Q Fever (*Coxiella burnetii*)

Manitoba
Public Health Branch

1. Case Definition

1.1 Acute Q Fever:

1.1.1 Confirmed Case:

Acute clinical illness* with laboratory confirmation[+] including at least one of the following:

- Detection of *Coxiella burnetii* nucleic acid in an appropriate clinical specimen (e.g., blood, biopsy tissue, cerebrospinal fluid {CSF}) (1);
- Seroconversion or fourfold or greater rise in IgG antibody titre to *C. burnetii* phase II antigen by IFA (indirect immunofluorescence antibody assay) in paired samples taken at least three to six weeks apart (1, 2);
- Detection of *C. burnetii* antigen by immunohistochemistry in an appropriate clinical specimen (e.g., blood, biopsy tissue, CSF) (1, 2);
- Isolation of *C. burnetii* from a clinical specimen by culture (1).

1.1.2 Probable Case:

Acute clinical illness* in a person with at least one of the following:

- A single IgG titre ≥ 1:128 to *C. burnetii* phase II antigen by IFA (phase I titres may be elevated as well) (1);
- Positive IgM antibody reactive with *C. burnetii* antigen by IFA.

* **Acute Clinical Illness**: Characterized by abrupt onset of fever, often with chills, weakness, fatigue, headache, cough and other nonspecific systemic symptoms (1, 3, 4). Acute hepatitis, pneumonia or elevated liver enzymes may occur (1, 3).
[+]Serologic test results should be interpreted with caution because baseline antibodies acquired as a result of previous exposure to Q fever might exist, especially in patients with rural or farming backgrounds (1).

1.2 Chronic Q fever:

1.2.1 Confirmed Case:

Chronic clinical illness[&] with laboratory confirmation[#] including at least one of the following:

- IgG titre ≥ 1:800 to *C. burnetii* phase I antigen by IFA;
- Detection of *Coxiella burnetii* nucleic acid in an appropriate clinical specimen (e.g., blood, biopsy tissue, CSF) (1);
- Detection of *C. burnetii* antigen by immunohistochemistry in an appropriate clinical specimen (e.g., blood, biopsy tissue, CSF) (1, 2);
- Isolation of *C. burnetii* from a clinical specimen by culture (1).

[&]**Chronic Clinical Illness:** Chronic Q fever manifests primarily as culture negative endocarditis or vascular infection and occurs mainly in patients with pre-existing valvular or vascular defects (3). Other presentations include chronic hepatitis, osteomyelitis, osteoarthritis or pneumonitis in the absence of other known etiology (1).
[#] Patients with suspected chronic Q fever should be evaluated for titres both to phase I and phase II antigens. Serologic test results should be interpreted with caution because baseline antibodies acquired as a result of previous exposure to Q fever might exist, especially in patients with rural or farming backgrounds (1).

1.2.2 Probable Case:

Evidence of chronic clinical illness[&] and:

- IFA IgG titre ≥ 1:128 to *C. burnetii* phase II antigen and < 1:800 to phase I antigen (1).

2. Reporting and Other Requirements

Laboratory:

- All positive laboratory results are reportable to the Public Health Surveillance Unit (204-948-3044 secure fax).

- Medical laboratories in Manitoba detecting *Coxiella burnetii* specific antibodies shall forward residual serum specimens to Cadham Provincial Laboratory within seven days of the detection.

Health Care Professional:

- Probable cases are reportable to the Public Health Surveillance Unit (form available at http://www.gov.mb.ca/health/publichealth/cdc/protocol/form13.pdf ONLY if a confirmatory positive lab result is not anticipated (e.g., poor or no specimen taken, person has recovered).
- Cooperation in Public Health investigations is appreciated.

Regional Public Health/First Nations Inuit Health Branch (FNIHB):

- Once the case has been referred to Regional Public Health/FNIHB, the *Communicable Disease Control Investigation Form* (www.gov.mb.ca/health/publichealth/cdc/protocol/form2.pdf) should be completed and returned to the Public Health Surveillance Unit by secure fax (204-948-3044).

3. Clinical Presentation/Natural History

Q fever has acute and chronic stages of illness that correspond to two distinct antigenic phases of antibody response (1).

Acute Q Fever:

Approximately 50% of Q fever infections are asymptomatic (4, 5). Symptomatic acute Q fever manifests primarily as a self-limited febrile illness that might occur in conjunction with pneumonia or hepatitis (1, 6). Acute Q fever is most often a mild disease that resolves spontaneously within two weeks (6). Symptoms may include fever, chills, headache, malaise, myalgia and sweats (3, 7). Headache may be severe and debilitating (1). Infection may present as fever of unknown origin (3).

Host factors rather than specific genetic bacterial determinants appear to be the main factors influencing the clinical course of *C. burnetii* infection (6). It has been hypothesized that the route of acquisition of *C. burnetii* infection may influence the clinical presentation of the disease (6). Hematogenous spread of *C. burnetii* may lead to involvement of other organs including the liver, spleen, lungs, bone marrow, and female genital tract (6). Life-threatening complications may occur including meningoencephalitis, myocarditis or pericarditis (6).

Q fever during pregnancy may result in obstetric complications, such as spontaneous abortion, intrauterine growth retardation, intrauterine fetal death, and premature delivery (8). Obstetric complications were found to occur more often in patients infected during the first trimester of pregnancy than in those infected later (8). Women infected with Q fever during pregnancy are at high risk for chronic Q fever or recrudescent infection activated during subsequent pregnancy (1).

Children with Q fever are less likely to have symptoms than adults and might have a milder illness (1). Gastrointestinal tract symptoms, including diarrhea, vomiting, abdominal pain, and anorexia, are reported in 50% to 80% of children (4). Rash is more common in children than in adults (1).

Post-Q fever fatigue syndrome, characterized by a debilitating fatigue has been reported in up to 20% of patients with acute Q fever and is distinct from chronic Q fever manifesting as endocarditis and osteomyelitis (1). The majority of patients diagnosed with this syndrome were previously healthy, with no underlying medical or psychological problems (1).

Chronic Q Fever:

Chronic Q fever is a serious complication of acute Q fever infection that develops in approximately 2% of acute symptomatic cases (5) and can become manifest even years after primary infection (9). Chronic Q fever may be defined by a clinical evolution lasting longer than six months, and is

biologically characterized by the presence of IgG antibody to phase I *C. burnetii* antigen (6). Q fever endocarditis is the most frequent manifestation of chronic Q fever (6). Q fever endocarditis occurs almost exclusively in patients with previous cardiac valve defects (6). Infection during pregnancy and immunosuppression (e.g., from chemotherapy) are both conditions that have been linked to chronic Q fever development (1). Case fatality for chronic Q fever may vary from 5% to 50% (5) but is less than 10% when appropriate antibiotic therapy is administered (6). Chronic Q fever is rarely reported in children (1).

4. Etiology

Q fever is caused by the intracellular bacterium *Coxiella burnetii* (3, 4). The infectious form of *C. burnetii* is highly resistant to heat, desiccation, and disinfectant chemicals and can persist for long periods of time in the environment (4). Shedding of *C. burnetii* into the environment occurs mainly during parturition of infected animals (6). *Coxiella burnetii* is deemed a potential bioterrorism agent because of its low infectious dose and environmental resilience (10).

5. Epidemiology

5.1 Reservoir and Source:

The main reservoirs for *C. burnetii* are sheep and goats as well as cattle (3). The organism has also been found in cats, dogs, wild mammals, birds and ticks (3). Ticks may play a role in maintaining *C. burnetii* in the environment but their role in human infection if any is unclear.

5.2 Transmission:

Transmission occurs mainly through airborne dissemination of *C. burnetii* in dust or aerosols from environments contaminated with placental tissues, birth fluids and excreta of infected animals (3). Animals infected with *C. burnetii* shed massive amounts of the organism at parturition (2). Airborne transmission includes long-distance (indirect) transmission of the aerosolized bacteria (5). Available evidence suggests an effective range of airborne spread of *C. burnetii* of less than 5 km (5). Raw milk from infected cattle or goats contains viable organisms and may be responsible for transmission to humans (3, 11). *Coxiella* has been identified in human breast milk but no case of transmission to the breastfed child has been validated (5). Transmission through coughing and sneezing is not a documented route of infection, and there is no evidence that Q fever is transmitted by any type of casual contact (e.g., hugging, shaking hands, kissing or sharing food) (1). Rarely, person-to-person transmission of Q fever has been described (12). Persistent infection of the genital tract has been documented in humans and both sexual and transplacental transmission of disease have been reported (1). Sporadic cases of nosocomial transmission associated with autopsies and obstetrical procedures of infected women have been reported (1). Direct transmission by blood or marrow transfusion has been rarely reported (3). An outbreak occurred in a factory that processes ovine fetal products for the cosmetics industry (13). Outbreaks have been associated with live or fresh cell therapy (the practice of injecting processed cells from organs or fetuses of nonhuman animals {e.g., sheep} into human recipients) (14).

5.3 Occurrence:

General: Q fever has been reported from all continents except Antarctica and is endemic in areas where reservoir animals are present (1, 3). Outbreaks have occurred among workers in stockyards, in meat packing and rendering plants, in laboratories and in medical and veterinary facilities that use sheep (especially pregnant ewes) in research (3). The majority of occupationally related Q fever outbreaks in the United States have occurred among biomedical research facility workers exposed to infected pregnant ewes (1). In 2009, a large outbreak originating from dairy goat and sheep farms with over 2,300 cases was reported in the Netherlands (15). Q fever cases are increasingly reported in urban areas, especially in persons in

contact with pets during parturition (6), particularly cats (16), as well as in suburban locations near forested areas (17).

Canada: Q fever is not a nationally notifiable disease; therefore, the national incidence is not known. Q fever is a notifiable disease in some provinces, including Manitoba. Ontario reported an average of eight cases per year between 2007 and 2011 (18). Alberta reported three cases of Q fever in 2003 and four cases in 2004 (19). An outbreak of 17 cases of Q fever was reported by Nova Scotia in 2008 (20); two cases were reported in 2009 (21). New Brunswick reported two cases of Q fever in 2012 (22) and one case in 2013 (23). British Columbia reported seven cases between 1998 and 2011 (2).

Manitoba: From 2000- 2014, a total of 14 cases of Q fever were reported to Manitoba Health, Healthy Living and Seniors. This included an outbreak consisting of six cases in 2002. The most recent case reported during this period was in 2011.

5.4 Incubation Period:

The incubation period for acute Q fever ranges from nine to 39 days, depending on the inoculum; but is usually 14 to 22 days (4). The incubation period may be prolonged when the infectious dose is small, which is likely in long-distance windborne transmission (24).

5.5 Risk Groups:

Veterinarians and veterinary researchers; sheep, goat and dairy farmers; and abattoir workers are at greater risk of coming into contact with *C. burnetii* (3). Laboratory personnel are at risk for Q fever infection, especially when manipulating animal or human products containing phase I *C. burnetii* (6). Persons in contact with pets (e.g., cats and dogs), especially when they give birth, are also at risk (6). Living near forested areas has been found to be a risk factor for suburban dwellers (17). Symptomatic Q fever is five times more likely to be diagnosed in people ≥ 15 years of age than in younger people (25). Men are more likely to experience symptomatic infection than women (25). This may be due to the protective role of female sex hormones (25). Persons with valvular heart disease or vascular defects, pregnant women, and persons who are immunosuppressed are at risk for chronic Q fever after an acute infection (3).

5.6 Period of Communicability:

Person-to-person transmission is possible but rarely reported (1).

6. Diagnosis

Diagnosis can be difficult because symptoms are nonspecific and can vary from patient to patient (14). Culture is not available in Manitoba due to the highly infectious nature of *C. burnetii* and the risk to laboratory operators when processing culture specimens. Biosafety level 3 containment is required for culturing specimens suspected or known to contain *C. burnetii*. *C. burnetii* undergoes antigenic phase variation, between a virulent phase I form and an avirulent phase II form (14).

6.1 Acute Q Fever:

Acute Q fever is diagnosed in Manitoba by detection of *C. burnetii* nucleic acid in an appropriate clinical specimen. The diagnosis of acute Q fever can also be established through serologic testing of paired samples taken at least 3 -6 weeks apart. Phase II antibodies are the first to be detected in acute Q fever (13), and are higher than phase I antibodies (14).

6.2 Chronic Q Fever:

Phase I antibodies to *C. burnetii* are associated with chronic infection (6). A phase I IgG antibody cutoff titer of 1:800, which is based on an in-house-developed immunofluorescence assay (IFA), has been internationally accepted for the diagnosis of chronic Q fever (9). Detection of *C. burnetii* nucleic acid is also used for diagnosis.

7. Key Investigations for Public Health Response

Detailed exposure history including:

- Recent animal contact, especially with birthing animals or their birthing products;
- Consumption of raw milk or milk products;
- Recent travel to areas with a higher risk for Q fever, such as agricultural communities, especially those that have experienced recent outbreaks;
- Sexual contact with a person who has recently had Q fever or contact with their contaminated clothing and linens which may lead to fomite transmission;
- Q fever symptoms in a person who has a partner or family member who has received a diagnosis of Q fever (1).

8. Control

8.1 Management of Cases:

- Because of the delay in seroconversion often necessary to confirm diagnosis, antibiotic treatment should not be withheld pending laboratory results or discontinued on the basis of negative acute specimen (1).
- Treatment of chronic Q fever should only be initiated after diagnostic confirmation (1).
- Women should be advised of the risk to the fetus should they become pregnant during the treatment or monitoring period for acute or chronic Q fever (1).

Infection Prevention and Control Measures:

- Routine Practices. For cases in health care facilities, refer to the Manitoba Health, Healthy Living and Seniors document *Routine Practices and Additional Precautions: Preventing the Transmission of Infection in Health Care* available at: http://www.gov.mb.ca/health/publichealth/cdc/docs/ipc/rpap.pdf .
- During procedures that put health care workers at risk for infection from splashing of infected material, such as the delivery of an infant from an infected woman, Routine Practices including the use of a face mask and eye protection or a face shield are recommended (1).
- Airborne precautions are recommended for any aerosol-generating procedures (e.g., performing autopsy on patient that has died of Q fever) (1).
- Procedures that do not generate aerosols such as drawing blood or performing physical examination do not pose a risk for transmission of Q fever (1).
- Samples known or suspected to contain viable *C. burnetii* (i.e., birth products or other biologic material from infected animals or humans) should be handled in a Biosafety level 3 laboratory and rendered nonviable or destroyed (1).
- Care should be used when handling soiled laundry (e.g., bedding, towels and personal clothing) of Q fever patients (1). Soiled laundry should not be shaken or handled in a way that might aerosolize infectious particles (1).

Treatment of Acute Q Fever in Adults:

- Acute Q fever is generally self-limited and many patients recover without antimicrobial therapy (4). Treatment for acute Q fever is not routinely recommended for asymptomatic persons or for those whose symptoms have resolved, although it might be considered in those at high risk of developing chronic Q fever (e.g., valvular heart disease, vascular graft, aneurysm, immunosuppression) (1). Refer to *Management of Acute and Chronic Q Fever in Pregnancy* below for treatment during pregnancy.
- Doxycycline (100 mg twice a day for 14 days) is the preferred treatment in adults (1). Other antibiotics that may be used if doxycycline is contraindicated due to allergy include moxifloxacin, clarithromycin,

trimethoprim/sulfamethoxazole, and rifampin (1). Treatment is most effective if given within the first three days of symptoms (1, 4).
- Closer observation during the convalescent period is recommended for patients at higher risk for chronic infection (1).

Follow-up Monitoring of Patients with Acute Q Fever:

- **Patients with no identified risk factors for chronic disease** and who are otherwise healthy should receive a clinical and serological evaluation (phase I and phase II IgG and IgM antibodies should be measured to endpoint by IFA and compared with previous titres) six months after diagnosis of acute infection to determine if progression to chronic disease has occurred (1).
    - Patients with a phase I IgG antibody titre ≥ 1:1024 (this cut-off value is different from the 1:800 cut-off in the case definition because twofold dilutions are used in the laboratory) should be carefully assessed for clinical evidence of progression to chronic Q fever infection (1). If the chronic Q fever case definition is met, refer to the management of chronic Q fever below.
    - If there is no serologic or clinical evidence of chronic Q fever at six months after acute Q fever diagnosis, serologic monitoring may be discontinued or reduced at the discretion of the health care provider (1).
    - Patients should be advised to seek medical care immediately should symptoms of chronic Q fever occur at any time throughout their lives (1).
- **Patients with identified risk factors for chronic disease** should be serologically monitored and receive a physical examination at intervals of 3, 6, 12, 18 and 24 months of acute Q fever diagnosis (1).
    - Patients with a phase I IgG antibody titre ≥ 1:1024 should be assessed for clinical evidence of chronic infection (1). If the chronic Q fever case definition is met, refer to the management of chronic Q fever below.
    - If there is no serologic or clinical evidence of chronic Q fever within 24 months, serologic monitoring may be discontinued or reduced at the discretion of the health care provider (1).
    - Patients should be advised to seek medical care immediately should symptoms occur at any time throughout their lives, because those with valvular defects or vascular abnormalities remain at high risk for chronic Q fever for life (1).

Treatment of Chronic Q Fever in Adults:

- Treatment should not be prescribed based on an elevated phase I IgG antibody titre alone (the exception is in pregnancy) (1). If clinical evidence of chronic Q fever (refer to *Case Definition*) is absent, a thorough search for the foci of infection (e.g., echocardiogram) should be undertaken (1).
- Consultation with an infectious diseases specialist is strongly recommended. Doxycycline (100 mg twice daily) in combination with hydroxychloroquine (200 mg three times daily) for a duration of at least 18 months is the preferred treatment unless contraindicated (5). Patients should be monitored closely.

Follow-up Monitoring of Patients with Chronic Q Fever:

- Patients should receive monthly serologic testing for *C. burnetii* phase I and phase II

IgG and IgM antibodies and monthly clinical evaluations (1).
    - When serologic monitoring demonstrates a fourfold decrease in phase I IgG antibody with complete disappearance of phase II IgM, and clinical recovery has occurred, antibiotic treatment can be discontinued (1). Serologic monitoring is recommended twice yearly (for potential relapse) for a minimum of 5 years (1).
    - Where serologic and/or clinical monitoring does not indicate improvement, a Q fever expert should be consulted (1).

Treatment of Acute and Chronic Q Fever in Pregnancy:

- Limited data are available on treatment of Q fever during pregnancy (1). Consultation with an expert in infectious diseases is recommended (1).
- To decrease the risk of adverse pregnancy outcomes and reduce the risk for development of chronic Q fever, women who develop acute Q fever in pregnancy are recommended to be treated with trimethoprim/sulfamethoxazole until 32 weeks gestation, when the antibiotic is discontinued due to the risk for hyperbilirubinemia (1, 5).
- Women infected during pregnancy should be serologically and clinically monitored at 3, 6, 12, 18 and 24 months after delivery (as described above for patients with risk factors for chronic disease) for postpartum progression to chronic disease, regardless of whether or not they were treated (1).
- Q fever serologic testing should be resumed for women previously treated during pregnancy who become pregnant again during the 24 month period (1). Long-term trimethoprim/sulfamethoxazole therapy should be reinitiated if recrudescent infection occurs (i.e., fourfold rise in IgG antibody titre) even if other signs of infection are not identified (1). In pregnant women, the nidus of infection is assumed to be the reproductive system (1).
- Monitoring for onset of chronic Q fever should occur during subsequent pregnancies as well (1).
- Consultation with an expert in infectious diseases should be sought for pregnant women diagnosed with chronic Q fever, as the treatment of choice (doxycycline and hydroxychloroquine) has not been evaluated during pregnancy (1).

Treatment of Acute and Chronic Q Fever in Children:

- Doxycycline (2.2 mg/kg per dose twice a day for 2 weeks, maximum 100 mg per dose) is recommended for acute Q fever in children ≥ 8 years and children of any age who are considered high risk (1). The clinical benefit of using doxycycline to treat Q fever in children < 8 years of age who meet the criteria for high risk is greater than the potential risk for dental staining (1).
  High risk is defined as children who:
    - have severe illness or who are hospitalized,
    - have pre-existing heart valvulopathy,
    - are immunocompromised,
    - have delayed Q fever diagnosis with illness for > 2 weeks without resolution of symptoms (1).
- For children < 8 years of age with mild or uncomplicated illness, a 5 day course of doxycycline, 2.2 mg/kg per dose twice a day, (which does not cause dental staining) could be considered (1). If patient is febrile beyond 5 days, the short course doxycycline could be followed with 14 days of trimethoprim/sulfamethoxazole (4-20 mg/kg /24 hours (dose based on trimethoprim component) in equally divided doses every 12 hours (maximum: 320 mg trimethoprim

per 24 hours) (1). Trimethoprim/sulfamethoxazole is contraindicated in children less than two months of age (1).
- Consultation with a pediatric infectious diseases specialist is strongly recommended for treatment and follow-up of chronic Q fever in children (1).

8.2 Management of Contacts and Other Potentially Exposed Individuals:

- Use of post-exposure prophylaxis is not recommended for workers with a known or potential exposure (1).
- Potentially exposed individuals (e.g., household or sexual contacts of a case, individuals with known or potential exposure to the same source as a case such as infected birthing animals) should be advised to seek immediate medical evaluation and treatment should any acute febrile illness occur within six weeks of exposure (1).

8.3 Management of Outbreaks:

An outbreak is defined as the occurrence of case(s) in a particular area and period of time in excess of the expected number of cases.

- Outbreaks should be investigated to identify a common source of infection and prevent further exposure to that source. The extent of outbreak investigations will depend upon the number of cases, the likely source of contamination and other factors.
- Public Health Inspectors may be asked to assist the Medial Officer of Health in outbreak investigations.
- Public notification should occur. The level of notification will usually be at the discretion of regional Public Health and/or the provincial Public Health Branch for local outbreaks but may be at the discretion of the Federal Government for nationally linked outbreaks.

8.4 Preventive Measures:

- Washing hands thoroughly with soap and water after contact with animals and their body excretions.
- Disinfection and disposal of animal birth products (3).
- Consumption of only pasteurized milk and dairy products (3).
- Deferral of blood donation for two years following the date of confirmed cure from acute infection should be considered for donors who have been diagnosed with acute Q fever infection (5).
- Avoidance of live cell therapy or any other type of xenotransplantation due to the public health risk for transmission of known (i.e., Q fever) and unknown infectious agents from the donor organism to the human recipient and possible recombination or reassortment to form new pathogens (14). No xenotansplantation products have been approved for sale in Canada; however; people travel to other countries (e.g., Germany) to receive them (14).
- The potential recipients of live cell therapy or other products of animal origin should be informed of the risks (26).
- Potential blood donors who have received animal cells as therapy should be rejected for donation (26).
- Early detection and treatment of acute Q fever is the best prevention for chronic Q fever (5).

Occupational Exposure Prevention:

- Improved screening of animal herds used by research facilities may decrease the risk of infection (4).
- Restricting access to sheds, barns, and laboratories harbouring potentially infected animals (3).
- Education of employees in high-risk occupations about the risk for exposure and the clinical presentation of Q fever (1). Educational efforts should describe the

groups who are at higher risk of chronic Q fever if infected, including workers who have pre-existing valvulopathy, a prosthetic heart valve, a vascular prosthesis, an aneurysm, are pregnant or might become pregnant, or are immunosuppressed (1). Workers who start jobs with increased risk of Q fever should be offered blood tests to determine if they have resistance to Q fever (7).

- Avoidance of occupations at risk for Q fever exposure by pregnant women, or persons with underlying medical conditions including valvulopathy and immunologic suppressive disorders known to be risk factors for acquisition or more severe Q fever (27).
- Immunization with *C. burnetii* vaccine for at risk occupations may be considered (e.g., laboratory workers working with live *C. burnetii*, abattoir workers) (3). A whole cell vaccine was developed in Australia, but it is not licensed in any other country (5). The need for pre-vaccination testing makes the vaccine more suitable for use in defined risk groups rather than for the general population (5).

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