


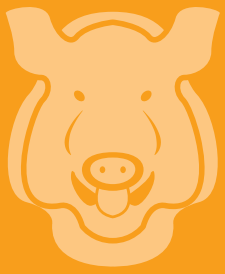




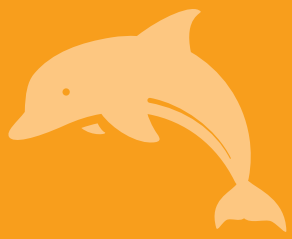
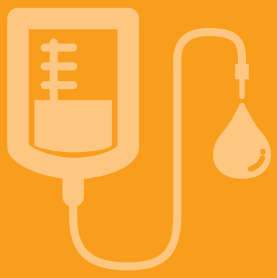

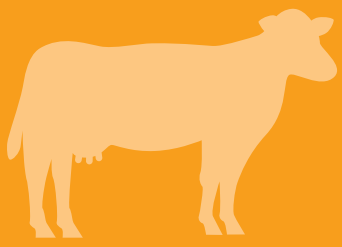

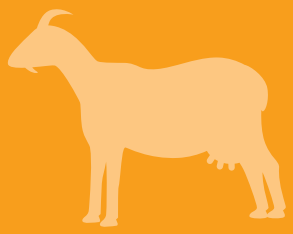





# BRUCELLOSIS REFERENCE GUIDE:
## EXPOSURES, TESTING, AND PREVENTION

**Centers for Disease Control and Prevention**
National Center for Emerging and Zoonotic Infectious Diseases

# CONTACT INFORMATION

**Bacterial Special Pathogens Branch (BSPB)**
Division of High-Consequence Pathogens and Pathology
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention
1600 Clifton Rd MS C–09, Atlanta, GA 30329-4027
(404) 639-1711, **BSPB@cdc.gov**

**Division of Select Agents and Toxins (DSAT)**
Centers for Disease Control and Prevention
1600 Clifton Rd MS A–46, Atlanta, GA 30329-4027
Fax: (404) 718-2096, **lrsat@cdc.gov**
**http://www.selectagents.gov/**

**Emergency Operations Center (EOC)**
Office of Public Health Preparedness and Response
Centers for Disease Control and Prevention
(770) 488-7100

**Laboratory Preparedness and Response Branch (LRN)**
Division of Preparedness and Emerging Infection
National Center for Emerging, Zoonotic and Infectious Disease
Centers for Disease Control and Prevention
1600 Clifton Rd MS C–18, Atlanta, GA 30329-4027
**LRN@cdc.gov**

Updated February 2017

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# DESCRIPTION

## *Clinical Description*

### Council of State and Territorial Epidemiologists (CSTE)[1] 2010 Case Definition

An illness characterized by acute or insidious onset of fever and one or more of the following: night sweats, arthralgia, headache, fatigue, anorexia, myalgia, weight loss, arthritis/spondylitis, meningitis, or focal organ involvement (endocarditis, orchitis/epididymitis, hepatomegaly, splenomegaly).

### Incubation Period

- Highly variable (5 days–6 months)
- Average onset 2–4 weeks

### Symptoms/Signs

- Acute
  - Non-specific: Fever, chills, sweats, headache, myalgia, arthralgia, anorexia, fatigue, weight loss
  - Sub-clinical infections are common
  - Lymphadenopathy (10–20%), splenomegaly (20–30%)
  - Chronic
  - Recurrent fever
  - Arthritis and spondylitis
  - Possible focal organ involvement (as indicated in the case definition)

## *Case Classification[1, 2]*

**Probable**—A clinically compatible illness with at least one of the following:

- Epidemiologically linked to a confirmed human or animal brucellosis case
- Presumptive laboratory evidence, but without definitive laboratory evidence, of *Brucella* infection

**Confirmed**—A clinically compatible illness with definitive laboratory evidence of *Brucella* infection

Please refer to the **CSTE Laboratory Criteria for Diagnosis** section for specifications regarding "presumptive" and "definitive" laboratory evidence of a *Brucella* infection.

# HUMAN PATHOGENS AND SELECT AGENT REPORTING

## *Select Agent Designation*

Select agents and toxins are a subset of biological agents and toxins that may pose a severe threat to public health.[3] *Brucella* species are easily aerosolized and have a low infectious dose, cited at levels between 10 and 100 microorganisms. These organisms also have a prolonged incubation period with the potential to induce a broad range of clinical manifestations, and therefore generate challenges for prompt diagnosis. The above factors have contributed to a select agent designation for *B. suis*, *B. melitensis*, and *B. abortus*.[4, 5]

Clinical or diagnostic laboratories and other entities that have identified *B. suis*, *B. melitensis*, or *B. abortus* are required to immediately (within 24 hours) notify the Division of Select Agents and Toxins (DSAT) at CDC (fax: 404-718-2096; email: **lrsat@cdc.gov**).

Facilities that use or transfer *B. suis*, *B. melitensis*, or *B. abortus* must immediately (within 24 hours) notify DSAT via phone, fax, or e-mail if they detect any theft, loss, or release of these select agents. The initial report should include as much information as possible about the incident, including the type of incident, date and time, agent and quantity, and a summary of the events (location of the incident, number of individuals potentially exposed, actions taken to respond, etc.). Additionally, appropriate local, state, or federal law enforcement agencies should be contacted of a theft or loss, and appropriate local, state, and federal health agencies notified of a release.[3]

### Forms for Reporting to CDC's Division of Select Agents and Toxins (DSAT)

**Form 4, Report of the Identification of a Select Agent or Toxin:** Clinical or APHIS/CDC Form 4A should be signed and submitted after a facility has identified *B. suis*, *B. melitensis*, or *B. abortus* contained in a clinical/diagnostic specimen. Entities must submit Form 4 to DSAT within 7 calendar days of identification. For assistance with the completion of this form, please contact CDC's Division of Select Agents and Toxins via email at **lrsat@cdc.gov**.

**Form 3, Report of Theft, Loss, or Release of Select Agents and Toxins:** The APHIS/CDC Form 3 should be submitted by facilities reporting a theft, loss, or release (laboratory exposure or release of an agent outside of the primary barriers of the biocontainment area) of *B. suis*, *B. melitensis*, or *B. abortus* within 7 calendar days of the event. For reporting of a theft or loss, complete sections 1 and 2 of Form 3; for reporting a release, complete sections 1, 2, and 3. With questions regarding the Form 3, please send an e-mail to **form3@cdc.gov**.

### Exclusions from Select Agent Reporting

Select agents in their naturally occurring environment are not subject to regulation and may include animals that are naturally infected with a select agent or toxin (e.g., milk samples that contain *B. abortus*). However, a select agent or toxin that has been intentionally introduced (e.g., animal experimentally infected with *B. suis*, *B. melitensis*, or *B. abortus*), or otherwise extracted from its natural source (e.g., blood from a culture bottle is plated onto agar and grows *B. suis*) is subject to select agent regulation.[3]

Attenuated vaccine strains of *B. abortus* Strain 19 live vaccine and *B. abortus* Strain RB51 are excluded from select agent reporting requirements, unless there is any reintroduction of factor(s) associated with virulence.[3] Visit the **Select Agents and Toxins Exclusions** site for a comprehensive list of attenuated *Brucella* strain exclusions. Please refer to the APHIS/CDC Form 5, **Request for Exemption of Select Agents and Toxins for an Investigational Product**, to request an exemption from the select agent regulations.

## *Laboratory Response Network (LRN)* [6]

The LRN is a national network of local, state, federal, military, and international public health, food testing, veterinary diagnostic, and environmental testing laboratories that provides laboratory infrastructure and capacity to respond to biological and chemical public health emergencies.

Upon obtaining high confidence presumptive or confirmatory *Brucella* spp. results, LRN laboratories are required to follow notification and messaging procedures.

**Notification:** Within 2 hours of obtaining high-confidence presumptive or confirmatory result, a LRN Laboratory Director or a designee must notify:

- their State Public Health Laboratory Director,
- the State Epidemiologist,
- the Health Officer for the State Public Health Department,
- the CDC Emergency Operations Center (EOC), and
- the FBI Weapons of Mass Destruction (WMD) POC.

**Messaging:** For emergency and non-emergency situations, LRN laboratories will submit data for all samples, including positive and negative results related to the event within 12 hours of obtaining each result.

Please refer to Table 1 below for information regarding personnel who should be contacted, along with a timeline for notification and messaging communication.

## *Reportable and Nationally Notifiable Disease Classification and Requirements* [7]

Brucellosis is a reportable disease in all 57 states and territories; it is mandatory that disease cases be reported to state and territorial jurisdictions when identified by a health provider, hospital, or laboratory. Reporting requirements vary by jurisdiction.

Brucellosis is also a nationally notifiable condition. Notification of brucellosis cases (without direct personal identifiers) to CDC by state and territorial jurisdictions is voluntary for nationwide aggregation and monitoring of disease data. The case definition for confirmed and probable brucellosis can be found on page 3 under the **Case Classification** section.

**Immediate, Urgent Notification Status:** For multiple confirmed and probable cases, temporally or spatially clustered, notify EOC within 24 hours of a case meeting the notification criteria, followed by submission of electronic case notification in the next regularly scheduled electronic transmission.

**Standard:** For confirmed and probable cases that are not temporally or spatially clustered, submit electronic case notification within the next reporting cycle.

**Table 1: Reporting Known *Brucella* spp. Human Pathogens**

| *Brucella* species | Select Agent Designation | Reporting Notification Status | | | | |
|---|---|---|---|---|---|---|
| | | DSAT | | | LRN | Nationally Notifiable Condition |
| | | Identification (Form 4) | | Exposure (Form 3) | | |
| *Brucella melitensis* | Select Agent | 24 hours *For registered entities* | 7 days *For non-registered entities* | 7 days | 2 hours | 24 hours or 7 days |
| *Brucella suis* | | | | 7 days | 2 hours | 24 hours or 7 days |
| *Brucella abortus* | | | | 7 days | 2 hours | 24 hours or 7 days |
| *Brucella canis* | Not a Select Agent | N/A | | N/A | 2 hours | 24 hours or 7 days |
| *Brucella ceti, pinnipedialis* | Not a Select Agent | N/A | | N/A | 2 hours | 24 hours or 7 days |

### *Case Report Form*

Health departments and providers are strongly encouraged to use the approved **case report form** to report brucellosis cases to the Bacterial Special Pathogens Branch. This mechanism will ensure improved collection of standardized data needed to assess risk factors and trends associated with brucellosis, so that targeted preventive strategies can be implemented. Patient identifiers such as full name, address, phone number, hospital name, and medical record number should not be included in forms sent to CDC. Instructions for completion and submission are included in pages 1 and 2 of the form.

## DIAGNOSTIC TESTING

### *CDC/CSTE Laboratory Criteria for Diagnosis*[1]

**Definitive**

- Culture and identification of *Brucella* spp. from clinical specimens
- Evidence of a four-fold or greater rise in *Brucella* antibody titer between acute and convalescent phase serum specimens obtained greater than or equal to 2 weeks apart

**Presumptive**

- *Brucella* total antibody titer of greater than or equal to 1:160 by standard tube agglutination test (SAT) or *Brucella* microagglutination test (BMAT) in one or more serum specimens obtained after onset of symptoms
- Detection of *Brucella* DNA in a clinical specimen by PCR assay

**NOTE:** Evidence of *Brucella* antibodies by nonagglutination-based tests DOES NOT meet the current CDC/CSTE case definition for a Presumptive Diagnosis of brucellosis.

However, ANY quantitative test can be used for confirmation if there is a four-fold or greater rise in *Brucella* antibody titer.

## Testing Performed at CDC

The Zoonotic and Select Agent Laboratory (ZSAL) at CDC performs CLIA-approved *Brucella* spp. diagnostic testing on human and animal samples.

**Table 2: Diagnostic Testing Provided by ZSAL**

| Test | Samples accepted | Pros | Cons | Submission Instructions |
|---|---|---|---|---|
| Culture | Tissue, whole blood, sera, plasma | Gold standard; allows for genotyping-molecular epidemiology | Requires BSL-3 | See Appendix 1: Submission of *Brucella* Isolates |
| LRN PCR (for suspect BT and response use) | Environmental samples, swabs, powders, whole blood, sera, tissue | Rapid detection; can be used on isolates and clinical specimens | Requires technical expertise to perform assay; reagents and equipment can be costly; optimal specimen type not clear | See Appendix 1: Submission of *Brucella* Isolates |
| MAT (serology) *Not available for B. canis or RB51* | Sera | Cheap, assay of choice in acute non-complicated cases; only equipment needed is reading apparatus | May not diagnose chronic or complicated cases; subjective | See Appendix 1: Submission of Serum for *Brucella* Serology |

## Results and Notification

- BMAT results take 2 to 3 weeks, depending on when your sample was received at CDC's Zoonotic and Select Agent Laboratory (ZSAL), which is part of the Bacterial Special Pathogens Branch (BSPB). Our lab will generally test your sample within 1 week; however, it can take longer to report results. Results will be sent to your State Laboratory.
- After checking with your State Laboratory, you can contact ZSAL or the BSPB epidemiology team if results are not received within 2 to 3 weeks.
- PCR results from primary specimens can be obtained within 24 hours.

## Testing Performed Elsewhere

- CDC does not provide medical consultation on individual patients, and cannot comment on results from laboratory assays that we have not performed.
- We recommend that you consult both with an infectious disease specialist assigned to the patient and the medical director for the diagnostic laboratory that ran the tests for interpretation of results, as they have the available parameters for the specific assay used.

## Diagnostic Difficulties

While culture is the gold standard, *Brucella* spp. can be fastidious, slow growers. Culture from primary specimens may require up to 21 days of incubation. Bone marrow culture is more sensitive than blood; however, the invasiveness of the procedure should be considered. Persons with chronic infections are less likely to be culture-positive.

Agglutination is a confirmatory serological test to diagnose brucellosis. The standard tube agglutination test (SAT) is the reference method, of which BMAT is a modified format.

- *Brucella*-specific agglutination tests involve direct agglutination of bacterial antigens by specific antibodies. Agglutination tests detect antibodies of IgM, IgG, and IgA classes.
- IgM antibodies are predominant in acute infection but decline within weeks. Relapses are accompanied by transient elevations of IgG and IgA antibodies but not IgM.

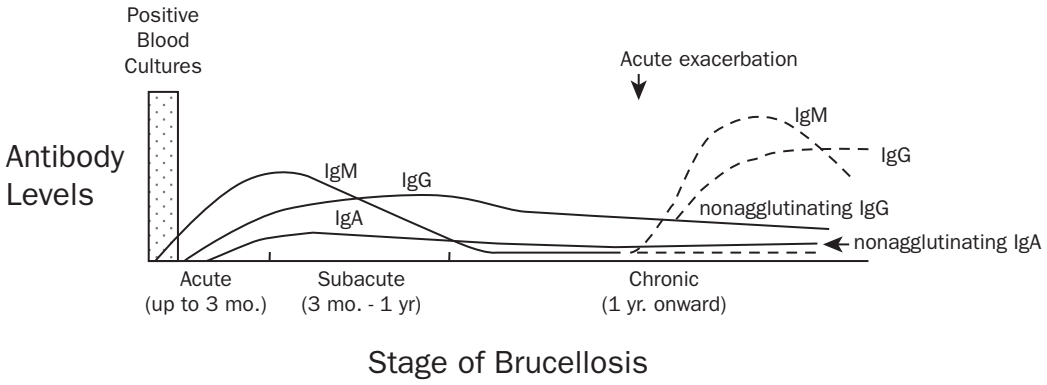


**Figure 1: Antibody Responses in Untreated Brucellosis.**[8]

IgM detection sensitivities using other EIA formats have been reported between 67% to 100% with limited specificity data.[9, 10] Such tests are qualitative, making them difficult to interpret in a clinical setting, and might have different performance characteristics and utility when used in areas with low disease prevalence, such as the United States. Results of EIA tests must be confirmed by a quantitative reference method such as BMAT.

## BMAT Testing Drawbacks

Cross-reactions and false-positive test results can occur in *Brucella* antibody tests, mainly with IgM.10

The primary immunodeterminant and virulence factor for *Brucella* species is smooth lipopolysaccharide (S-LPS) on the outer cell membrane, which is antigenically similar to the lipopolysaccharide of other gram-negative rods. False-positive *Brucella* test results can be caused by cross-reactivity of antibodies to *Escherichia coli* O157, *Francisella tularensis*, *Moraxella phenylpyruvica*, *Yersinia enterocolitica*, certain *Salmonella* serotypes, and from persons vaccinated against *Vibrio cholerae*.

BMAT tends to perform better for diagnosing acute cases rather than chronic cases.[11] Additionally, BMAT is not as useful in detecting chronic brucellosis cases or neurobrucellosis. In a suspected chronic case, an IgG ELISA would be more informative.[12]

# TREATMENT [13, 14]

The table below provides a summary of the Red Book treatment recommendations, as well as several recommended treatment documents. Information about post-exposure prophylaxis is provided below in the section titled "Laboratory, Surgical, and Clinical Exposures."

**Table 3: Brucellosis Treatment Options**

| Subject | Summary |
|---|---|
| **Adults, Children > 8 years** | Combination therapy to decrease the incidence of relapse:<br>• Oral doxycycline *(2–4 mg/kg per day, maximum 200 mg/day, in 2 divided doses)* or oral tetracycline *(30–40 mg/kg per day, maximum 2 g/day, in 4 divided doses)* **-and-**<br>• Rifampin (*15–20 mg/kg per day, maximum 600–900 mg/day, in 1 or 2 divided doses*).<br>• Recommended for a **minimum** of 6 weeks.<br>Combination therapy with trimethoprim-sulfamethoxazole (TMP-SMZ) can be used if tetracyclines are contraindicated. |
| **Children < 8 years** | • Oral TMP-SMZ (*trimethoprim, 10 mg/kg per day, maximum 480 mg/day; and sulfamethoxazole, 50 mg/kg per day, maximum 2.4 g/day*) divided in 2 doses for 4 to 6 weeks.<br>Combination therapy: consider adding rifampin. Consult physician for dosing or if rifampin is contraindicated. **Tetracyclines (such as doxycycline) should be avoided in children less than 8 years of age.** |
| **Pregnancy** | **Tetracyclines are contraindicated for pregnant patients.** Consult obstetrician regarding specific antimicrobial therapy instructions. |
| **Complicated Cases (endocarditis, meningitis, osteomyelitis, etc.)** | • Streptomycin* or gentamicin for the first 14 days of therapy in addition to a tetracycline for 6 weeks (or TMP-SMZ if tetracyclines are contraindicated).<br>• Rifampin can be used in combination with this regimen to decrease the rate of relapse.<br>• For life-threatening complications, such as meningitis or endocarditis, duration of therapy often is extended for 4 to 6 months.<br>• Case-fatality rate is < 1%.<br>• Surgical intervention should be considered in patients with complications such as deep tissue abscesses.<br>**May not be readily available in the U.S.* |
| **References for Treatment Recommendations** | • Ariza J *et al*. 2007. Perspectives for the Treatment of Brucellosis in the 21st Century: The Ioannina Recommendations. PLoS Med. 4(12): e317. **http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.0040317**<br>• Al-Tawfiq JA. 2008. Therapeutic options for human brucellosis. Expert Rev Anti Infect Ther. 6(1): 109-120. **http://www.ncbi.nlm.nih.gov/pubmed/18251668**<br>• Solera J. 2010. Update on brucellosis: therapeutic challenges. Intl J Antimicrob Agent. 36S, S18–S20. **http://www.ncbi.nlm.nih.gov/pubmed/20692127** |

**Note:** The *B. abortus* strain used in the RB51 vaccine was derived by selection in rifampin-enriched media and is resistant to rifampin *in vitro*. This strain is also resistant to penicillin. If infection is due to this vaccine strain, treatment should be determined accordingly (example: doxycycline and TMP/SMX in place of rifampin). Specifics on the regimen and dose should be established in consultation with the person's health care provider in case of contraindications to the aforementioned.

# LABORATORY, SURGICAL, AND CLINICAL EXPOSURES

## *Laboratory Exposures*[4, 15]

Once a potential exposure is recognized, **the first task is to determine the activities performed that may have led to the exposure**. Then identify:

1. who was in the laboratory during the suspected time(s) of exposure
2. where they were in relation to the exposure
3. what they did with the isolates

The identified individuals should be assessed for exposure risk using the descriptions in Table 4.

**Table 4. Laboratory Risk Assessment and Post-Exposure Prophylaxis (PEP): Minimal (but not zero) Risk**

| Specimen handling | Exposure scenario | PEP | Follow-up/monitoring |
|---|---|---|---|
| Routine clinical specimen (e.g., blood, serum, cerebrospinal fluid) | Person who manipulates a routine clinical specimen (e.g., blood, serum, cerebrospinal fluid) in a certified Class II biosafety cabinet, with appropriate personal protective equipment (i.e., gloves, gown, eye protection). | None | N/A |
| | Person present in the lab while someone manipulates a routine clinical specimen (e.g., blood, serum, cerebrospinal fluid) in a certified Class II biosafety cabinet, or on an open bench where manipulation did not involve occurrence of aerosol-generating events (e.g., centrifuging without sealed carriers, vortexing, sonicating, spillage/splashes). | | May consider symptom watch for following scenarios:<br>• Person who manipulates a routine clinical specimen (e.g., blood, serum, cerebrospinal fluid) on an open bench with or without appropriate personal protective equipment (i.e., gloves, gown, eye protection), or in a certified Class II biosafety cabinet without appropriate personal protective equipment.<br>• Person present in the lab while someone manipulates a routine clinical specimen (e.g., blood, serum, cerebrospinal fluid) on an open bench, resulting in occurrence of aerosol-generating events (e.g., centrifuging without sealed carriers, vortexing, sonicating, spillage/splashes). |
| Enriched material (e.g., a *Brucella* isolate, positive blood bottle) or reproductive clinical specimen (e.g., amniotic fluid, placental products) | Person who manipulates enriched material (e.g., a *Brucella* isolate, positive blood bottle) or reproductive clinical specimen (e.g., amniotic fluid, placental products) in a certified Class II biosafety cabinet, with appropriate personal protective equipment (i.e., gloves, gown, eye protection). | | |
| | Person present in the lab while someone manipulates enriched material (e.g., a *Brucella* isolate, positive blood bottle) or reproductive clinical specimen (e.g., amniotic fluid, placental products) in a certified Class II biosafety cabinet. | | |

**Table 4. Laboratory Risk Assessment and Post-Exposure Prophylaxis (PEP): Low Risk**

| Specimen handling | Exposure scenario | PEP | Follow-up/ monitoring |
|---|---|---|---|
| Enriched material (e.g., a *Brucella* isolate, positive blood bottle) or reproductive clinical specimen (e.g., amniotic fluid, placental products) | Person present in the lab at a distance of greater than 5 feet from someone manipulating enriched material (e.g., a *Brucella* isolate, positive blood bottle) or reproductive clinical specimen (e.g., amniotic fluid, placental products), on an open bench, with no occurrence of aerosol-generating events (e.g., centrifuging without sealed carriers, vortexing, sonicating, spillage/splashes). | May consider if immunocompromised or pregnant.<br><br>Discuss with health care provider (HCP).<br><br>**Note:** RB51 is resistant to rifampin *in vitro*, and therefore this drug should not be used for PEP or treatment courses. | Regular symptom watch (e.g., weekly) and daily self-fever checks through 24 weeks post-exposure, after last known exposure.<br><br>Sequential serological monitoring at 0 (baseline), 6, 12, 18, and 24 weeks post-exposure, after last known exposure.<br><br>**Note:** no serological monitoring currently available for RB51 and B. canis exposures in humans. |

Table 4. Laboratory Risk Assessment and Post-Exposure Prophylaxis (PEP): **High Risk**

| Specimen handling | Exposure scenario | PEP | Follow-up/ monitoring |
|---|---|---|---|
| Routine clinical specimen (e.g., blood, serum, cerebrospinal fluid) | Person who manipulates a routine clinical specimen (e.g., blood, serum, cerebrospinal fluid), resulting in contact with broken skin or mucous membranes, regardless of working in a certified Class II biosafety cabinet, with or without appropriate personal protective equipment (i.e., gloves, gown, eye protection). | Doxycycline 100mg twice daily, and rifampin 600 mg once daily, for three weeks.<br><br>For patients with contraindications to doxycycline or rifampin: TMP-SMZ, in addition to another appropriate antimicrobial, should be considered. Two antimicrobials effective against *Brucella* should be given.<br><br>Pregnant women should consult their obstetrician.<br><br>**Note**: RB51 is resistant to rifampin *in vitro*, and therefore this drug should not be used for PEP or treatment courses. | Regular symptom watch (e.g., weekly) and daily self-fever checks through 24 weeks post-exposure, after last known exposure.<br><br>Sequential serological monitoring at 0 (baseline), 6, 12, 18, and 24 weeks post-exposure, after last known exposure.<br><br>**Note:** no serological monitoring currently available for RB51 and *B. canis* exposures in humans. |
| Enriched material (e.g., a *Brucella* isolate, positive blood bottle) or reproductive clinical specimen (e.g., amniotic fluid, placental products) | Person who manipulates (or is ≤ 5 feet from someone manipulating) enriched material (e.g., a *Brucella* isolate, positive blood bottle) or reproductive clinical specimen (e.g., amniotic fluid, placental products), outside of a certified Class II biosafety cabinet. | | |
| | Person who manipulates enriched material (e.g., a *Brucella* isolate, positive blood bottle) or reproductive clinical specimen (e.g., amniotic fluid, placental products), within a certified Class II biosafety cabinet, without appropriate personal protective equipment (i.e., gloves, gown, eye protection). | | |
| | All persons present during the occurrence of aerosol-generating events (e.g., centrifuging without sealed carriers, vortexing, sonicating, spillage/splashes) with manipulation of enriched material (e.g., a *Brucella* isolate, positive blood bottle) or reproductive clinical specimen (e.g., amniotic fluid, placental products) on an open bench. | | |

Widespread aerosol generating procedures include, but are not limited to: centrifuging without sealed carriers, vortexing, sonicating, or 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 the specimen, blending the specimen, 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).

### Antimicrobial Post-Exposure Prophylaxis (PEP) [4, 15]

Workers with high-risk exposures should begin antimicrobial post-exposure prophylaxis as soon as possible. Prophylaxis can be initiated up to 24 weeks after exposure. PEP is generally not recommended for low-risk exposures, though it may be considered on a case-by-case basis. PEP courses should include doxycycline (100 mg) orally twice daily and rifampin (600 mg) once daily for a minimum of 21 days. Trimethoprim-sulfamethoxazole (TMP-SMZ) or another antimicrobial agent effective against *Brucella* should be selected (for

at least 21 days) if doxycycline or rifampin are contraindicated. All PEP regimen and dosing decisions should be made in consultation with the worker's health care provider. If clinical symptoms develop at any point while on PEP and brucellosis infection is confirmed by culture and isolation or serology, PEP is no longer appropriate and treatment and monitoring is required.

Persons who are pregnant, less than 8 years old, or have contraindications to these antimicrobial agents, should consult with their health care provider for alternative PEP. Suitable combinations of agents may be selected from the treatment references listed previously.

- **Exposure to *B. abortus* RB51:** Upon exposure to rifampin-resistant *B. abortus* RB51 vaccine, PEP should be comprised of doxycycline in addition to another suitable antimicrobial (such as TMP-SMX) for 21 days.[16] Specifics on the regimen and dose should be established in consultation with the person's health care provider in case of contraindications to the aforementioned.

### Symptom Surveillance[4]

An occupational health provider should arrange for regular (at least weekly) monitoring for febrile illness or symptoms consistent with brucellosis for all exposed workers. In addition, daily self-administered temperature checks are recommended for 24 weeks post-exposure, from the last known date of exposure. Exposed persons should be informed of common brucellosis symptoms, and are encouraged to seek immediate medical treatment if illness develops within 6 months of the exposure, regardless of whether or not the patient has already undergone PEP. It is important for workers to notify their health care provider of their recent *Brucella* exposure so that receiving diagnostic laboratories may be notified and take precautions. Individuals who have risk factors for relapse of brucellosis[17] may require a follow-up time that extends beyond 24 weeks.

- ***B. canis* and *B. abortus* RB51:** Symptom monitoring should be emphasized following exposures to *Brucella canis* and *Brucella abortus* RB51 vaccine due to the lack of serological tests available to identify seroconversion.

Specific information regarding common symptoms of brucellosis and a symptom-monitoring table are available in Appendix 2. These tools can be distributed to occupational health staff.

### Serological Monitoring[4]

All exposed workers should undergo quantitative serological testing in order to detect an immune response to *Brucella* spp. Evidence suggests that seroconversion can occur shortly before symptoms appear, and therefore may be an earlier indicator of infection. It is recommended that sera be drawn and submitted to the same laboratory at 0 (baseline), 6, 12, 18, and 24 weeks following the exposure event.

CDC's Zoonotic and Select Agent Laboratory (ZSAL) is able to perform serial serological monitoring at no cost. If monitoring is conducted by other laboratories, it is recommended that an agglutination assay is used to quantify seroconversion. Instructions for serology submission to ZSAL are available in Appendix 1.

- ***B. canis* and *B. abortus RB51:*** Serological testing is currently not available for *Brucella canis* and *Brucella abortus* RB51 vaccine. Serological monitoring following exposure to these strains is not recommended, except to collect a baseline serum sample in order to rule out infection with other *Brucella* spp.

## Clinical Exposure

Universal precautions and personal protective equipment (PPE) are essential when working with body fluids or tissues from a brucellosis patient. When standard precautions are followed, most clinical procedures are considered to be low-risk activities. Higher-risk activities may include handling of tissues with potentially high concentrations of *Brucella* organisms (e.g., placental tissues), direct contact with infected blood and body fluids through breaks in the skin, or mucosal exposure to aerosolized *Brucella* organisms after an aerosol-generating procedure.

**Aerosol-Generating Procedures:** Aerosols are defined as particulates (diameter < 10 µm) suspended in the air. Aerosol-generating procedures are those that produce aerosols as a result of mechanical disturbance of the blood or another body fluid[18]. Aerosol-generating procedures may include, but are not limited to, cardiopulmonary resuscitation, disturbance of fluids from an abscess, the use of saws or other electrical devices, and high-pressure irrigation. Additional information on the utilization of electrical and irrigation devices can be found in the Surgical Exposure section below.

To the best of our knowledge, seven cases of occupationally acquired brucellosis have been reported in the English literature among health care workers since 1990, including four infections acquired during obstetrical delivery, and three infections through the provision of medical care to brucellosis patients. In each case, it is likely that the health care workers were exposed through the high-risk routes of transmission previously listed (handling of placental tissues, direct contact with infected blood/tissues, and mucosal exposure to aerosolized *Brucella*).[19-21]

## Surgical Exposure[22, 23]

In the event of a *Brucella* exposure during a surgical procedure, the potential risk of exposure should be evaluated for all personnel who pass through the surgical unit. Assessments should be based on adherence to PPE requirements, types of surgical devices utilized, risk of aerosolization, and duration of the surgical procedure. The following paragraph, along with Table 5, may be used as a resource for risk assessment.

**Risk Assessment:** High-risk exposures within surgical settings have previously been defined as presence within an operating room during aerosol-generating event, and cleaning the operating room after an aerosol-generating procedure. Aerosol-generating procedures may include, but are not limited to, the use of saws or other electrical devices, cardiopulmonary resuscitation, disturbance of fluids from an abscess, and high-pressure irrigation. Risk of aerosolization subsequent to irrigation should be assessed based upon the water pressure from the irrigation tool used. High-pressure washes and pulsed lavages are generally considered to be high-pressure irrigation, and the use of such devices should be treated as an aerosol-generating event. While hand bulbs are typically considered to be a low-pressure irrigation device, additional factors, like surgical technique, should be considered before ruling out this mechanism as an aerosol-generating procedure.

**Pre-Operative Recommendations for Surgery on a Brucellosis Patient:**

- The patient should be started on antibiotic therapy to decrease the bacterial load of the surrounding tissues. Table 3 can be utilized for treatment guidance.
- Precautions to be taken by medical staff prior to and during the operation:
  - Minimize aerosol-generating procedures during the surgical procedure
  - Only essential personnel should be present in the operating room during the procedure
  - All staff members present in the operating room should wear appropriate PPE, including:
    - Gloves, masks, and eyewear
    - Respiratory protection (e.g., N95) if there is potential for aerosol-generating procedures

**Post-Operative Recommendations for Surgery on a Brucellosis Patient:**

- Evaluation of staff after potential exposure to *Brucella* organisms should include:
  - A review of appropriate PPE and possible breaches in PPE protocol during the surgical procedure, including:
    - Symptom and serological monitoring (as applicable) for all personnel for whom a breach of PPE is identified.
    - Consideration of PEP for all personnel who were present during or after a potential aerosol-generating procedure was done.
- Serological monitoring (as applicable) and PEP consideration for staff who are pregnant or immunocompromised.
  - Workers are advised to seek medical consultation with their health care provider.

# VETERINARY EXPOSURES

## *Vaccine Exposure*

Accidental exposures to live, attenuated vaccine strains of *Brucella* spp. in veterinarians have been reported via needle stick injury, as well as through spray exposure to the conjunctiva and open wounds. Personnel administering RB51, S19, and Rev-1 vaccinations should wear proper PPE, including gloves and eye protection. Proper animal restraint should be used to minimize needle sticks or conjunctival splashes.

### *Brucella abortus* RB51 Vaccine [16, 24]

The *Brucella abortus* RB51 vaccine is currently the only vaccine used in the United States for prevention of brucellosis in cattle herds. Although RB51 was developed to be less pathogenic and abortifacient than the S19 strain in animals, it does retain pathogenicity for humans. Local adverse events have been reported less than 24 hours after exposure, and systemic reactions may begin 1 to 15 days subsequent to exposure.

- **Risk Assessment:** Vaccine exposures typically occur through direct contact; therefore, all individuals exposed to RB51 should be considered as having a high-risk exposure.
- **Symptom Monitoring:** Symptom monitoring should be emphasized following exposures to RB51 vaccine because of the lack of serological tests available to identify seroconversion. The symptom monitoring table in Appendix 2 can be given to exposed individuals.
- **Antimicrobial Post-Exposure Prophylaxis (PEP):** Antibiotic post-exposure prophylaxis has been recommended for individuals accidentally exposed to B. abortus RB51 vaccine. Refer to Table 4 for PEP guidance. Because RB51 was derived by selection in rifampin-enriched media and is resistant to rifampin *in vitro*, rifampin should not be used for PEP. The strain is also resistant to penicillin.
- **Serological Monitoring:** The RB51 vaccine is a modified live culture vaccine and there are currently no serological assays available to detect an antibody response to RB51.

### *Brucella abortus* S19 Vaccine and *Brucella melitensis* Rev-1 Vaccine [25, 26]

The *B. abortus* S19 and the *B. melitensis* Rev-1 animal brucellosis vaccines are available outside the U.S. and have been known to cause systemic disease in humans. With the scope of human travel and animal trading, potential cases in the U.S. may arise in persons exposed to the vaccine or to animals previously vaccinated.

- **Risk Assessment:** Vaccine exposures typically occur through direct contact; therefore, all individuals exposed to S19 or Rev-1 strains should be considered as having a high-risk exposure.
- **Symptom Monitoring:** Guidelines for symptom monitoring can be found in Appendix 2.
- **Antimicrobial Post-Exposure Prophylaxis (PEP):** CDC recommends a concomitant prophylaxis regimen of doxycycline and rifampin for three weeks following exposure to the S19 and Rev-1 vaccine strains. Refer to Table 4 for PEP guidance. Rev-1 is resistant to streptomycin, and therefore this drug should not be used for PEP or treatment courses.[25]

- **Serological Monitoring:** Serological monitoring is available for S19 and Rev-1 exposures. Quantitative serological monitoring should be emphasized to detect a B. abortus S19 infection among veterinary workers, as patients may present with mild clinical symptoms or as asymptomatic.[26]

## *Clinical Exposure*

Veterinarians and breeders have a higher risk of contracting brucellosis because of close direct contact with infected animals, and in part because of inconsistency in the implementation of standard precautions in veterinary practice.

Risk of exposure is greatest when veterinarians handle aborting animals or those undergoing parturition, though high-risk activities may also include specimen draws during clinical examination, surgical procedures, or disinfection and cleaning of contaminated environments. Inhalation of aerosolized *Brucella* organisms and contamination of the conjunctiva or broken skin are common routes of exposure during the aforementioned high-risk procedures.

### Exposure to *Brucella canis*

While dogs can become infected with various *Brucella* spp., they serve as the primary host for *Brucella canis*. *B. canis* is thought to be less virulent than other strains of *Brucella* species and few human cases have been documented, though this may be a result of difficulty in diagnosis and underreporting.[27]

- **Symptom Monitoring:** Symptom monitoring should be emphasized following exposures to dogs infected with brucellosis because of the lack of serological tests available to identify seroconversion. The symptom monitoring table in Appendix 2 can be given to exposed individuals.
- **Serological Monitoring:** While serological monitoring is not available for B. canis exposures, it is recommended that baseline serum is drawn for serological testing to rule out titers to other *Brucella* spp., as veterinary personnel may be exposed to a variety of species.
- **Antimicrobial Post-Exposure Prophylaxis (PEP):** A prophylaxis regimen should be considered for all personnel with high-risk exposures. See Table 4 for PEP guidance.

## *Marine Mammal Exposure*[28, 29]

Multiple marine mammals that have been stranded in the Gulf of Mexico, Atlantic, and Pacific coasts since 2010 have had laboratory evidence of brucellosis infection. While marine-associated brucellosis in humans has not been documented in the U.S., four human cases are known to have occurred worldwide. One individual was exposed in a laboratory while handling samples from an infected dolphin, and three individuals became sick after consuming raw fish or shellfish. Individuals who come in contact with marine mammals, particularly those stranded or visibly ill, are potentially at risk for infection from *B. ceti* or *B. pinnipedialis*.

- **Risk Assessment:** Higher-risk activities when working with infected marine mammals include aerosol-generating procedures (use of saws) or cleaning of facilities with high-pressure equipment during and after a necropsy. Failure to use PPE, including proper respiratory protection, during the aforementioned activities places individuals at a greater risk for occupational exposure to *Brucella* spp. An excerpt of the Revised Interim Marine Mammal *Brucella* Specific Biosafety Guidelines for the National Marine Mammal Stranding Network is provided in Appendix 3, and may be used as a resource for post-exposure risk assessment.

- **Symptom Monitoring:** Persons experiencing signs and symptoms through 24 weeks post-exposure to infected marine mammals are encouraged to visit their local health care provider as soon as possible for diagnosis, informing their doctor that they may have been exposed to an infectious zoonotic disease such as *Brucella*. The symptom-monitoring table in Appendix 2 can be distributed to individuals who have potentially been exposed.
- **Serological Monitoring:** Serologic testing for *B. ceti* and *B. pinnipedialis* can be done with the BMAT. Baseline sera should be drawn for individuals at high risk as soon as the exposure is recognized, and subsequently at 6-week intervals through 24 weeks post-exposure following the sequence for laboratory exposures.

- **Antimicrobial Post-Exposure Prophylaxis (PEP):** Antimicrobial post-exposure prophylaxis recommendations in the case of a marine mammal exposure are based on risk assessment for the exposed person. See Table 4 for PEP guidance.
- **Reporting:** Any human illness related to zoonotic disease exposure should be reported to the stranding facility and the **National Marine Fisheries Service (NMFS) Regional Office** as soon as possible by emailing the Regional Stranding Coordinators. The Regional Stranding Coordinators will notify the Marine Mammal Health and Stranding Response Program (MMHSRP), who will contact the State Public Health Veterinarian, the county and/or state department public health official and CDC.

## FOODBORNE EXPOSURE

Approximately 70 to 75% of U.S. brucellosis cases reported annually to CDC are due to *B. melitensis* and *B. abortus*, and occur after individuals consume unpasteurized dairy products from countries where brucellosis remains endemic. Areas currently listed as high-risk include: the Mediterranean Basin (Portugal, Spain, Southern France, Italy, Greece, Turkey, and North Africa), Mexico, South and Central America, Eastern Europe, Asia, Africa, the Caribbean, and the Middle East. Prevention measures should focus on educating immigrants and international travelers about the risks of consuming unpasteurized dairy products from these regions. Feral swine hunters who consume raw or undercooked pork are also at risk for food-borne exposure to brucellosis (via *B. suis*).

In cases of foodborne brucellosis, systemic symptoms are more commonly reported than gastrointestinal complaints. A subset of patients experience nausea, vomiting, and abdominal discomfort, and rare cases of ileitis, colitis, and spontaneous bacterial peritonitis have also been reported.[30] Individuals who become sick with a febrile illness after consumption of unpasteurized dairy products or meat from feral swine should be encouraged to submit samples of the food for culture and PCR to confirm the route of transmission.

# RECREATIONAL EXPOSURE

## *Feral Swine Hunting*

Approximately 25 to 30% of U.S. brucellosis cases reported annually to CDC are due to *B. suis* and almost all are diagnosed in feral swine hunters (CDC, unpublished data). Feral swine have been reported in at least 41 states, and serologic surveys have detected endemic feral swine infection with *B. suis* in 13 states (Arkansas, California, Florida, Georgia, Hawaii, Louisiana, Mississippi, Missouri, South Carolina, and Texas). Feral swine hunting is allowed in most states with feral swine presence. Out-of-state hunters often bring swine meat back to their home states; therefore cases may occur even in regions where *B. suis* is not endemic in feral swine populations.[31]

Efforts to prevent B. suis infection should focus on education of hunters and partnerships between state and local public health, wildlife and agricultural agencies, as well as sportsmen's associations. CDC feral swine hunter brochures are available for public dissemination and can be found in the **Additional Sources of Brucellosis Information** section.

### *B. suis* in Hunting Dogs

It is important to recognize that dogs are able to contract brucellosis from feral swine.[32] Transmission may occur through direct contact with the swine or by consumption of uncooked pork or scraps. Non-hunting dogs can also become infected by contact with hunting dogs through urine or breeding. Individuals who hunt with dogs should be encouraged not to allow their dogs to play with the animal carcass or eat raw meat. If dogs develop symptoms consistent with brucellosis (see **Additional Sources of Brucellosis Information, Brucellosis in Animals**), they should be tested for *Brucella* spp.

# BRUCELLOSIS IN PREGNANT WOMEN

Brucellosis during pregnancy carries the risk of causing spontaneous abortion, particularly during the first and second trimesters; therefore, women should receive prompt medical treatment with the proper antimicrobials.[33] The most widely recommended antimicrobial therapy for use in pregnant women is rifampin 15-20 mg/kg per day (maximum 600-900 mg/day) for 6 weeks.[14, 17, 30, 33] Rifampin is a FDA Pregnancy Category C drug, which indicates that there are no adequate studies or data demonstrating risk in humans, but animal studies have shown adverse effects on the fetus from use of this drug.[34] Also, a combination therapy regimen of rifampin 15-20 mg/kg per day (maximum 600-900 mg/day) plus trimethoprim-sulfamethoxazole (TMP-SMZ) 160mg-800 mg BID for six weeks has been cited in the literature.[15, 17, 33]

- It is important to note that TMP-SMZ should not be used after 36 weeks of pregnancy because of the risk of kernicterus caused by elevated levels of bilirubin.[14, 17] Additionally, the teratogenic potential of many antimicrobials, including rifampin and TMP-SMZ, is unknown in humans.[30]

- Information on doxycycline use during pregnancy is limited and FDA classifies it as a Pregnancy Category D drug on the basis of data extrapolated from the use of tetracycline in humans and animals; FDA Pregnancy Category D indicates that data have shown positive evidence of human fetal risk but benefits of drug use may outweigh potential risks in certain situations.[34] For tetracyclines, infant dental staining, fetal growth delays, and maternal fatty liver have been demonstrated. Reviews of studies of doxycycline use among pregnant women have not demonstrated these findings.[35] The risk-benefit ratio for use of doxycycline must be carefully considered if rifampin is unavailable or contraindicated.
- Specific brucellosis treatment instructions should be made in consultation with the patient's obstetrician.

# PERSON-TO-PERSON TRANSMISSION

## *Neonatal Brucellosis*[36-40]

While neonatal brucellosis cases are rare, infection may occur through transplacental transmission of *Brucella* spp. during a maternal bacteremic phase, from exposure to blood, urine, or vaginal secretions during delivery, or through breastfeeding. The majority of documented neonatal brucellosis cases involve *B. melitensis*, though cases of *B. abortus* have been reported as well.

- **Signs and Symptoms:** Clinical manifestations typically resemble sepsis and include fever, resistance to feeding, irritability, vomiting, jaundice, respiratory distress, pulmonary infiltrates, hypotension, hyperbilirubinema, and thrombocytopenia. Progression of the disease state may be evidenced by hepatomegaly, splenomegaly, and lymphadenitis. In some cases, patients may be asymptomatic or clinical symptoms may present later in infancy.
- **Serological Testing:** Information found in peer-reviewed literature suggests that *Brucella* spp. may be isolated from neonatal patients with titer levels lower than 1:160.[39, 40]
- **Treatment:** Dual-combination antimicrobial therapy should be administered for several weeks. Duration and dose of treatment should be made in consultation with the patient's neonatologist or pediatrician.
- **Prevention:** As *Brucella* bacteremia during pregnancy carries the risk of causing spontaneous abortion (particularly during the first and second trimester) or transmission to the infant, women who are pregnant should avoid consuming unpasteurized dairy products and engaging in high-risk occupational activities such as contact with infected animals or administration of live attenuated *Brucella* vaccines. Prompt diagnosis and treatment is essential to secure a healthy pregnancy. Women who have been exposed to *Brucella* spp. or have contracted brucellosis should consult their obstetrician for PEP and treatment options.

### Sexual Transmission[41-48]

Since 1966, there have been nine case reports published in English literature that document evidence of person-to-person transmission of brucellosis. In each of the cases, a male patient who presented symptoms consistent with brucellosis was thought to have transmitted *Brucella* spp. to a female partner via sexual intercourse. Although rare, it is important to recognize that sexual partners of infected patients may be at risk for exposure to brucellosis.

### Organ Donations and Blood Transfusions

While uncommon, transmission of *Brucella* spp. may also occur via tissue transplantation or blood transfusions. There are few reported cases of brucellosis caused by blood transfusion, the earliest dating from 1955 and all occurring outside of the United States.[49,50] There are several reports of transmission due to transplantation, two of which are attributed to bone marrow donation between siblings.[51,52] In other published reports of brucellosis in transplant recipients, it is difficult to ascertain if infection was acquired from the transplant or through other modes of infection.[53,54] If a patient who has undergone a recent transfusion or transplant develops symptoms consistent with brucellosis, the CDC **Office of Blood, Organ, and Other Tissue Safety** should be contacted for assistance with trace-back investigations.

## PREVENTION

### Occupational Exposures

Exposures to *Brucella* spp. can occur in occupational environments, which include but are not limited to: laboratories, clinical and surgical settings, and veterinary settings. In cases involving high-risk exposures (see Table 4 for risk assessment), post-exposure antimicrobial prophylaxis is recommended.

Clinicians should inform laboratory personnel when patient specimens are suspect or rule-outs for brucellosis. Laboratory personnel should work with *Brucella* spp. in at least a class II Biological Safety Cabinet (BSC), with proper personal protective equipment (PPE) and use of primary and secondary barriers, in compliance with the **Biosafety in Microbiological and Biomedical Laboratories** (BMBL), which provides information and recommendations on laboratory containment methods and microbiological procedures. When working with *Brucella* spp. or other infectious organisms, ensure procedures are in place to minimize risk of exposure through spills, splashes, and aerosol-generating events.

In clinical, surgical, and veterinary settings, procedures should also be performed judiciously to minimize spills, splashes, and aerosols.[22] Depending on the types of procedures that are performed, PPE should include adequate protection to minimize direct contact (to skin and mucous membranes) and aerosol exposures. Examples of appropriate PPE include gloves, closed footwear, eye protection, face shield (as necessary, depending on procedure), and respiratory protection (as necessary, depending on procedure).

## *Recreational Exposures (Hunter Safety)*

Hunting wild animals carries with it the potential for risk of exposure to infectious diseases. Certain wild animals (e.g., feral swine, elk, moose, bison, deer, caribou) can carry brucellosis and be a source of transmission. Predatory animals may also be prone to brucellosis after feeding on infected animals. When hunting, it is important to avoid contact with animals that are found dead or are otherwise visibly ill. Animals that appear to be healthy can still have brucellosis; in these cases, safe field dressing techniques can help protect hunters.

- Use clean, sharp knives for field dressing and butchering.
- Wear eye protection and nonporous, disposable gloves (e.g., rubber, nitrile, or latex gloves) when handling carcasses.
- Avoid direct (bare skin) contact with fluid or organs from the animal.
- Avoid direct (bare skin) contact with hunting dogs that may have come into contact with hunted animals.
- After butchering, burn or bury disposable gloves and parts of the carcass that will not be eaten.
- Do not feed dogs with raw meat or other parts of the carcass.
- Wash hands as soon as possible with soap and warm water for 20 seconds or more. Dry hands with a clean cloth.
- Clean all tools and reusable gloves with a disinfectant, like dilute bleach (Follow the safety instructions on the product label).
- Thoroughly cook meat from any animal that is known to be a possible carrier of brucellosis.
- Be aware that freezing, smoking, drying and pickling do not kill *Brucella*.

This information can be found on the CDC **Hunter Safety web feature**.

## *Travel to Endemic Areas*

Brucellosis is endemic in many parts of the world. High-risk areas include: Mexico, South and Central America, Eastern Europe, Asia, Africa, the Caribbean, the Middle East, and the Mediterranean Basin (Portugal, Spain, Southern France, Italy, Greece, Turkey, and North Africa). When traveling to these areas, be cautious of and avoid contact with livestock and consumption of raw animal products. Consumption of raw or undercooked meat, as well as raw or unpasteurized dairy products, can result in transmission of *Brucella* and potentially lead to illness.

See CDC **Brucellosis – Areas at Risk**.

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- CDC Brucellosis webpage: **http://www.cdc.gov/brucellosis**

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- Solera J. 2010. Update on brucellosis: therapeutic challenges. Intl J Antimicrob Agent. 36S, S18–S20. **http://www.ncbi.nlm.nih.gov/pubmed/20692127**

## *Laboratory Exposures:*

- Laboratory-Acquired Brucellosis --- Indiana and Minnesota **http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5702a3.htm**

## *RB51 Exposures:*

- Update: Potential Exposures to Attenuated Vaccine Strain *Brucella abortus* RB51 During a Laboratory Proficiency Test --- United States and Canada, 2007 **http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5702a2.htm**
- Ashford *et al.* (2004) Adverse events in humans associated with accidental exposure to the livestock brucellosis vaccine RB51. Vaccine 22(25-26): 3435–3439.

## *Rev-1 Exposures:*

- Immunization with viable *Brucella* organisms: Results of a safety test in humans. 1962. Bull. Wld Hlth Org. 22: 409–419. **http://whqlibdoc.who.int/bulletin/1962/Vol26/Vol26-No3/bulletin_1962_26(3)_409-419.pdf**

## *Brucellosis in Feral Swine Hunters:*

- *Brucella suis* Infection Associated with Feral Swine Hunting --- Three States, 2007–2008 **http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5822a3.htm**
- Feral Swine Hunter Brochure **http://www.cdc.gov/brucellosis/pdf/brucellosis_and_hoghunters.pdf**
- Davis J. and Ivey M. 2011. "Kill Feral Hogs, But Handle Them Carefully For Your Health and Dogs." Georgia Outdoor News. **http://www.gon.com/article.php?id=2866**

## *Brucellosis in Animals:*

- Shin S and Carmichael LE. 1999. Canine Brucellosis Caused by *Brucella canis*. Recent Advances in Canine Infectious Diseases. Avail at: International Veterinary Information Service: **http://www.ivis.org/advances/Infect_Dis_Carmichael/shin/ivis.pdf**
- WHO Brucellosis in humans and animals 2006. **http://www.who.int/entity/csr/resources/publications/deliberate/WHO_CDS_EPR_2006_7/en**
- Compendium of Measures to Prevent Disease Associated with Animals in Public Settings, 2009. National Association of State Public Health Veterinarians, Inc. (NASPHV) **http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5805a1.htm**

- **Canine Brucellosis**
  - Shin S and Carmichael LE. 1999. Canine Brucellosis Caused by *Brucella* canis. Recent Advances in Canine Infectious Diseases. Avail at: International Veterinary Information Service: **http://www.ivis.org/advances/Infect_Dis_Carmichael/shin/ivis.pdf**
  - Center for Food Security and Public Health, Iowa State University. Canine Brucellosis: *Brucella* canis. **http://www.cfsph.iastate.edu/Factsheets/pdfs/brucellosis_canis.pdf**
- **Marine Mammal Brucellosis**
  - American Association of Zoo Veterinarians **http://c.ymcdn.com/sites/www.aazv.org/resource/resmgr/imported/marine%20mammal%20Brucella.pdf**
  - CDC Marine Mammal *Brucella* Genotype Associated with Zoonotic Infection **http://wwwnc.cdc.gov/eid/article/14/3/07-0829_article.htm**
  - Center for Food Security and Public Health, Iowa State University **http://www.cfsph.iastate.edu/Factsheets/pdfs/brucellosis_marine.pdf**
  - National Oceanic and Atmospheric Administration (NOAA) Fisheries **http://www.nmfs.noaa.gov/pr/health/mmume/midatlantic2013/brucella_factsheet2013.pdf**

# APPENDIX 1: SPECIMEN SUBMISSION

## *Submission of Serum for Brucella Serology*
## *Zoonotic and Select Agent Laboratory, Bacterial Special Pathogens Branch*

1. Acute- and convalescent-phase serum specimens that are shipped together are preferred.
2. Please send serum, not whole blood.
3. Serum should be sent in Sarstedt 2 ml micro tube with an O-ring in the lid (ref #72.694.006). The O-ring helps to prevent leaking or drying of sample.
4. Refrigeration during shipment is preferred. If the sample was previously frozen please ship frozen.
   A. If this is a large-scale exposure (~15 samples), please ship thawed.
5. Specimens are supposed to go first to the physician's state health laboratory (SHL), and if the SHL does not perform the test requested, the SHL will forward the specimens to CDC. If the physician knows that the SHL cannot perform the test and the SHL has given the physician permission to by-pass it, specimens can be sent directly to CDC (to DASH) at the following address:

   Centers for Disease Control & Prevention
   Data & Specimen Handling Section (DASH)
   Mailstop G12
   1600 Clifton Rd NE
   Atlanta, GA 30329-4027

6. CDC Form 50.34 should accompany the specimens; the form is included.
7. When filling out the form, the more complete the form the better. The minimal information should include the following: test requested (*Brucella* serology), submitter's name and address, patient's name/ sex/ DOB, type of specimen, collection dates, date of onset of symptoms, and history of travel, water, animal, or other suspected exposures.

**Please contact if you have additional questions regarding *Brucella* serology:**

**Dr. Robyn Stoddard**
Tel: (404) 639–2053
Fax: (404) 639–3022
RAStoddard@cdc.gov

**Renee Galloway**
Tel: (404) 639–5461
Fax: (404) 639–3022
RGalloway@cdc.gov

## *Submission of Brucella Isolate(s) Zoonotic and Select Agent Laboratory, Bacterial Special Pathogens Branch*

**AS A DIAGNOSTIC SAMPLE:** Any suspected *Brucella* isolate that requires confirmatory testing in our lab:

1. Fill out the CDC 50.34 DASH form
   - When filling out the CDC 50.34 form, the more complete the form, the better.
   - The minimal information should include the following: suspected *Brucella* species, submitter's name and address, patient's name/sex/DOB, type of specimen, collection dates, date of onset of symptoms, and history of travel, water, animal, or other suspected exposures (and any other pertinent epidemiological data).
2. Send the culture on an agar slant (**not a plate**) directly to CDC via DASH to:

   Centers for Disease Control & Prevention
   Data & Specimen Handling Section (DASH)
   Mailstop G12
   1600 Clifton Rd NE
   Atlanta, GA 30329-4027
   ATTN: Rebekah Tiller or Elke Saile

**AS A SELECT AGENT:** Any *B. melitensis, B. suis* or *B. abortus* isolate that has been previously identified/confirmed by another lab that has prepared and submitted a *"Form 4: Identification of a Select Agent or Toxin."*

1. Because CDC is the recipient lab, we will request certain information from the sending lab, so that we can complete the *"Form 2: Request to Transfer Select Agents and Toxins"* and submit to DSAT for approval to transfer.
2. We will both be notified by DSAT of the approval, upon which we have 30 days to complete the transfer. At this time, we will send you an e-mail with detailed information on the shipping of the strain(s) to our lab.
3. We do not receive shipments after business hours or on the weekends so it is best to ensure your shipment arrives Monday-Thursday
4. Please send the culture on an agar slant (not a plate).
5. The shipment may be addressed to:

   Rebekah Tiller or Elke Saile
   1600 Clifton Rd, NE
   Bldg 17 Room 2021
   Atlanta, GA 30329-4027

6. *Brucella* canis is **NOT** a select agent. Therefore, you can send a slant culture directly to CDC via DASH using the CDC 50.34 DASH form only.

**Please contact us if you have additional questions regarding isolate submission or Brucella molecular detection:**


**Rebekah Tiller**
Tel: (404) 639–4507
Fax: (404) 639–3023
RVaughnTiller@cdc.gov

**Elke Saile**
Tel: (404) 639–0716
Fax: (404) 639–3023
ESaile@cdc.gov

# APPENDIX 2: POST-EXPOSURE MONITORING

## *Follow-up of Brucella occupational exposure*

*(The following should only be used **as a guide** by healthcare professionals who are assessing an exposure.)*

Name: _____ Title/Occupation: _____

Exposure Date(s): ____/____/_____ -- ____/____/_____

Years of experience (as a clinician/veterinarian/lab technician): _____

Years working in this facility: _____

Sex: ___M ___F Pregnant? __Yes __No __Unknown

Based on CDC risk assessment guidelines, what risk level applies to this employee?

____ High ____ Low ____ None

## *Serologic Monitoring*

***Note:** Individuals should be monitored for an antibody response to Brucella sp. depending on their level of risk of exposure. Serological testing is not available for B. canis or B. abortus RB51; it is available for S19 and Rev-1 exposures.*

*The Week 0 specimen should be drawn as close to the last date of exposure as possible. A banked serum sample may substitute for the Week 0 sample. The following samples in the series should be drawn at the specified week after the exposure, not from the time the exposure was identified. For example, if a baseline sample is drawn at Week 2 following the exposure incident, the second draw should take place at Week 6 and not Week 8 (six weeks from the baseline draw).*

***If an exposed worker seroconverts, please contact your state health department immediately. Brucellosis is a reportable disease, and the individual will need to undergo brucellosis treatment and confirmatory testing.***

| Week Collection Date | Agglutination Test Used | Titer Complete (Total antibody) | Titer Reduced (IgG) | Positive? | Name of Testing Facility |
|---|---|---|---|---|---|
| 0<br>___/___/___ | ☐ BMAT<br>☐ SAT<br>☐ Other _____ | | | ☐ Yes<br>☐ No<br>☐ IND | |
| 6<br>___/___/___ | ☐ BMAT<br>☐ SAT<br>☐ Other _____ | | | ☐ Yes<br>☐ No<br>☐ IND | |
| 12<br>___/___/___ | ☐ BMAT<br>☐ SAT<br>☐ Other _____ | | | ☐ Yes<br>☐ No<br>☐ IND | |
| 18<br>___/___/___ | ☐ BMAT<br>☐ SAT<br>☐ Other _____ | | | ☐ Yes<br>☐ No<br>☐ IND | |
| 24<br>___/___/___ | ☐ BMAT<br>☐ SAT<br>☐ Other _____ | | | ☐ Yes<br>☐ No<br>☐ IND | |

## *Post-Exposure Prophylaxis Regimen*

If the worker was recommended to take PEP, please ask the individual the following questions:

**1. Which antibiotics were recommended to you? Please mark all that apply.**
☐ Unsure/Don't Know ☐ Doxycycline ☐ Rifampin ☐ TMP-SMZ/Bactrim
☐ Other *(Antibiotic Name)*: _____

**2A. Did you start taking the medication?** ☐ Yes ☐ No

**2B. If yes, when?** ____/____/____ ☐ Unsure/Don't Know

**2C. If no, why didn't you start?** *Complete, then skip to Section H*
☐ Did not feel that I was at risk for becoming sick ☐ Pregnancy
☐ Side effects of antibiotics
☐ Other: _____

**3A. Did you miss any doses of the antibiotics?** *Note this indicates doses not days missed.*
☐ Yes ☐ No *If "No", skip to Q4*

**3B. Which antibiotics did you miss doses for and how many total doses do you think you missed?**
☐ Unsure/Don't Know ☐ Doxycycline *(Doses)*:_____ ☐ Rifampin *(Doses)*:_____
☐ TMP-SMZ/Bactrim *(Doses)*:_____ ☐ Other: *(Antibiotic Name)*: _____
*(Doses)*:_____

**3C. Why did you miss doses of the antibiotics?** ☐ Side effects (adverse events) ☐ Forgot to take
☐ Other:_____

**4A. Did you complete the full 3-week course of antibiotics, as recommended?** ☐ Yes ☐ No

**4B. If no, why didn't you finish?**
☐ Did not feel that I was at risk ☐ Side effects ☐ Switched antibiotics ☐ Pregnancy
☐ Other: _____

**5A. Did you have any side effects that were caused by the medication?**
☐ Yes ☐ No ☐ Unsure/Don't Know

*If "Yes," please fill out the table below. Rate the severity of each reaction on a scale of 1 to 5, with 5 being most severe.*

| Sign/symptom | If Yes, check 1 *(least)* ←→ 5 *(most)* | | | | | No |
|---|---|---|---|---|---|---|
| Nausea/ upset stomach | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 | ☐ |
| Vomiting | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 | ☐ |
| Diarrhea | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 | ☐ |
| Headache | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 | ☐ |
| Dizziness | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 | ☐ |
| Unusual bruising or bleeding | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 | ☐ |
| Yellow skin or eyes | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 | ☐ |
| Other: _____ | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 | ☐ |

**5B. If yes, did any of these reactions cause you to miss work?**

☐ Yes **How much work did you miss?** _____ ☐ Hours ☐ Days

☐ No

## *Symptom Monitoring*

All exposed individuals, regardless of risk status, should be monitored for the development of symptoms. Arrange for regular (e.g., weekly) active surveillance for febrile illness among all workers exposed to *Brucella* isolates for six months after last exposure. Broader symptoms of brucellosis should be passively monitored for six months from the last exposure.

At each regular appointment, ask the worker if he/she has experienced any of the following signs or symptoms. Mark if the worker has had any of the following signs or symptoms **not attributed to a pre-existing medical condition**. If the worker has experienced any of these, please indicate the date the sign or symptom started.

If you choose to use this table, enter the date the worker is seen by Occupational Health (OH). It is up to the OH personnel to decide the frequency of surveillance, whether it is daily, weekly, or a combination for six months following the exposure. Place a check mark in the box if a worker has experienced a specific symptom since the last time he or she was seen by the OH.

**Use of the Symptom Monitoring table on the following page is optional.**

## Signs and Symptoms of Brucellosis

| Symptoms | Date Worker Seen at Occupational Health (daily or weekly symptom watch) | | | | | | | | | | | | | | | | | | | | | | | | Symptom Onset | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ | __/__/__ | N/A | UNK | Date |
| Fever (> 100.4 F) | | | | | | | | | | | | | | | | | | | | | | | | | ☐ | ☐ | |
| Sweats | | | | | | | | | | | | | | | | | | | | | | | | | ☐ | ☐ | |
| Chills | | | | | | | | | | | | | | | | | | | | | | | | | ☐ | ☐ | |
| More tired/less energy than usual | | | | | | | | | | | | | | | | | | | | | | | | | ☐ | ☐ | |
| Severe/persistent headache | | | | | | | | | | | | | | | | | | | | | | | | | ☐ | ☐ | |
| Muscle pains | | | | | | | | | | | | | | | | | | | | | | | | | ☐ | ☐ | |
| Joint pains | | | | | | | | | | | | | | | | | | | | | | | | | ☐ | ☐ | |
| Unintended weight loss | | | | | | | | | | | | | | | | | | | | | | | | | ☐ | ☐ | |
| Loss of appetite | | | | | | | | | | | | | | | | | | | | | | | | | ☐ | ☐ | |
| Vomiting | | | | | | | | | | | | | | | | | | | | | | | | | ☐ | ☐ | |
| Diarrhea | | | | | | | | | | | | | | | | | | | | | | | | | ☐ | ☐ | |
| Other:_____ | | | | | | | | | | | | | | | | | | | | | | | | | ☐ | ☐ | |

# APPENDIX 3: INTERIM MARINE MAMMAL BIOSAFETY GUIDELINES

**EXCERPT FROM: Revised Interim Marine Mammal *Brucella* Specific Biosafety Guidelines for the National Marine Mammal Stranding Network:**

Below are current recommendations from the NMFS Marine Mammal Health and Stranding Response Program (MMHSRP) to protect the health of stranding network personnel when handling cetaceans or pinnipeds suspected of being infected with *Brucella*.

A. High Risk Categories of Animals for Suspect *Brucella* Infection in Marine Mammals: (Use these case definitions when assessing risk and PPE requirements)

- Cetaceans:
  - Any Species – Perinates/Neonates
  - Any Species – Juveniles/Sub-adults/Adults with skin or bony lesions
  - Any Species – Pregnant Females*
- Pinnipeds
  - Any Species – Pregnant Females*
  - Harbor Seals – Weaned pups, Yearlings and Sub-adults (with active lungworm infections)**

*Also are a high risk age class for Q Fever, Leptospirosis infections
**Based upon studies in the Pacific NW

B. Personal Protective Equipment (PPE) for Handling Animals with Suspect Infectious Diseases including *Brucella*

All personnel are recommended to wear appropriate PPE, see list below, personnel can choose to wear more PPE than the minimum recommendations

- **Minimum Recommended PPE for Collecting Stranded Live Animals from the Field**
  - Gloves (disposable or can be disinfected)
  - Closed footwear (that can be disinfected)
  - Eye protection (goggles, glasses, etc.) if feasible
- **Minimum Recommended PPE for Rehabilitating Stranded Cetaceans – For Cetaceans with Skin Lesions (not old scars):**
  - No persons with open cuts or wounds should handle the animal
  - Long-sleeved rash guards and long pants or shorts and/or full wetsuits/skins
  - Gloves (disposable or dive gloves)
  - Dive boots/footwear
  - Eye protection (goggles, glasses, etc.) if feasible
- **Minimum Recommended PPE for Collecting Dead Animals from the Field**
  - Gloves (disposable or can be disinfected)
  - Closed footwear (that can be disinfected)
  - Face shields if carcass is open, has open wounds/skin lesions or if placenta/umbilicus is present (when feasible dependent upon field conditions)

- **Minimum Recommended PPE for Necropsy (field or laboratory)**
  - Gloves (disposable, preferably double-glove during necropsy)
  - Rubber boots or closed footwear (that can be disinfected)
  - Face shields (for field necropsies use if appropriate environmental conditions)
  - Tyvek suits, slickers, other coverall type clothing, waterproof aprons, and/or full wetsuits/skins as appropriate for environmental conditions including temperature and necropsy location
- **Special Necropsy PPE for Procedures that Create Aerosols (Stryker Saw/High Pressure Hose Cleaning).** Wear Minimum Recommended Necropsy PPE as listed above with additional recommendations:
  - Respiratory protection such as a NIOSH-certified N95 (or greater) filtering facepiece respiratory or equivalent is recommended. All respirator users should be fit-tested before use and respirators should be used within the context of a complete respiratory program that meets the requirements in the OSHA Respiratory Protection Standard (29 CFR 1910.134)
  - See CDC Safe Work Practices Guidelines-Appendix I for more information and
  - **http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_id=9780&p_table=STANDARDS**
- General Protective Guidelines—In general, precautionary measures to prevent skin and mucous membrane (eyes, nose, and mouth) exposure to fluids, excretions, and tissues from stranded marine mammals or aborted fetuses can decrease risk of infection. The following recommendations are listed in order of importance.
  - Hand hygiene. Proper hand washing is the most important element of infection control. Wearing gloves does not replace the need for proper hand washing with soap and water, or alcohol-based hand sanitizer if soap and water are not available.
  - When appropriate for environmental conditions wear protective clothing during necropsy, including coveralls or coat, rubber or plastic apron, or rain slicker. Impermeable outer garments are recommended if potential exists for clothing to become soaked with animal fluids. Waterproof boots that can be cleaned and disinfected are recommended. Disinfect boots after each use.
  - Outer clothes worn when working with animals or tissues should be cleaned at work when feasible. Disposable items should not be reused, and wash and dry soiled clothing separately from other items.
  - Disposable gloves are recommended when handling potentially infected animals, tissues, fluids, or excretions.
  - Clean and treat cuts and scratches with an antiseptic and cover with a bandage. Report injuries to your supervisor and document appropriate medical treatment.
  - A face shield that covers the entire face is recommended to be worn during all necropsy procedures and especially if splashes or sprays are anticipated. Full-face plastic shields are preferred over goggles as they provide additional protection for the mouth and nose. Should any potentially infectious material enter the eye, the eye should be flushed for at least 10 minutes with water under clean or aseptic conditions. Exposure should be documented and prompt medical attention is recommended.
  - Activities that generate dust or aerosols should be avoided as much as possible to limit the potential for respiratory exposure. Wet mopping, High-Efficiency Particulate Air (HEPA) vacuums, and avoiding the use of high pressure water sprayers for cleaning is recommended. PPE as described above are recommended to be worn during necropsy and cleaning activities.
  - If feasible, staff should consider participating in a medical surveillance program. Baseline serology should be considered for new staff before starting work.

- People under 18 years of age, pregnant women and people with weakened immune systems are recommended to be excluded from handling potentially infected animals or tissues because these people are at higher risk for infection.