injectable products from occurring in the future.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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