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CASE REPORT

Review of Brucellosis Cases from Laboratory Exposures in the United States in 2008 to 2011 and Improved Strategies for Disease Prevention

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Five laboratory-acquired brucellosis (LAB) cases that occurred in the United States between 2008 and 2011 are presented. The Centers for Disease Control and Prevention (CDC) reviewed the recommendations published in 2008 and the published literature to identify strategies to further prevent LAB. The improved prevention strategies are described.

CASE REPORTS

Case 1. A university laboratory researcher (case 1) reported an illness with undulating fever, weakness, and arthralgia in the back and ankle of approximately 10 weeks' duration. Several blood specimens for culture were collected over a period of weeks and submitted to laboratory A; an atypical *Staphylococcus* sp. was identified. One specimen was eventually found to be positive for Gram-negative coccobacilli and was sent to laboratory B; it was identified as a presumptive *Brucella* species. Laboratory B sent the specimens to the Wisconsin State Laboratory of Hygiene, where PCR and biochemical tests (dye, urea, and fluorescence) confirmed the species as *Brucella melitensis* (Table 1). Case 1 had worked with this organism, but the only recalled exposure event had occurred a few months previously, when goggles had been removed for cleaning while the individual was working with the bacterium.

Eleven staff who worked in the research laboratory with case 1 were determined to be at risk of exposure. Antimicrobial postexposure prophylaxis (PEP) was not offered. Twelve staff, including the case were serologically monitored at 2, 4, 6, and 24 weeks after the case was diagnosed; staff had previously had baseline serum samples drawn. Weekly symptom surveillance was also conducted for 24 weeks following the diagnosis. No other laboratory staff seroconverted during the follow-up.

Laboratory procedures were reviewed, and recommendations were made to improve respiratory protection, disinfection, sharps management, training, and emergency planning. Key objectives of the review included education about the symptoms of brucellosis and all infectious agents manipulated in the laboratory, reporting all potential exposures, and contacting supervisors or occupational health staff if symptoms occur.

Case 2. Blood culture specimens were drawn by a Florida clinician on 29 June and 2 July 2009 from a febrile 7-year- old female (patient A) who had assisted with butchering a feral swine. The specimens were sent to laboratory C in North Carolina for testing. On 13 and 14 July, Gram stain, spot indole, and oxidase tests were performed on an open bench. The culture was again manipulated on an open bench on 18 July, when it was identified as a possible *Brucella* species and forwarded to the North Carolina State Laboratory of Public Health (NCSLPH) for identification. NCSLPH identified *Brucella* by PCR on 21 July, and the identity was confirmed as *Brucella suis* by the Florida Department of Health, Bureau of Public Health Laboratories. The isolate was destroyed after confirmation.

Five laboratory C staff handled the culture and had high-risk exposures; a sixth individual was in the laboratory but did not manipulate the culture, and her exposure was classified as low risk. All exposed workers began PEP and serological and symptom monitoring.

The worker with the low-risk exposure (case 2), a 32-year-old female, began PEP 13 days after the exposure (27 July) and reported completing 21 days of PEP. Serology from 12 and 21 August was negative. In late October, she began to experience mild undulating fever and fatigue. On 24 November, she experienced an increase in fever, fatigue, headache, and arthralgia. She was seen on 7 December at hospital A, and blood cultures were drawn; the recent *Brucella* exposure was not included on the lab submission form.

Hospital A admitted case 2 on December 10 with suspected brucellosis after her culture was read as Gram-negative coccobacilli. The specimen was PCR positive for *Brucella* spp. at the NCSLPH on 11 December and confirmed at the Centers for Disease Control and Prevention (CDC) as *B. suis* (Table 1). Case 2 was discharged in good condition on December 11 and received 6 weeks of doxycycline and rifampin. The other five workers with high-risk exposures did not seroconvert. The North Carolina Division of Public Health (NCDPH) reclassified her exposure as

Received 26 March 2013 **Returned for modification** 17 April 2013
Accepted 18 June 2013
Published ahead of print 3 July 2013
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doi:10.1128/JCM.00813-13

TABLE 1 Laboratory-acquired brucellosis cases reported to CDC (2008–2010)

Case	Risk	Date of last exposure (mo/day/yr)	Incubation period	PEP		Date of diagnosis (mo/yr or mo/day/yr)	Serologic titer (wk[s])[a]	Culture result (species)
				Begun	Completed			
1	Unk[b]	Unk	Unk	NA[c]	NA	8/08	Not available	+ (*B. melitensis*)
2	Low	7/14/09	19 wks	7/27/09	Yes[d]	12/11/09	<1:20 (3, 5); 1:1,280 (23)	+ (*B. suis*)
3	High	11/3/09[e]	29 wks	NA	NA	6/6/10	Not available	+ (*B. suis*)
4	Unk	11/3/09[e]	19 wks	NA	NA	6/11/10	1:640 (26)	No growth
5	High	6/2/10	17 wks	NA	NA	10/18/10	<1:20 (4, 6, 8, 10) 1:2,560 (20)	+ (*B. suis*)

[a] A titer of ≥1:160 in one or more serum specimens or a 4-fold rise in titer, is considered a presumptive or definitive evidence of infection, respectively (21).
[b] Unk, unknown.
[c] NA, not available.
[d] Case 2 was prescribed 3 weeks of doxycycline and rifampin; good compliance was reported.
[e] Exposures may have also occurred in January, March, and October 2009.

high risk because she was likely within five feet of cultures from patient A.

Hospital A notified the NCDPH on December 10 of a laboratory exposure to *Brucella* following work on case 2's blood cultures from 7 to 10 December; 10 laboratory workers had high-risk exposures. All began PEP and serologic and symptom monitoring on 11 and 12 December; none seroconverted. Biosafety training was later performed with laboratory C and hospital A staff.

Cases 3 and 4. A 62-year-old female (patient B) had blood cultures done at hospital B in January and March 2009 which were identified as *Ochrobactrum anthropi* (Gram-negative bacillus) by the hospital B laboratory. On 27 October 2009, she had hip replacement surgery; purulent exudate from the hip was submitted for culture, and the organisms were initially identified as *Corynebacterium*-like bacteria. After further manipulation, a *Brucella* sp. was identified and reported to the Kansas Department of Health and Environment (KDHE) on November 4. It was determined that the previous blood cultures were misidentified *Brucella* spp.; all cultures were destroyed. Patient B was lost to follow-up, and the source of infection was unidentified.

During the week of 24 May 2010 a laboratory worker (case 3) at hospital B developed a low-grade fever and night sweats. Case 3 contacted an infectious disease physician on 3 June after her symptoms worsened. She recalled extended manipulation of cultures from patient B in October and November without following *Brucella*-specific protocols. Based on this exposure history, brucellosis was suspected; blood culture specimens were collected from case 3 and submitted to the Kansas Health and Environmental Laboratories (KHEL) and laboratory D on June 3. Laboratory D was not notified that brucellosis was suspected.

On June 7, KHEL identified the culture from case 3 as *Brucella suis*, and immediately notified KDHE and laboratory D (Table 1). Laboratory D conducted a risk assessment of its employees and found 12 low-risk and 4 high-risk exposures. The four workers with high-risk exposures received antimicrobial PEP, and all exposed workers were monitored serologically and for symptoms; none reportedly seroconverted or developed brucellosis.

Hospital B also conducted a risk assessment in June 2010 of the laboratory and surgical staff that had been potentially exposed in January, March, or October 2009. All 19 hospital B laboratory workers were classified with high-risk exposures. Four surgical staff were classified with low-risk exposures despite the potential aerosolization of the culture-positive purulent exudate when a bone saw was used during the surgical procedure. PEP was not offered because the exposure was recognized more than 24 weeks after the last known exposure. Serum specimens were drawn from the exposed workers; one worker (case 4) had an elevated *Brucella* antibody titer of 1:640 on 11 June 2010 (Table 1). Case 4 had developed extreme fatigue, chills, fever, and arthralgia on 15 March 2010 but did not seek treatment. She received azithromycin (which has activity against *Brucella* spp.) in May for a sinus infection and symptoms abated. On June 18, case 4 began 6 weeks of doxycycline and rifampin; she had a reaction to rifampin 3 days later, and it was replaced with 2 weeks of gentamicin. She had a blood culture drawn on June 25 which yielded no *Brucella* growth. No additional cases were identified.

Case 5. In April 2010, a 44-year-old male (patient C) underwent arthroscopic surgery to repair a meniscal tear. He began to experience intermittent fever, headache, night sweats, malaise, myalgia, anorexia, knee pain, and inflammation in mid-May. On 2 June, arthrocentesis was performed. The aspirate culture was preliminarily positive for *Brucella* spp. at hospital C. The Mississippi State Department of Health (MSDH) Public Health Laboratory (PHL) confirmed the isolate as a *Brucella* sp. on 11 June, and CDC identified it as *Brucella suis*. Patient C had extensive contact with feral hogs; he was referred to an infectious disease physician for treatment.

The culture plates were manipulated on an open bench at the hospital C laboratory. Three laboratory workers were identified with high-risk and 25 with low-risk exposures. MSDH recommended PEP with doxycycline and rifampin for all exposed staff; one accepted PEP but stopped after 2 weeks due to side effects. Sixteen potentially exposed laboratory workers initiated serological monitoring, but only seven participated for 24 weeks. All were assessed weekly for symptoms.

On 18 October 2010, an infection control practitioner at hospital C notified MSDH that a laboratory worker with a high-risk exposure (case 5) reported intermittent fever, malaise, and shoulder and back pain for 3 weeks (Table 1). She had attributed her early symptoms to the influenza immunization she received shortly before onset. She had declined PEP but had provided sera for a *Brucella* microagglutination test (BMAT) at 4, 6, 8, and 10 weeks postexposure (last collected 17 August 2010); all were negative. Blood and serum were collected from case 5 on October 18; *B. suis* was isolated, and BMAT titers were elevated. The isolates from patient C and case 5 matched according to the multiple-locus variable-number tandem repeat (VNTR) analysis (MLVA) method (1). Case 5 completed 6 weeks of doxycycline and rifampin.

MSDH instructed hospital C to obtain blood from case 5 and refer any positive blood cultures directly to the PHL without sub-

TABLE 2 Risk classification criteria

Risk level	Persons at risk
High	All persons manipulating a *Brucella* isolate in a class II biosafety cabinet without using biosafety level 3 precautions or on an open bench and any person present within a 5-ft radius of these activities; all persons present in a laboratory room during widespread aerosol generating procedures[a]
Low	All persons present in a laboratory room at a distance greater than 5 ft from manipulation of a *Brucella* isolate but without high-risk exposures as defined above
None	None if all handling and testing of a *Brucella* isolate was done in a class II biosafety cabinet using biosafety level 3 precautions

[a] Widespread aerosol generating procedures include, but are not limited to, centrifuging without sealed carriers, vortexing, sonicating, and accidents resulting in spillage or splashes (i.e., breakage of tube containing specimen). Other manipulations such as automated pipetting of a suspension containing the organism, grinding, blending, or shaking the specimen, or procedures for suspension in liquid to produce standard concentration for identification may require further investigation (i.e., inclusion of steps that could be considered major aerosol generating activities).

culturing. Hospital C failed to disseminate these instructions to all staff, and a laboratory worker subcultured the blood culture outside a biological safety cabinet (BSC) and was classified with high-risk exposure. She completed PEP and did not seroconvert or develop symptoms through 24 weeks. Two other laboratory staff were also in the room. They were classified with low-risk exposures, and PEP was recommended by MSDH; both declined PEP. One completed three serum draws; all were negative. Both individuals were symptom free at 24 weeks.

Due to these exposures, hospital C instituted policy changes and provided additional education to staff and external partners. Hospital C personnel will manipulate all cultures under a BSC, and specimens will be labeled to alert personnel of suspicious infectious agents. Providers are to notify the laboratory if specific diseases (e.g., brucellosis) are suspected.

Brucellosis is a bacterial zoonotic disease caused by pathogenic *Brucella* species. The clinical presentation is often characterized by an undulant fever, fatigue, and arthralgia (2, 3); focal organ involvement may occur (2). The incubation period is considered to be 2 to 4 weeks but can range from 5 days to 5 months (2, 4).

Brucellosis is one of the most commonly reported laboratory-acquired infections (5–7). The organism is easily aerosolized and has a low infectious dose (8, 9). Aerosol exposure during routine manipulation of unidentified *Brucella* isolates outside a BSC is the most common source of laboratory-acquired brucellosis (LAB) (7). Less frequently, individuals in the vicinity of a *Brucella* isolate have developed brucellosis (10–12). LAB is associated with most pathogenic *Brucella* spp. and vaccine strains (10, 11, 13–16). As a result of low incidence (17, 18) and nonspecific symptoms, physicians may not consider brucellosis in the differential diagnosis of acute febrile illness, and the laboratory may not be notified to take precautions or may be unaware of the potential risks (19, 20).

Brucellosis is a reportable disease in all 57 U.S. reporting jurisdictions and a Nationally Notifiable Condition (21). *Brucella abortus*, *B. melitensis*, and *B. suis* are select agents; isolation or release (e.g., laboratory exposure) of these species requires prompt reporting to the National Select Agent Program (22). Each reported case or isolation should prompt an inquiry into laboratory safety by local and state public health agencies.

Based on expert opinion and existing literature, CDC published recommendations in 2008 to reduce the risk of LAB in workers exposed to *Brucella* spp. (23); surveillance of exposures was initiated after publication. These recommendations include classification of exposed laboratory workers, PEP for high-risk exposures, and serological and symptom monitoring for all exposed workers. Since 2008, CDC has provided consultation to state public health agencies concerning the recommendations and has provided serological testing using the BMAT. From 2008 to 2011, CDC was notified of 153 incidents in 36 states involving 1,724 laboratory workers potentially exposed to *Brucella* isolates; 55 (36%) incidents occurred in 3 states (California, Florida, and Texas). Of the exposed workers, 839 (49%) exposures were classified as high risk and 775 (45%) as low risk; the risk level was not available for 110 (6%) workers. Of the 1,724 workers, the 5 (0.3%) LAB cases described above developed LAB.

Due to these LAB cases and the volume of exposures, the CDC recommendations were reviewed and the accompanying literature review was conducted (24) to identify strategies to further prevent LAB; the improved strategies are described below.

Risk classification. Exposure risk classification criteria were described as part of the 2008 recommendations (23); specific high-risk and low-risk activities are summarized in Table 2. Risk classification is often difficult to ascertain for individuals who did not manipulate a *Brucella* isolate; recalling close proximity to an isolate (a high-risk exposure) may be difficult once an exposure is identified, especially when the exposure is not recognized immediately. Thus, erring on the side of a higher-risk classification is prudent. CDC staff can assist state and local health agencies with determination of an exposure and risk classification.

Antimicrobial postexposure prophylaxis. Antimicrobial PEP has been shown to prevent LAB (24) and should be given for high-risk exposures when they are identified within 24 weeks of the exposure. Although not recommended for low-risk exposures, PEP may be considered on an individual basis. Immunocompromised or pregnant workers should discuss PEP with their health care providers (HCP) in consultation with public health officials, with consideration of the risks of LAB for the worker and fetus (25).

One to 6 weeks of PEP has been shown to prevent LAB (24); however, there is insufficient evidence to determine the most effective duration. PEP should consist of a combination regimen of doxycycline and rifampin for 3 weeks, a conservative duration that balances compliance and prevention (Table 3). For those with contraindications or intolerance to doxycycline or rifampin, 160 mg/800 mg trimethoprim-sulfamethoxazole (TMP-SMZ) or another antimicrobial agent effective against *Brucella* should be selected to ensure at least two antimicrobials are prescribed (26, 27). Although antimicrobial resistance is rare, variable susceptibility and the risk of community resistance exist for TMP-SMZ and rifampin (27).

TABLE 3 Comparison of *Brucella* postexposure follow-up recommendations

Procedure	CDC recommendations, 2008 (23)	Modifications to recommendations[a]
Antimicrobial PEP	High risk: doxycycline (100 mg) twice daily and rifampin (600 mg) once daily for 3 weeks; TMP-SMZ should be considered for patients with contraindications for doxycycline	Doxycycline (100 mg) twice daily and rifampin (600 mg) once daily for 3 weeks; TMP-SMZ or another antimicrobial agent effective against *Brucella* should be selected for persons with contraindications to doxycycline or rifampin; regimen and dosing should be chosen in consultation with the person's HCP; pregnant women should consult an obstetrician
	Low risk: discuss with HCP; consider if patient is immunocompromised or pregnant	No change
Serologic monitoring[b]	Baseline, 2, 4, 6, 24 weeks after last known exposure	Sequential serologic testing at baseline, 6, 12, 18 and 24 weeks post exposure *(after last known exposure)*
Symptom surveillance	Regular (e.g., weekly) symptom watch for febrile illness through 24 weeks after last known exposure	Regular (e.g., weekly) symptom watch and daily self temp checks through 24 weeks post-exposure *(after last known exposure)*

[a] These modifications are based on the above case reports and a review of the literature (24).
[b] Obtain baseline and periodic serum samples from all workers exposed to *Brucella*, unless they have been exposed to *B. abortus* strain RB51 or *B. canis*, which do not elicit a measurable serologic response in available *B. abortus* antigen-based assays.

Following exposure to the rifampin-resistant *Brucella abortus* RB51 vaccine, PEP should consist of doxycycline and another suitable antimicrobial for 3 weeks (26–28). The actual regimen and dose should be determined in consultation with the exposed worker's HCP.

Only 1 (case 2) of the 733 exposed laboratory workers who CDC was informed had received PEP developed brucellosis, although she started 2 weeks after exposure. This may indicate the need for prompt initiation of PEP; however, there are insufficient data to determine when PEP is no longer effective.

Serologic monitoring. Quantitative serological testing (e.g., BMAT) should be performed for all exposed workers to identify immune response. Seroconversion has been shown to occur shortly before symptom onset (10) and may be the initial and most objective indicator of early infection. Baseline sera should be drawn as soon as the exposure is recognized. Sera should again be drawn and submitted to the same laboratory every 6 weeks through 24 weeks from the last known exposure.

Regular serological monitoring at 6-week intervals can identify seroconversion within the 8-week acute stage (29) of infection if symptom surveillance does not prompt medical evaluation. The median incubation period calculated from 80 LAB cases in the literature (24) and cases 2 to 5 was 9 weeks (range 1 to 40). Of those cases, 21% had symptom onset more than 12 weeks after exposure; case 3 and one other reported case developed symptoms more than 24 weeks postexposure (24). This monitoring interval will be evaluated as more data are collected.

The BMAT detects antibodies to smooth *Brucella* species (i.e., *B. abortus*, *B. ceti*, *B. melitensis*, *B. pinnipedialis*, and *B. suis*); currently, there are no approved serological tests in the United States to detect *Brucella abortus* RB51 or *B. canis* antibodies in humans.

Symptom surveillance. Although there is evidence that antimicrobial PEP and serological monitoring effectively prevent or promptly detect LAB, cases 1 to 5 demonstrate the need to conduct extended symptom surveillance to identify infections, particularly among individuals who decline or delay initiation of PEP. Symptom surveillance includes fever watch and patient reporting of brucellosis-consistent symptoms (21). An occupational health care provider should arrange regular (e.g., weekly) symptom surveillance for febrile illness for all exposed workers, along with daily self temperature checks for 24 weeks postexposure (Table 3). Blood cultures and sera should be obtained from workers who report brucellosis-consistent symptoms.

Exposed workers should be made aware of the symptoms associated with brucellosis, the difficult and prolonged treatment required, and the potential for complications if untreated (16). It is essential that workers understand the importance of seeking prompt medical treatment if symptoms develop within 24 weeks following an exposure regardless of PEP and the importance of communicating the exposure to their HCP so receiving laboratories can be notified and take precautions. Individuals who develop LAB and have risk factors for relapse (30) may require longer follow-up.

Secondary exposures occurred during the laboratory diagnosis of three cases in this report, despite a history of recent exposure to *Brucella* spp. or suspicion of brucellosis. Therefore, physicians should be aware of the clinical presentation of brucellosis and the need to notify laboratory staff. In addition, clinical laboratories may consider requiring suspect and differential diagnoses for all specimen submissions to prevent exposures when dangerous pathogens are suspected.

Laboratories should institute and regularly review published guidelines (31, 32) which may help prevent exposures to *Brucella* and other potentially dangerous pathogens. Submitting laboratories should notify receiving laboratories of Gram stain results or suspected diagnoses. All suspected *Brucella* isolates should be manipulated in a class II or higher BSC until an identification of *Brucella* is ruled out (31, 32). The local or state health department should be promptly notified if a *Brucella* exposure or a LAB case is suspected, in order to initiate evaluation, prophylaxis, and monitoring. Prompt notification of suspected exposures will assist in the prevention or early identification of most LAB.

Although it is not possible to demonstrate the effectiveness of the 2008 recommendations due to limited data, they have likely been successful in preventing illness. The information summarized in this article is intended to further prevent infections. Timely risk assessment of a potential exposure is encouraged, as is increasing awareness of the prolonged incubation period.

ACKNOWLEDGMENTS

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of CDC or the U.S. Department of Health and Human Services.

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