A. Agent[1,2,3,4]:
Brucella species are small, non-motile, Gram-negative coccobaccilli. The species that commonly infect humans are *B. abortus*, *B. melitensis*, *B. suis*, and rarely, *B. canis*, however, these are all biovars of *Brucella melitensis*, which are genetically identical by DNA sequencing. Other *Brucella* spp. such as *B. ceti*, and novel *B. pinnepedialis* can also cause human infection. *Brucella spp.* will grow only in aerobic blood culture bottles after 2–4 days; followed by isolation as typical colonies on BAP and CHOC within 48 hours. Presumptively identified as a small, gram-negative coccobacilli that is oxidase, catalase, and urea positive.

Of note, in 2023, *Ochrobactrum* species were reclassified to the genus *Brucella* based on gene-content studies done in 2020, all *Ochrobactrum* species are now classified by clinical laboratories as *Brucella* species (e.g., *Ochrobactrum anthropi* is now classified as *Brucella anthropi*). [11] However, these *Ochrobactrum* species that were reclassified are non-brucellosis-causing *Brucella* species, therefore a lab report identifying the following Brucella species should not count as a report of brucellosis.

B. Clinical Description[1,2,3]:
In the acute form (less than 8 weeks from illness onset), nonspecific and "flu-like" symptoms including fever, sweats, malaise, anorexia, headache, myalgia, and back pain. In the undulant form (less than 1 year from illness onset), symptoms include undulant (recurrent) fevers, arthritis, and epididymo-orchitis in males. Neurologic symptoms may occur acutely in up to 5% of cases. In the chronic form (more than 1 year from onset), symptoms may include chronic fatigue syndrome, depression, and arthritis. Mortality is low (less than 2%), and is usually associated with endocarditis.

Sequelae are variable, including granulomatous hepatitis, peripheral arthritis, spondylitis, anemia, leukopenia, thrombocytopenia, meningitis, uveitis, optic neuritis, papilledema, and endocarditis.

- Differential Diagnosis:
  Due to the non-specific presentation and numerous, varied complications of brucellosis in humans, the differential diagnosis is vast and will not be addressed in detail here. However, due to similarities in modes of transmission, reservoirs, and early clinical picture, Q fever (*Coxiella burnetii*) should be considered as a differential.
  Diagnosis of brucellosis cannot be made solely on clinical symptoms, due both to the non-specific presentation and to the potentially long/variable incubation period, but should take into account the common risk factors (travel to the Mediterranean Basin and other countries, occupational risk for slaughterhouse workers and similar professions, consumption of unpasteurized dairy products and hunting, etc).

C. Reservoirs[1,2,3]:
The main reservoir for *Brucella* species is animals. The most common species are usually associated with the following animals: *B. abortus* (cattle), *B. melitensis*, *B. ovis* (sheep, and

goats), *B. suis* (pigs), rarely *B. canis* (dogs). Other animals that have been associated with *Brucella* infections include: camels, elk, deer, moose, wild pigs and several other animals.

D. Mode of Transmission[1,2,3]:
By contact with tissues, blood, urine, vaginal discharges, aborted fetuses and especially placentas, and by ingestion of raw, unpasteurized milk and dairy products from infected animals. Airborne infection of animals occurs in pens and stables, and of humans in laboratories and abattoirs. *Brucella* is rarely transmitted from person-to-person. Mothers may transmit the infection to their infants congenitally or through breast-feeding. Sexual transmission has also been reported. For both sexual and breast-feeding transmission, if the infant or person at risk is treated for brucellosis, their risk of becoming infected will probably be eliminated within 3 days. Although uncommon, transmission may also occur via contaminated tissue transplantation.

E. Incubation Period[1,2]:
Highly variable and difficult to ascertain; usually 2 to 4 weeks but can range from 5 days to 5 months. Incubation period may last for years in cases where the patient is not diagnosed and does not receive treatment.

F. Period of Communicability[1,2]:
Rare person-to-person communicability. Risk may exist for medical personnel in endemic regions participating in activities characterized by gross exposure to contaminated fomites or tissue or massive bleeding, such as certain obstetric procedures.

G. Susceptibility and Resistance[1,2]:
Severity and duration of clinical illness will vary. The duration of acquired immunity is uncertain, so reinfection should be presumed possible.

H. Treatment[1,2,3]:
Treatment can be difficult. Doctors can prescribe effective antibiotics. Usually doxycycline and rifampin are used in combination for 6-8 weeks to prevent reoccurring infection. Depending on the timing of treatment and severity of illness, recovery may take a few weeks to several months.

Disease Management

I. Clinical Case Definition[4]:

An illness characterized by:

- Acute or insidious onset of fever; AND
- Two or more of the following signs and symptoms:
    - Night sweats,
    - Arthralgia,
    - Headache,
    - Fatigue,
    - Anorexia,

○ Myalgia,
○ Weight loss,
○ Arthritis,
○ Spondylitis,
○ Meningitis, encephalitis, or other neurologic abnormalities,
○ Discitis or osteomyelitis,
○ Abscesses,
○ Focal organ involvement (including, but not limited to: endocarditis, orchitis/epididymitis, hepatomegaly, splenomegaly).

J. Laboratory Criteria for Diagnosis[4]:

Confirmatory laboratory evidence:

Category 1:

- Identification of a *Brucella* isolate as a brucellosis-causing *Brucella* species 1 (BBS) by methods specific for BBS (e.g., culture, PCR assay with documented specificity for BBS, biochemical tests, whole genome sequencing of *Brucella* isolate).

Category 2:

- Evidence of a fourfold or greater rise in *Brucella* antibody titer between acute- and convalescent-phase serum specimens obtained greater than or equal to 2 weeks apart.

Presumptive laboratory evidence:

Brucella total antibody titer ≥1:160 by standard tube agglutination test (SAT) or *Brucella* microagglutination test (BMAT) in one or more serum samples obtained after onset of symptoms.

***Supportive* laboratory evidence**:

Detection of *Brucella* IgG antibodies by ELISA in a sample collected at least 2 weeks after onset of symptoms.

K. Case Classification: Refer to the ADHS case definition manual.

L. Classification of Import Status:

A case is considered imported if the person became infected outside the US. This should be considered when there is opportunity for exposure and epidemiologic evidence more suggestive of infection elsewhere. A case may also be imported from one state into another or one local jurisdiction to another. All opportunities for exposure and epidemiologic evidence should be documented for assessment of import status. If the exposure is thought to have occurred in Mexico/Canada, mark as *bi-national* in MEDSIS.

M. Laboratory Testing[5,6]:

Gold Standard: Culture or paired serum.

NOTE: Reference isolates may be submitted on agar slants.

TEST	SPECIMEN & TRANSPORT	AVAILABILITY
PCR	Whole blood with EDTA or liquid or plated isolate. Keep refrigerated.	ASPHL
Culture (isolation)	Blood, bone marrow, spleen, liver, tissue aspirate and/ or abscess in standard bacterial transport media. Keep and send refrigerated.	ASPHL
Serology (tube agglutination)	Single or paired sera*. Keep and send at refrigerated temperature.	CDC

*Note on single or paired sera: 10 to 15 ml of whole blood should be collected aseptically in a red top vacutainer tube. For pediatric patients, smaller volumes of blood may be collected in pediatric tubes. After collection, the red top tube may be transported directly to the State Laboratory or the tube may be centrifuged and the serum poured off into a separate vial. The optimal volume of serum for routine submissions is 2–3 ml. Acute and convalescent serums should be collected at least 2 weeks apart.

N. Assessing Laboratory Results:

Blood culture is the diagnostic gold standard, but is not always positive. If blood or bone marrow culture is used, the laboratory must be informed that *Brucella* is suspected, so that they will process the sample for a longer period of time and protect laboratory personnel. A serum agglutination test is the most common serologic approach, but other serology, ELISA, and PCR have been used to make a diagnosis.

O. Outbreak Definition:

There are no formal outbreak definitions; however, the investigator may consider the possibility of an outbreak when there is an unusual clustering of cases in time and/or space.

Investigation Guidelines

P. Time Frame of Reporting[7]:

Submit a report to the local county health department within 1 working day after a case or suspect case is diagnosed, treated, or detected.

Q. Investigation and Reporting Formats:

Please refer to the Department-provided formats for submitting Epidemiologic Investigation Reports [Excel] for guidance on the required investigation fields and forms for the relevant morbidity. All the investigation forms can be found on the ADHS Forms for Reporting and Investigation.

R. Investigation Steps:

Confirm Diagnosis

Collect demographic data

- Birth date, county, sex, race/ethnicity.
- Identify any symptoms of brucellosis.
- If case was hospitalized obtain medical records including admission notes, progress notes, lab report, discharge summary, and outcome (recovered or date of death).

- Obtain possible exposure information (travel, occupation, consumption of unpasteurized dairy products, etc.) from the medical records or interview.
- Provide education and classify the case.
- Follow up with submitting lab to ensure no lab exposures happened.

Per **A.A.C. R9-6-204**[8], ensure that an isolate or a specimen is submitted to ASPHL for confirmation.

Conduct Case Investigation

- All confirmed and probable cases of brucellosis will immediately be investigated.
- Using the CDC Brucellosis Investigation Form, the investigator will attempt to collect as much data from the patient as well as from medical records. The investigator will attempt to contact the patient with three phone calls/texts before sending a letter to the patient's address.
  - Record onset date (if a reoccurrence – record the earliest onset date).
  - Record the duration of the current illness in weeks.
  - Examine and record the therapy that the case received.
- Focus within up to 6 months prior to onset (incubation period) on potential sources of infection:
  - Travel: occurs worldwide, especially in Mediterranean Basin (Portugal, Spain, Southern France, Italy, Greece, Turkey, North Africa), Eastern Europe, the Middle East, Africa, central Asia, central and South America, the Caribbean.
  - Occupation: farming, ranching, veterinary medicine, abattoir/slaughterhouse workers, meat processing plant workers, butchers, meat inspectors, laboratory personnel.
  - Animal exposures: particularly farm animals or wild game, petting zoo, around birthing or aborting animals, exposure to blood, semen, or placenta or other animal body fluid.
  - Vaccine exposure: administrating vaccine, or working with vaccine strains in laboratory.
  - Exposure to or consumption of raw milk or unpasteurized dairy products: milk, cheese (such as Queso Fresco), ice cream, where and when purchased, other persons who consumed or were exposed to same product.
  - Hunting: cleaning an animal for meat consumption.
- Examine all potential exposures based on possible source and potential modes of transmission, including inoculations, sprays into eyes, nose or mouth, or direct skin contact with substances containing *Brucella* spp.
- Identify sick contacts.

Conduct Contact Investigation

- Contacts are those with possible exposure to the same source of infection as the case. Contacts are not persons in close proximity to a case only. Consider acquaintances, household members, associates, co-workers and others.
- Identify persons who participated with the case in any of the at-risk activities and contact them to identify if they are experiencing any symptoms.
- Contacts showing symptoms and with same exposures may be interviewed. A detailed contact and environmental investigation will be completed if a particular source is considered highly likely to be the cause of illness among groups of people.

Initiate Control and Prevention Measures

All laboratories handling specimens with confirmed *Brucella* should be contacted and investigated to identify possible contacts to *Brucella* isolates.

Isolation, Work and Child Care Restrictions

In addition to standard precautions, contacts precautions are indicated for patients with draining wounds. Since person to person transmission is rare, exclusion or quarantine is not applicable.

Case Management

None required.

Contact Management

- Symptomatic contacts should be strongly urged to contact their physician for a medical evaluation.
- Persons who are not ill but who were potentially exposed to the same source should begin a fever watch. From their last exposure, temperature should be actively monitored for fever for four weeks.
- Broader symptoms of brucellosis should be passively monitored for six months from the last exposure. Broader symptoms include:
  - Acute: fever, chills, headache, low back pain, joint pain, malaise, diarrhea
  - Sub-Acute: malaise, muscle pain, headache, neck pain, fever, sweats
  - Chronic: anorexia, weight loss, abdominal pain, joint pain, depression, constipation
- For laboratory personnel, refer to managing special situations.
- For vaccine exposure, refer to managing special situations.

Notifications

- Organize, collect and report data utilizing the DSI fields in MEDSIS and the CDC Brucellosis Investigation Form.
- Report data electronically via MEDSIS, include:
  - All essential data that was collected during the investigation, especially data that helps to confirm or classify a case.
  - Remember to verify all key DSO fields are filled out in MEDSIS.
- For epi-linked cases, include the MEDSIS ID of the related case in the case notes section.

S. Outbreak Guidelines:

Report within 24 hours of detecting a possible outbreak via Outbreak Module in MEDSIS. There are no formal outbreak definitions; however, the investigator may consider the possibility of an outbreak when there is an unusual clustering of cases in time and/or space.

T. Special Situations[6,9,10]:
Intentional Contamination:
Brucellosis is a potential bioterrorism weapon—as little as 10-100 organisms will cause disease. If the case has no known exposures or is not employed in an occupation that is prone to exposure, then consider a bioterrorist event. An attack may take the form of dissemination of an aerosol among a large gathering of people or by the contamination of food or water. Because the laboratory confirmation could be delayed, specific epidemiological, clinical, and microbiological findings that suggest an intentional release of *Brucella* should result in the issue of a health alert.

- If suspected:
  - Notify the Program Manager/Supervisor, Office Chief, Bureau Chief, Preparedness manager (and ADHS epidemiologists if local jurisdiction) immediately.
  - If samples are collected they will be considered evidence in a criminal investigation. Implement Chain of Custody procedures for all samples.
  - Through investigation, define population at risk to help guide response activities. Public health authorities will play the lead role in this effort, but must consult with law enforcement, emergency response and other professionals in the process. The definition may have to be re-evaluated and redefined at various steps in the investigation and response.
  - Once the mechanism and scope of delivery has been defined, identify symptomatic and asymptomatic individuals among the exposed and recommend treatment and/or chemoprophylaxis.
  - Establish and maintain a detailed line listing of all cases and contacts with accurate identifying and locating information.
- Safety Considerations: Risks to public health, health care and emergency response personnel are not significant.
- Diagnosis: Physicians who suspect brucellosis should promptly collect specimens for culture, serology, or PCR. Liver, spleen, joint fluid and abscesses can also be cultured. See laboratory diagnosis table above.

IMPORTANT: Alert the laboratory to the possibility of *Brucella* and need for special safety procedures. Level A laboratories should consult with state public health laboratory director (or designate) prior to or concurrent with testing if *Brucella* species is suspected by the physician.

- Treatment: Drug-resistant organisms might be used as a weapon, conduct antimicrobial susceptibility testing quickly and alter treatments as needed.
- Antibiotics for treating patients infected with brucellosis in a bioterrorist event are included in the national pharmaceutical stockpile maintained by CDC, as are ventilators and other emergency equipment.
- Post-exposure prophylaxis (PEP): In most brucellosis threat situations PEP is not recommended. However, if the level of suspicion is high, exposed individuals may begin antimicrobial therapy if a definitive determination cannot be made within 5 days. The recommended treatment is: rifampin (600 mg/day) and doxycycline (100 mg twice daily) for 6 weeks. PEP of close contacts of brucellosis patients is not recommended because person-to-person transmission is rare.

- Surveillance: Arrange for active surveillance for 4 weeks for the development of febrile illness and 6 months of passive monitoring for other signs and symptoms of brucellosis among all individuals exposed.

Exposure to *Brucella* containing Vaccine:

- Exposure is defined as a needle stick, splash of vaccine onto broken skin, open wounds, or in the eyes.
- Identify the strain contained in the vaccine. There are three vaccine strains: strain 19, RB51, and REV-1.
- Exposed person should see a health care provider. A baseline blood sample should be collected for testing for antibodies. CDC recommends the exposed person take antibiotics (see below). At the end of that time they should be rechecked and a second blood sample should be collected. The sample can also be collected at 2 weeks.

NOTE: Exposure to RB51 does not induce a measurable antibody response. Monitoring serum specimens in those exposed to RB51 will not provide a useful indicator of infection.

- Post-exposure prophylaxis should be considered in an exposed person:
  - Doxycycline and rifampin for strain 19 and REV-1, for 3 weeks.
  - Doxycycline alone for RB-51 for 3 weeks.
  - 6 weeks of treatment if sprayed vaccine in eyes or onto open wounds on the skin.

Laboratory exposure to *Brucella* isolates:

Refer to CDC's Laboratory Risks for Brucellosis guidance.

- Determine number of workers exposed to *Brucella* and classify exposures into high- and low-risk.
  - High-risk exposure: Performing a specifically implicated practice such as sniffing bacteriological cultures, manipulating cultures while on an open bench, or mouth pipetting; being within 5 feet of work with cultures on an open bench, or being present in the lab during an aerosol-generating event.
  - Low-risk exposure: In lab at time of manipulation on an open bench but no other high-risk exposures.
- Recommend PEP for workers with high-risk exposures to *Brucella*:
  - Doxycycline 100 mg twice daily and rifampin 600 mg once daily for a minimum of 3 weeks. (Note: If you're exposed to the rifampin-resistant B. abortus RB51 from vaccine, PEP should include doxycycline plus another antibiotic effective against Brucella, such as TMP-SMZ, for 21 days. The spraying of any *Brucella* containing vaccine in the eyes may require 6 weeks of treatment.)
  - Trimethoprim-sulfamethoxazole as an alternative for patients with contraindications to doxycycline.
  - Pregnant contacts with high-risk exposure should consider PEP in consultation with their obstetricians.
- Discuss PEP with workers with only low-risk exposures.
- Obtain baseline serum samples from all workers as soon as possible after potential *Brucella* exposure is recognized. (If available, obtain pre-exposure stored specimens.)
- Arrange for serologic testing on all workers exposed at 6, 12, 18, and 24 weeks post exposure using a quantitative serological test (CDC is able to perform serial serological monitoring at no cost).

See the ADHS Vector-borne and Zoonotic Diseases Resources webpage for more resources.

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