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Laboratory-Acquired Brucellosis --- Indiana and Minnesota, 2006

In November 2006, two cases of brucellosis in microbiologists at two clinical laboratories were reported to state health departments in Indiana and Minnesota. The Minnesota Department of Health (MDH) contacted CDC regarding this suspected multistate cluster of laboratory-acquired brucellosis. MDH and the Indiana State Department of Health (ISDH) asked CDC to conduct further testing on *Brucella* isolates suspected of causing the infections and to provide recommendations for appropriate response by the laboratories. This report summarizes the investigation conducted jointly by MDH, ISDH, and CDC, provides guidance on safe laboratory handling of *Brucella* spp., and makes recommendations for responding to *Brucella* laboratory exposures. The results of that investigation determined that 146 workers at the two laboratories had been exposed to *Brucella* and that, although two *Brucella* isolates had been handled by both laboratories, infections in the two microbiologists were caused by two unrelated isolates. Because *Brucella* spp. pose a risk for aerosol-transmitted infection, CDC recommended risk assessment for all *Brucella*-exposed laboratory workers, postexposure prophylaxis (PEP) for those at high risk, surveillance for symptoms of disease, and serologic follow-up with workers. The events in Indiana and Minnesota emphasize the importance of adhering to recommended biosafety practices, timely sharing of information regarding laboratory exposures, and rapid implementation of response protocols.

Case Reports

Indiana. On September 28, 2006, a microbiologist aged 47 years (microbiologist A) who worked at a clinical laboratory had onset of high fever, sweating, malaise, anorexia, headache, and hip pain. Initially, her symptoms were not severe; she did not seek medical treatment until 3 weeks later, after her symptoms had progressively worsened. The microbiologist was hospitalized on October 22 and recovered fully with treatment. On October 26, an unidentified blood culture isolate from microbiologist A (isolate A) was submitted for identification to a Minnesota clinical laboratory and determined to be *Brucella* spp.; both MDH and ISDH were notified of the finding. Epidemiologic investigation later revealed that, on July 17, microbiologist A had subcultured on an open laboratory bench an unidentified isolate (isolate C) from a referring laboratory. Isolate C subsequently was forwarded for identification to the same Minnesota clinical laboratory and identified as *Brucella* spp.

Minnesota. On October 25, a microbiologist aged 61 years (microbiologist B), who worked at the same Minnesota clinical laboratory that received microbiologist A's isolate, had onset of low-grade fever, fatigue, and night sweats. She was hospitalized and recovered with treatment. On November 9, the Minnesota laboratory identified a blood culture isolate from microbiologist B (isolate B) as *Brucella* spp. and notified MDH. The subsequent investigation determined that microbiologist B had not handled isolate A from microbiologist A. However, previously she had handled on an open bench two unidentified isolates subsequently identified as *Brucella* spp. Her first exposure had occurred on July 21 while she was handling isolate C, which had been forwarded from the Indiana clinical laboratory. The second exposure had occurred on August 8 during testing of an isolate from a Texas referring

clinical laboratory (isolate D).

Investigation and Response

The investigation revealed that all potentially implicated specimens or isolates had been manipulated on an open bench, the routine practice for handling unidentified isolates in these laboratories. No spills or aerosol-generating procedures had occurred. Neither laboratory had formal protocols for 1) notification and follow-up of staff members who worked with isolates identified as *Brucella* spp. or 2) notification of laboratories that forwarded isolates later identified as *Brucella* spp.

Brucella-exposed workers* from each laboratory were identified, and their exposures were classified as either high risk or low risk.[†] In Indiana, 105 staff members were exposed; 15 of those exposures were classified as high risk, including the exposure of microbiologist A. In Minnesota, 41 staff members were exposed; 13 of those exposures were classified as high risk, including the exposure of microbiologist B. All staff members classified with high-risk exposure, other than the two microbiologists who received antimicrobial therapy, were advised to receive PEP.

To determine the source of the *Brucella* infections, CDC compared blood culture isolates from the two microbiologists with the isolates they handled, using multiple-locus variable number tandem repeats analysis at 21 genomic regions. All isolates were identified as *Brucella melitensis* biovar 3. Matching of 16 genomic amplicons suggested that isolate C was the source of infection for microbiologist A, the Indiana microbiologist. Matching of 17 genomic amplicons suggested that isolate D was the source of infection for microbiologist B, the Minnesota microbiologist.

Serial serum samples from the 105 exposed Indiana laboratory staff members, excluding microbiologist A, were tested at CDC for anti-*Brucella* antibodies, using the *Brucella* microagglutination test (BMAT); the Minnesota laboratory conducted voluntary serial BMAT testing for 11 exposed laboratory staff members. No additional infections were detected in either group.

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Editorial Note:

Brucellosis is a bacterial zoonotic infection usually caused by *Brucella abortus*, *B. melitensis*, *Brucella suis*, or less commonly by *Brucella canis*. Humans usually are infected by occupational exposure to infected animals, consumption of unpasteurized dairy products from infected animals, or inhalation of infectious aerosols. The average incubation period for brucellosis is 2--10 weeks but ranges from a few days to 6 months. Symptoms include intermittent fever, chills, malaise, sweating, joint and lower back pain, headache, anorexia, and fatigue (1). Untreated brucellosis can last from several weeks to several years. Chronic untreated brucellosis can lead to abscesses in the liver, spleen, heart valves, brain, or bone; osteoarticular complications; and, in rare cases, death. A definitive diagnosis requires that bacteria be cultured from clinical specimens. A presumptive diagnosis requires demonstrating high or rising titers of specific antibodies in the serum (1).

Since 1986, fewer than 150 cases of brucellosis have been reported annually in the United States (2; CDC, unpublished data, 2007). However, brucellosis is among the most commonly reported laboratory-acquired bacterial infections (3). In a review of laboratory-associated infections during 1979--1999, *Brucella* spp. accounted for approximately 8% of all laboratory infections, 16% of bacterial infections, and 4% of deaths (4). Infections have occurred from sniffing culture plates, spilling blood-culture bottles, mucocutaneous exposure to sprays of

organism-containing suspensions, aerosol generation from ruptured centrifuge tubes, or routine laboratory work with *Brucella* cultures outside of biological safety cabinets (5--9).

Biosafety level 3 (BSL-3) practices, containment equipment, and facilities are recommended for all manipulations of *Brucella* cultures ([Box 1](#)) (10). Because unidentified isolates are commonly manipulated on an open bench, inadvertent exposure can occur when *Brucella* unexpectedly grows in a culture. A formal notification and response protocol must be used after identification of *Brucella* spp. Timely identification, notification, and appropriate follow-up of potentially exposed workers, in combination with worker training to maximize awareness and observance of appropriate safety practices, can prevent unnecessary illness and hospitalization from brucellosis. Exposures can be minimized by clinicians and forwarding laboratories clearly identifying specimens they suspect to be *Brucella*.

Once *Brucella* has been identified (or is highly suspect), clinical laboratories should notify the state health department and send the isolate to the state public health laboratory or nearest Laboratory Reference Network laboratory for confirmation and species identification. When *Brucella* is confirmed, the state public health laboratory should notify all other laboratories that handled the specimen, and exposure to workers should be assessed at the submitting laboratory and other laboratories involved.

Classification of exposures as high risk or low risk by practitioners of occupational health, infection control, or public health determines PEP recommendations. PEP is recommended for persons with high-risk exposure ([Box 2](#)). Serologic follow-up for exposed persons using quantitative assays (e.g., BMAT) should be performed at the time of exposure and at weeks 2, 4, 6, and 24 after exposure. Active, regular (e.g., weekly) surveillance for symptoms consistent with brucellosis should be conducted for all exposed laboratory workers for 6 months after exposure. PEP and monitoring differ for persons exposed to *B. abortus* RB51, an attenuated veterinary vaccine strain that is less commonly associated with human illness, is rifampin resistant in vitro, and does not elicit a measurable serologic response using available tests ([Box 2](#)). Laboratory workers who might have been exposed to *Brucella* and who have unexplained febrile illness consistent with brucellosis should be referred to health-care providers for evaluation. Evaluation should include blood culture and anti-*Brucella* antibody serologic testing, and treatment for brucellosis should be initiated when compatible illness is confirmed.

Brucella spp. are dangerous infectious bacteria listed among CDC's category B bioterrorism agents.[§] CDC and the Animal and Plant Health Inspection Service (APHIS) regulate the transfer, possession, or use of such agents in the United States. New isolations, laboratory exposures, and other incidents associated with the intentional or unintentional release of *B. abortus* (excluding RB51), *B. melitensis*, or *B. suis* must be reported as soon as possible to either CDC or APHIS.[¶] Persons seeking assistance in identifying *Brucella* spp. or serologic monitoring of exposed persons should contact their state health departments or the CDC Bacterial Zoonoses Branch at telephone, 404-639-1711.

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* A *Brucella*-exposed worker was defined as any person present in the microbiology laboratory from the time the culture was first manipulated until all culture isolates were destroyed or removed from the laboratory.

† A high-risk exposure was defined as 1) having direct personal exposure (e.g., sniffing bacteriologic cultures; direct skin contact; pipetting by mouth; inoculation; or spraying into the eyes, nose, or mouth), 2) performing work on an open bench (i.e., outside of biosafety level 3 containment equipment) with an open culture plate containing a *Brucella* isolate or being in close proximity to such work (e.g., across an open bench top or within 5 feet), or 3) presence in the laboratory during any procedure conducted on a *Brucella* isolate that might result in generation of aerosolized organisms and inhalational exposure (e.g., vortexing or catalase testing). A low-risk exposure was defined as being present in the laboratory during an exposure but not meeting the definition for a high-risk exposure.

§ Available at <http://www.bt.cdc.gov/agent/agentlist-category.asp>.

¶ Instructions for reporting are available at <http://www.selectagents.gov/>.

Box 1

BOX 1. Recommendations for safe laboratory practices to avoid exposure to *Brucella* spp.

- When brucellosis is suspected, clinicians or forwarding laboratories should note on the laboratory submission: “Suspect or rule out brucellosis.”
- Review laboratory containment methods and microbiologic procedures to ensure compliance with recommendations in the *Biosafety in Microbiological and Biomedical Laboratories, Fifth Edition*.
- Use primary barriers (i.e., safety centrifuge cups, personal protective equipment, and Class II or higher biological safety cabinets [BSCs]) for procedures with a high likelihood of producing droplet splashes or aerosols.
- Use secondary barriers: restrict access to the laboratory when work is being performed and maintain the integrity of the laboratory air-handling system by keeping external doors and windows closed.
- Avoid causing splashes or aerosols when performing procedures on unidentified isolates.
- Prohibit sniffing of open culture plates to assist in the identification of isolates.
- Manipulate isolates of small gram-negative or gram-variable rods initially inside a BSC.

[Return to top.](#)

Box 2

BOX 2. Recommendations for surveillance and postexposure prophylaxis (PEP) after laboratory exposure to *Brucella* isolates

- Evaluate all workers exposed to *Brucella* isolates* and classify exposures as either high risk or low risk.†
- Recommend PEP for workers with high-risk exposures to *Brucella* isolates. PEP should be offered as soon as *Brucella* exposure has been identified, up to the end of the 6-month incubation period.
 - Administer doxycycline 100 mg twice daily and rifampin 600 mg once daily for 3 weeks or doxycycline alone if exposed to *Brucella abortus* RB51 strain, which is resistant to rifampin.
 - Trimethoprim-sulfamethoxazole (160 mg/800 mg) should be considered for patients with contraindications to doxycycline.
 - Pregnant workers with high-risk exposures should be considered for PEP in consultation with their obstetricians.
- Discuss potential PEP with workers who have low-risk exposures to *Brucella* isolates.
- Obtain baseline serum samples from all workers exposed to *Brucella*, unless exposed to *B. abortus* RB51 strain, which does not elicit a measurable serologic response using available assays.
- Arrange for serologic testing on all workers exposed to *Brucella* (e.g., 2, 4, 6, and 24 weeks postexposure) using agglutination testing (e.g., tube or *Brucella* microagglutination testing) at the state public health laboratory or CDC; serologic testing is not recommended for workers exposed to *B. abortus* RB51 strain.
- Arrange for regular (e.g., weekly) active surveillance for febrile illness among all workers exposed to *Brucella* isolates for 6 months after last exposure.

*A *Brucella*-exposed worker is defined as any worker present in the microbiology laboratory during workup and identification of a *Brucella* isolate, from the time the culture is first manipulated until all culture isolates are destroyed or removed from the laboratory.

† A high-risk exposure is defined as 1) having direct personal exposure to *Brucella* (e.g., sniffing bacteriologic cultures, direct skin contact, pipetting by mouth, inoculation, or spraying into the eyes, nose, or mouth), 2) performing work on an open bench (i.e., outside of biosafety level 3 containment equipment) with an open culture plate containing a *Brucella* isolate or being in close proximity to such work (e.g., across an open bench top or within 5 feet), or 3) presence in the laboratory during any procedure conducted on a *Brucella* isolate that might result in generation of aerosolized organisms and inhalational exposure (e.g., vortexing or catalase testing). A low-risk exposure is defined as being present in the laboratory during an exposure but not meeting the definition for a high-risk exposure.

[Return to top.](#)

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