

# Outbreak of *Francisella novicida* Bacteremia Among Inmates at a Louisiana Correctional Facility

Meghan E. Brett,<sup>1,2</sup> Laurel B. Respicio-Kingry,<sup>2</sup> Stephanie Yendell,<sup>1,3</sup> Raoult Ratard,<sup>4</sup> Julie Hand,<sup>4</sup> Gary Balsamo,<sup>4</sup> Christine Scott-Waldron,<sup>4</sup> Catherine O'Neal,<sup>5</sup> Donna Kidwell,<sup>6</sup> Brook Yockey,<sup>2</sup> Preety Singh,<sup>7</sup> Joseph Carpenter,<sup>8</sup> Vincent Hill,<sup>9</sup> Jeannine M. Petersen,<sup>2</sup> and Paul Mead<sup>2</sup>

<sup>1</sup>Epidemic Intelligence Service, Centers for Disease Control and Prevention (CDC), Atlanta, Georgia; <sup>2</sup>Bacterial Diseases Branch, and <sup>3</sup>Arboviral Diseases Branch, Division of Vector-Borne Diseases, CDC, Fort Collins, Colorado; <sup>4</sup>Louisiana Office of Public Health, New Orleans, <sup>5</sup>Infectious Diseases, Louisiana State University Medical Center, Baton Rouge, <sup>6</sup>Louisiana Office of Public Health, Shreveport Regional Laboratory, Shreveport, and <sup>7</sup>Louisiana Department of Corrections, Baton Rouge; and <sup>8</sup>Division of Healthcare Quality Promotion and <sup>9</sup>Waterborne Disease Prevention Branch, CDC, Atlanta, Georgia

**Background.** *Francisella novicida* is a rare cause of human illness despite its close genetic relationship to *Francisella tularensis*, the agent of tularemia. During April–July 2011, 3 inmates at a Louisiana correctional facility developed *F. novicida* bacteremia; 1 inmate died acutely.

**Methods.** We interviewed surviving inmates; reviewed laboratory, medical, and housing records; and conducted an environmental investigation. Clinical and environmental samples were tested by culture, real-time polymerase chain reaction (PCR), and multigene sequencing. Isolates were typed by pulsed-field gel electrophoresis (PFGE).

**Results.** Clinical isolates were identified as *F. novicida* based on sequence analyses of the 16S ribosomal RNA, *pgm*, and *pdpD* genes. *PmeI* PFGE patterns for the clinical isolates were indistinguishable. Source patients were aged 40–56 years, male, and African American, and all were immunocompromised. Two patients presented with signs of bacterial peritonitis; the third had pyomyositis of the thigh. The 3 inmates had no contact with one another; their only shared exposures were consumption of municipal water and of ice that was mass-produced at the prison in an unenclosed building. Swabs from one set of ice machines and associated ice scoops yielded evidence of *F. novicida* by PCR and sequencing. All other environmental specimens tested negative.

**Conclusions.** To our knowledge, this is the first reported common-source outbreak of *F. novicida* infections in humans. Epidemiological and laboratory evidence implicate contaminated ice as the likely vehicle of transmission; liver disease may be a predisposing factor. Clinicians, laboratorians, and public health officials should be aware of the potential for misidentification of *F. novicida* as *F. tularensis*.

**Keywords.** *Francisella novicida*; ice; outbreak; prison.

*Francisella novicida* is a gram-negative coccobacillus first isolated in 1951 from water taken from the Great Salt Lake, Utah [1]. Although identified as a subspecies of *Francisella tularensis* based on DNA hybridization, whole-genome sequencing and phenotypic features

suggest that it should be considered a separate species [2, 3]. Unlike *F. tularensis*, *F. novicida* has not been associated with animal reservoirs or arthropod vectors; environmental sources have been limited to salt water, brackish water, and soil [1, 4–6]. Human infection is exceptionally rare. Only 9 cases have been reported in the English literature, 4 of them in immunocompromised patients and all of them sporadic infections [7–13]. Two previously reported cases were associated with near-drowning events [8, 12], consistent with water as a known environmental source.

In May 2011, the Louisiana Office of Public Health and Centers for Disease Control and Prevention (CDC) were notified of suspected *F. tularensis* bacteremia

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Correspondence: Paul Mead, MD, MPH, Bacterial Diseases Branch, Division of Vector-Borne Diseases, CDC, 3156 Rampart Rd, Fort Collins, CO 80521 (pfm0@cdc.gov).

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in 2 patients, one of whom had died acutely. Both patients were inmates at a Louisiana correctional facility (prison A), and both had been admitted to a nearby hospital (hospital B). Blood cultures drawn during hospitalization yielded gram-negative isolates that were forwarded to a commercial laboratory in North Carolina for identification. The laboratory identified the isolates as *F. tularensis* based on 16S ribosomal RNA (rRNA) gene sequencing. Subsequent testing in public health laboratories suggested that the organism might be *F. novicida*. A few weeks later, in July 2011, hospital B staff reported isolating a similar organism from the blood of a third patient, also an inmate at prison A. We report results of an investigation to determine the source of these infections and to identify and characterize the etiologic agent.

## METHODS

### Epidemiological Investigation

Medical and housing records for the 3 patients were examined, and both surviving inmates were interviewed regarding potential exposures, including food, water, and arthropod or animal contacts. Prison A facilities and operations were reviewed with prison staff. Prison medical logs were reviewed for clusters of fever, lymphadenopathy, or gastroenteritis that might indicate additional cases or a specific contamination event involving the water or food supply. Details of all blood cultures performed at hospital B during 1 March–31 July 2011 were reviewed using written records.

### Laboratory Investigation

Isolates from all 3 patients were grown on cysteine heart agar with 9% chocolate sheep blood (CHAB) and DNA purified as previously described [14]. *Francisella tularensis* multitarget, type A, and type B real-time TaqMan polymerase chain reaction (PCR) assays and sequencing of the 16S ribosomal RNA (rRNA), *pgm*, and *pdpD* genes was performed as described previously [8, 14–16]. All nucleotide positions included in analyses were sequenced at least twice, and sequence data were analyzed in Lasergene (version 8.0). Homologous sequences from other *Francisella* strains were obtained from GenBank. Neighbor-joining trees were constructed using the Jukes-Cantor algorithm with 1000 bootstrap replicates. The *pdpD* sequence alignments were performed in MEGA (version 5.0) using ClustalW. Pulsed-field gel electrophoresis (PFGE) typing of the 3 clinical isolates was performed with the *PmeI* restriction enzyme as previously described [17], and patterns were compared with 10 *F. novicida* isolates from the CDC reference collection. Dendrograms were constructed using Dice similarity coefficients and unweighted pair group method with averages. Formalin-fixed, paraffin-embedded palate ulcer biopsy tissues from patient 1 were tested via DNA extraction followed by IS*Ftu2* TaqMan PCR and *pdpD* PCR and sequencing. Clinical isolates were tested for susceptibility to ciprofloxacin, levofloxacin, doxycycline, tetracycline,

gentamicin, streptomycin, and chloramphenicol using broth microdilution and breakpoints for *F. tularensis*.

### Environmental Investigation

Based on results of the epidemiologic investigation and a prior association of *F. novicida* with water sources, particular attention was given to review of prison A's water, heating, and cooling systems. High-volume water filtration samples were collected from 6 locations throughout the prison using previously described methods [18]. Total chlorine levels were measured using the colorimetric *N,N*-diethyl-*p*-phenylenediamine method. Grab samples of potable water (250 mL) were taken throughout the prison. Additionally, water from 2 cooling towers and mud from the prison yard were collected for culture. Samples were collected from 4 indoor ice machines and 11 machines located in an unenclosed ice shed. Samples from ice machines included screens, composite swabs of collecting bins, associated ice scoops, drains, and floor areas.

Water grab samples were tested for total coliforms and *Escherichia coli* using an Environmental Protection Agency–approved testing method [19]. All water samples were centrifuged and the resulting pellet was resuspended in 200  $\mu$ L of saline. Mud was processed by resuspending 250 mL in 125 mL of saline and removing 3 mL of supernatant. Ice machine screens and filters were vortexed in 3 mL of saline, and swabs of ice machines, ice scoops, and drains were eluted in 200  $\mu$ L of saline. For all processed environmental samples, DNA was extracted from 100  $\mu$ L and 100  $\mu$ L was used for culture. All environmental samples were streaked for isolation onto CHAB supplemented with antimicrobials including polymyxin B, amphotericin B, cyclohexamide, cefepime, and vancomycin (CHAB-PACCV) [20] and incubated at 35°C for 7 days. Colonies resembling *F. novicida* morphology were subcultured to new plates. DNA was extracted using the QIAmp DNA Mini Kit and tested by PCR using 16S rDNA primers F5 and F11 specific to the *Francisella* genus [21]. For PCR testing of environmental samples, DNA was extracted from all samples and tested by both the IS*Ftu2* and *tul4* TaqMan real-time PCR assays. Samples positive for both targets were further analyzed by PCR and sequencing of the *pdpD* gene.

## RESULTS

### Case Histories

Patient 1 was a 56-year-old male inmate with hepatitis C–induced cirrhosis was admitted to hospital B in late March for presumed hepatic encephalopathy and spontaneous bacterial peritonitis. At the time of admission, he was confused, hypothermic, and tachycardic. Physical exam revealed a distended tender abdomen, lower extremity edema, and an ulcerated palate lesion that had been noted during a dental visit 2 days earlier. Cultures of blood and ascites were obtained, and empiric therapy with

vancomycin, piperacillin-tazobactam, and lactulose was initiated. All 4 blood culture bottles yielded *Streptococcus mitis* after 6 hours of incubation; ascites cultures remained negative. On hospital day 2, the antibiotic regimen was changed to ceftriaxone and the palate ulcer biopsied. Histopathology revealed an abscess, but culture yielded only oral flora. The patient had episodic fevers over the next week but his mental status gradually improved. On hospital day 8, he developed acute hematochezia accompanied by hypotension, tachycardia, and confusion. The patient remained obtunded following resuscitation. Medical support was withdrawn and the patient died on hospital day 12. Blood cultures obtained at the time of resuscitation yielded an unusual gram-negative cocci from one aerobic bottle after 72 hours of incubation. An autopsy was not performed.

Patient 2 was a 40-year-old male inmate with type 2 diabetes and chronic hepatitis B who was admitted to the prison A infirmary in early April with a fever of 40.2°C (104.3°F). Physical exam revealed new-onset ascites, a tender abdomen, and lower extremity edema. Paracentesis was not performed due to thrombocytopenia. The patient was treated empirically with piperacillin-tazobactam for suspected bacterial peritonitis. Three days later, he remained febrile and was transferred to hospital B where blood cultures were drawn. Computed tomography of the abdomen revealed a nodular liver and a moderate volume of ascites. Vancomycin was added to the antibiotic regimen. After 72 hours of incubation, the aerobic bottle of the admission blood cultures yielded a gram-negative bacillus. Antibiotic treatment continued unchanged, and the patient's condition gradually improved. He was discharged to the prison infirmary on hospital day 8.

Patient 3, a 40-year-old male inmate, was admitted to hospital B in July for progressive right thigh and knee pain. The patient had been hospitalized 6 weeks earlier for pyomyositis of the right thigh. Past medical history included a dental extraction performed during the previous hospitalization, myasthenia gravis treated with chronic high-dose prednisone, and insulin-dependent diabetes. Although the patient was afebrile at the time of admission, blood and synovial fluid cultures were obtained and intravenous vancomycin was administered. Analysis and culture of the synovial fluid were unrevealing. Three of 4 blood culture bottles yielded gram-negative coccobacilli after 48 hours of incubation, and intravenous ciprofloxacin was added to the patient's antibiotic regimen. On hospital day 4, magnetic resonance imaging revealed a fluid collection along the right vastus medialis. Irrigation and debridement yielded purulent material; cultures were not obtained. The patient was transferred to the prison infirmary on hospital day 15 to complete a course of intravenous piperacillin-tazobactam for pyomyositis.

### Epidemiological Investigation

Prison A is located in southern Louisiana and housed approximately 2000 inmates at the time of the investigation. All

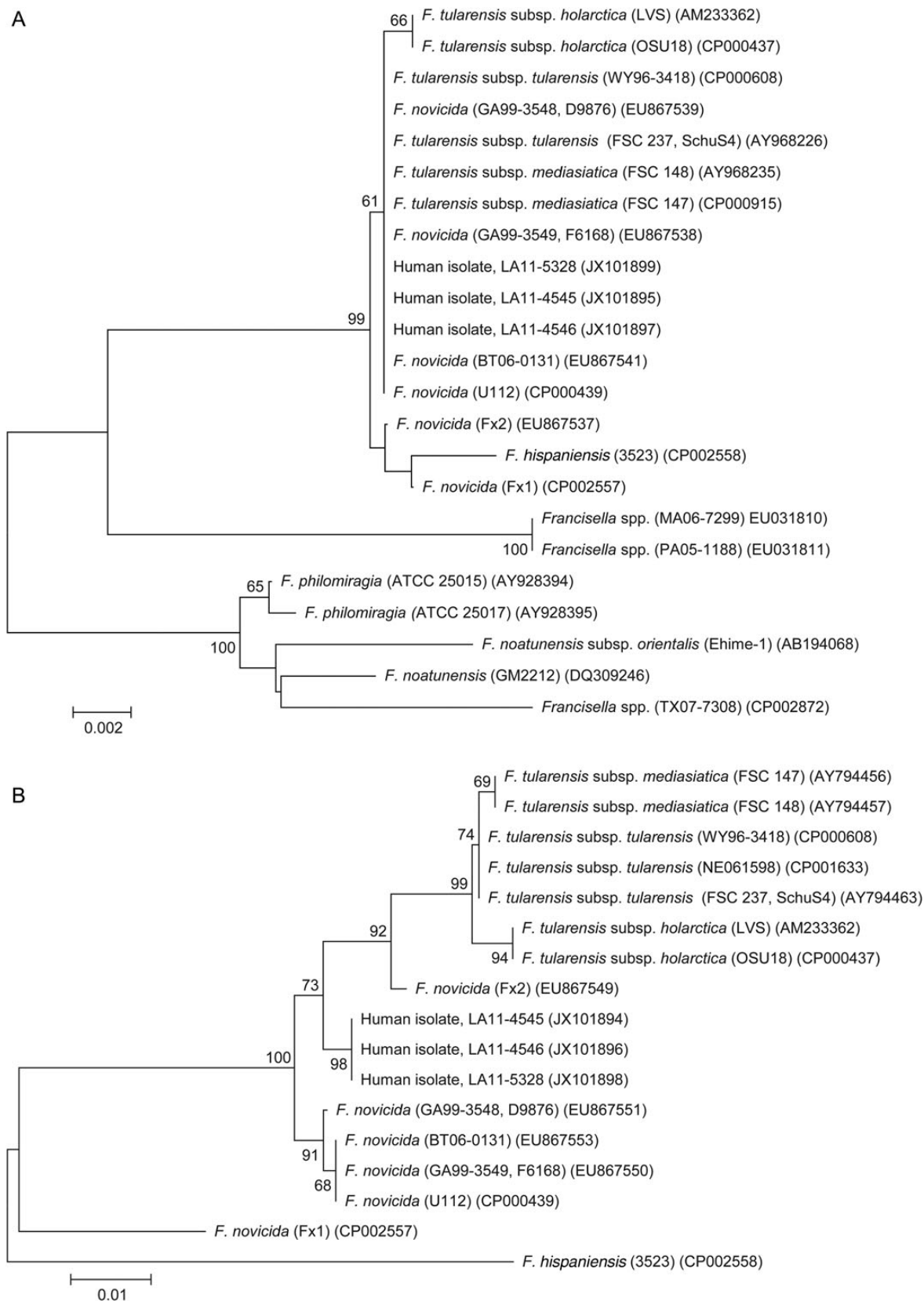
inmates were male, with a mean age of 40 years (range, 18 to >65 years), and 72% were African American. Prison officials estimated that 1%–2% of inmates had a known immunocompromising condition. Minor or chronic illnesses were managed at the prison clinic or infirmary; inmates with serious acute illness were routinely referred to hospital B. Review of prison medical records identified individual cases of fever, lymphadenopathy, or gastroenteritis during the 3 months before the first patient's bacteremia; however, no particular clustering was evident. Among 1981 blood cultures processed at the hospital B laboratory during 1 March–31 July, 7% of which were from prison A inmates, no other unusual gram-negative organisms were identified.

The only exposures shared by all 3 inmates were potable water, ice produced in a central "ice shed," and 6 commercially produced, highly processed food items purchased at the prison canteen. The inmates were housed in 3 separate cell blocks, one of which was located in a separate fenced area of the prison and served by a separate kitchen. They had had no potential for direct contact with one another for at least 1 month before their bacteremia was identified. All 3 had been seen at the prison clinic, and 2 had stayed in the infirmary at different times; however, no single medical procedure or medication was common to all 3 inmates. The 2 surviving inmates did not report exposure to rodents, rabbits, ticks, or mosquitoes. Both preferred tap water over other available beverages, and both reported frequent ice consumption. Patient 3 reported chewing ice habitually.

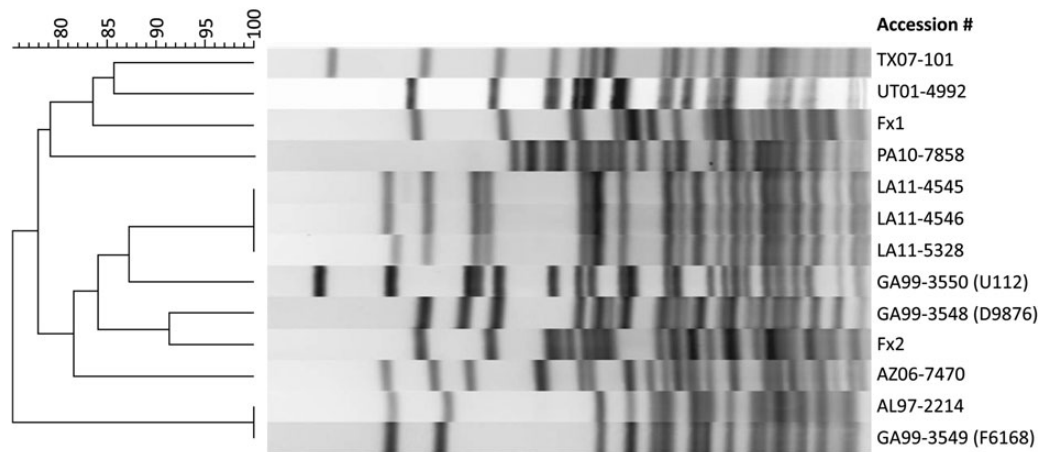
### Laboratory Investigation

Clinical isolates from the first 2 patients were initially identified as *F. tularensis* based on 16S rRNA gene sequencing performed at a commercial laboratory. When tested at the North Carolina State Laboratory of Public Health and the Shreveport Regional Laboratory in Louisiana, real-time PCR assays using Laboratory Response Network (LRN) primers were positive for *F. tularensis* (3 of 3 targets); however, direct fluorescent antibody (DFA) testing using fluorescein isothiocyanate-labeled anti-whole cells and a slide agglutination assay for *F. tularensis* yielded equivocal or negative results.

When tested at the CDC, the 3 patient isolates were positive for all 3 targets of a *F. tularensis* multitarget TaqMan PCR assay that detects both *F. tularensis* and *F. novicida* [14]. However, all tested negative using *F. tularensis* subspecies *tularensis* (type A)– and *F. tularensis* subspecies *holarctica* (type B)–specific TaqMan PCR assays [16]. DNA sequences corresponding to a 1013-bp and 507-bp region of the 16S rRNA and *pgm* genes, respectively, showed 100% identity to each other. The 16S rDNA sequence was most similar to *F. tularensis* and *F. novicida*, sharing >99.8% identity, compared with 99.5% identity with *Francisella hispaniensis* and 97.2%–97.9% identity with *Francisella philomiragia*, *Francisella noatunensis*, and other *Francisella* species (Figure 1A). A neighbor-joining tree based on *pgm*



**Figure 1.** Neighbor-joining trees showing the relationship of the clinical isolates, LA11-4545, LA11-4546, and LA11-5328, to other Francisellaceae members based on sequencing a 1013-bp region of the 16S rRNA gene (A) and a 507-bp region of the *pgm* gene (B). Bootstrap support values >60% are indicated. GenBank accession numbers are indicated following the strain ID.



**Figure 2.** Dendrogram based on *PmeI* pulsed-field gel electrophoresis patterns of the clinical isolates LA11-4545, LA11-4546, and LA11-5328, and 10 other *Francisella novicida* isolates. The dendrogram was constructed using Dice similarity coefficients (1.5% optimization and 1.5% tolerance) and unweighted pair group method with averages.

gene sequences grouped the patient isolates with *F. novicida* (Figure 1B), and the *pdpD* sequences revealed the presence of a 144-bp insert in the *pdpD* gene. *Francisella novicida* strains contain a 144-bp insert in *pdpD*; type A strains lack this insert and type B strains lack the *pdpD* gene [22]. *Francisella hispaniense* and *F. tularensis* subspecies *mediasiatica* do contain the 144-bp insert within the *pdpD* gene; however, distance comparison of a 172-bp fragment of the *pdpD* gene, inclusive of the 144-bp insert, revealed that the patient isolates shared 100% sequence identity with the *F. novicida* strains U112, Fx1, and GA99-3548, as compared with 99.4% and 93.6% with *F. subsp. mediasiatica* and *F. hispaniense*, respectively. Taken together, these results identify the clinical isolates as *F. novicida*. All 3 isolates were susceptible to all antimicrobial agents tested.

Testing of remnant biopsy tissue from patient 1's palate ulcer also yielded evidence of *F. novicida*. DNA extracted from the unused tissue block was positive by IS*Ftu2* and *pdpD* PCR, and sequencing of the *pdpD* PCR product revealed a 144-bp insert with 100% identity to the 144-bp insert present within the *pdpD* gene of the isolate from patient 1. This biopsy was obtained 6 days before the blood cultures from which *F. novicida* was isolated.

*PmeI* PFGE typing of the 3 patient isolates was performed to determine if the outbreak was associated with a single strain of *F. novicida*. The *PmeI* PFGE patterns for the 3 patient isolates were indistinguishable from each other and also distinct from the *PmeI* PFGE patterns for 10 other *F. novicida* strains (Figure 2). Similar results were obtained when a second enzyme, *BlnI*, was used for PFGE typing (data not shown). These results are consistent with the same or similar *F. novicida* strains infecting all 3 patients and a single point source for infection.

### Environmental Investigation

Prison A obtains potable ground water that has been treated with monochloramine from the local municipal water system. No water quality violations were identified with the municipal water, and no major disruptions involving the prison water system were identified. Total chlorine residuals  $\geq 0.4$  ppm were measured throughout the prison distribution system and were present in both the hot and cold water systems. All water samples tested negative for coliforms.

Ice produced in 11 industrial ice machines located in a central "ice shed" was distributed throughout the prison 3 times daily. The unenclosed shed was located adjacent to agricultural fields. Five-gallon buckets were used to scoop ice from the machines into 30-gallon plastic drums for transport to the cell blocks. Water from the machines pooled on the floor of the shed, and the 5-gallon buckets were observed sitting in this water. Maintenance staff indicated that ice machines were not routinely cleaned.

All 31 environmental samples, collected in August 2011, were negative by culture for *F. novicida* and other *Francisella* species. However, DNA extracted from 2 of 6 swabs from the ice shed, one swab of 3 ice machines on the east side of the shed, and one swab of the scoops used to transfer ice from these machines was positive by both the IS*Ftu2* and *tul4* PCR assays (Table 1). Further PCR analysis of the *pdpD* gene in these 2 samples confirmed the 144-bp insert in the *pdpD* gene, indicating the presence of *F. novicida* DNA in 2 linked samples from the ice shed. PCR testing of DNA extracted from the remaining environmental samples indicated that all of the water samples as well as all samples related to indoor ice machines were negative for *Francisella* species (Table 1). The single mud sample was



**Table 1. Description of Environmental Samples and Associated Laboratory Results**

Sample Type	No. of Samples	<i>F. tularensis</i> IS <i>Ftu2</i> PCR	<i>F. tularensis</i> <i>tul4</i> PCR	<i>pdpD</i> PCR	Presence of Insert in <i>pdpD</i> Gene
Potable water	6	...	...	ND	ND
High volume of water filtration eluents	6	...	...	ND	ND
Mud	1	+	...	...	ND
Cooling tower water	1	...	...	ND	ND
Indoor ice machine screens and filter	5	...	...	ND	ND
Culture swabs					
Indoor ice machines	5				
Intake drain		...	...	ND	ND
Ice machines (A & B)		...	...	ND	ND
Ice machines (C & D)		...	...	ND	ND
Ice scoops		...	...	ND	ND
Drain		...	...	ND	ND
Outdoor ice shed	7				
Ice machines—East		+	+	+	+
Ice machines—West		...	...	ND	ND
Ice machines—not working		...	...	ND	ND
5-gallon buckets (scoops)		+	+	+	+
Ice machine drain		...	...	ND	ND
Floor drains		...	...	ND	ND
Floor		...	...	ND	ND

Bank of ice machines referred to by letters A–D.

Abbreviations: *F. tularensis*, *Francisella tularensis*; ND, not done; PCR, polymerase chain reaction.

PCR positive by the IS*Ftu2* PCR assay, but PCR negative by the *tul4* and *pdpD* PCR assays (Table 1), inconsistent with the presence of *F. novicida*.

## DISCUSSION

We describe an outbreak of *F. novicida* bacteremia among immunocompromised inmates at a correctional facility. The exceptional rarity of *F. novicida* infections in humans and the results of isolate subtyping strongly suggest a common source. The likely vehicle of transmission was ice, linked both epidemiologically and by detection of *F. novicida* DNA in ice machines and scoops. The implicated ice machines were housed in an unenclosed shed with ample opportunity for contamination with soil, insects, or other organic material.

Defining the role of *F. novicida* in each inmate's illness is difficult given the complexity of their underlying medical conditions. Patient 1 had advanced cirrhosis and his death was likely precipitated by an acute gastrointestinal hemorrhage. Nevertheless, his initial hospitalization was for bacteremia with oral flora (*S. mitis*), coincident with a prominent palatal abscess. Biopsy of the abscess on hospital day 2 yielded evidence of *F. novicida*, suggesting a possible pathogenic role for the organism. This is further supported by isolation of *F. novicida*

from blood cultures obtained 6 days later. Although the patient was treated with ceftriaxone during this time, experience with *F. tularensis* suggests that cephalosporins have limited clinical efficacy against *Francisella* species [23].

For patient 2, no organisms other than *F. novicida* were identified to explain his fevers. His symptoms resolved promptly when treated with piperacillin-tazobactam, which is likely active against *Francisella* species [24]. Patient 3, with 3 positive blood cultures, has the strongest microbiological evidence for significant infection. His bacteremia was preceded by a dental extraction which, given the likely enteric route of exposure, may have increased the risk of infection. He was treated with ciprofloxacin, to which the organism was sensitive. Identification of his bacteremia 2 months after the first 2 patients may reflect either a more indolent course of infection or later exposure to a persistent environmental nidus.

Our investigation is subject to limitations. We were unable to screen for subclinical *F. novicida* infections among the prison population for lack of a serologic assay. Although an effort was made to develop one, serum from the infected patients did not react, possibly as a result of their immunocompromised conditions. The duration and frequency of exposure could not be determined with the available data. Finally, because of the small number of cases, it was not possible to conduct a formal

**Table 2. Characteristics of Previously Reported and Current Cases of *Francisella novicida* Infection<sup>a</sup>**

Age/ Sex	Year	Location	Symptom Duration	Fever	Adenopathy	Medical History	Liver Disease	Chest Radiography	Isolate Source	Isolate No. in Figure 2	Reference
26 M	1977	LA	2–3 wk	No	Yes	None	No	NA	Lymph node	GA99-3548	[10]
15 M	2006	AZ	2–3 wk	No	Yes	None	No	NA	Lymph node	AZ06-7470	[7]
52 M	1984	CA	3 d	Yes	No	Peptic ulcer disease	Alcohol-related	NA	Blood	GA99-3549	[10]
55 M	1991	TX	3 wk	Yes	No	Diabetes, uncharacterized nodular skin disease (on prednisone)	Unknown etiology	Infiltrate present	Blood	Fx1	[9]
43 M	1995	TX	1 wk	Yes	No	Pustular dermatitis, pancytopenia	Granulomatous (unknown etiology)	Infiltrate present	Blood	Fx2	[9]
46 M	2001	UT	9 d	Yes	No	Near-drowning; alcohol abuse	Unknown	Infiltrate present	Blood	UT01-4592	[12]
37 F	2007	Thailand	1 wk	Yes	No	Metastatic ovarian adenocarcinoma (recent chemotherapy)	Chronic hepatitis B	NA	Blood	NA	[11]
69 M	2010	SC/PA	10 d	Yes	No	Near-drowning	No	Infiltrate present	Blood	PA10-7858	[8]
56 M	2011	LA	Unknown	No	Chronic (above diaphragm)	Remote history of lymphoma	Chronic hepatitis C	NA	Blood	LA11-4545	This study
40 M	2011	LA	5 d	Yes	No	Diabetes	Chronic hepatitis B	Infiltrate present	Blood	LA11-4546	This study
40 /M	2011	LA	Unknown	No	No	Diabetes	None	NA	Blood	LA11-5328	This study

Abbreviations: AZ, Arizona; CA, California; LA, Louisiana; NA, not applicable; SC/PA, South Carolina/Pennsylvania; TX, Texas; UT, Utah.

<sup>a</sup> One case of *Francisella novicida* infection not included due to lack of clinical information; a case from Australia previously attributed to an “*F. novicida*-like” organism was subsequently shown to be due to *Francisella hispaniensis* and is also not included (see [13]).

case-control study. Identification of ice as the vehicle is somewhat speculative insofar as it is based on laboratory testing and a shared exposure rather than an established statistical association.

Although human *F. novicida* infections are rare, a review of reported cases suggests that clinical features vary according to the host’s immune status (Table 2). Regional lymphadenopathy without constitutional symptoms has been reported in 2 otherwise healthy individuals; in these cases *F. novicida* was isolated from lymph nodes [7, 10]. Conversely, immunocompromised patients appear more likely to have fever and bacteremia [9–11]. Underlying liver disease appears to be especially common among bacteremic patients (Table 2). Cirrhosis impairs antibody-mediated immunity [25], and, although the basis of human resistance to *F. novicida* is unknown [26], murine studies suggest that immunoglobulins play a more prominent role in defense against *F. novicida* than *F. tularensis* [27].

In the United States, reagents and protocols have been established through the LRN to aid in identification of *Francisella* species. Definitive identification can be challenging nevertheless, as 16s rDNA sequencing does not readily distinguish *F. novicida* from *F. tularensis*. Instead, *F. novicida* should be suspected when a *Francisella* isolate tests positive by PCR but negative or equivocal by DFA and slide agglutination assays using LRN protocols. Public health officials should be consulted promptly whenever suspected *Francisella* isolates are encountered. This report demonstrates that common-source outbreaks can occur with *F. novicida* and suggests that enhanced vigilance may be needed when a single case of *F. novicida* bacteremia is identified in a setting involving immunocompromised individuals.

## Notes

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**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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