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## CONSENSUS STATEMENTS

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# Management of *Coxiella burnetii* infection in livestock populations and the associated zoonotic risk: A consensus statement

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Infections caused by *Coxiella burnetii*, commonly referred to as coxiellosis when occurring in animals and Query fever when occurring in humans, are an important cause of abortions, decreased reproductive efficiency, and subclinical infections in ruminants. The organism also represents an important zoonotic concern associated with its ability to aerosolize easily and its low infectious dose. Available diagnostic tests have limited sensitivity, which combined with the absence of treatment options in animals and limited approaches to prevention, result in difficulty managing this agent for optimal animal health and zoonotic disease outcomes. The purpose of this consensus statement is to provide veterinarians and public health officials with a summary of the available information regarding management of *C. burnetii* infection in livestock populations. A discussion of currently available testing options and their interpretation is provided, along with recommendations on management practices that can be implemented on-farm in the face of an outbreak to mitigate losses. Emphasis is placed on biosecurity measures that can be considered for minimizing the zoonotic transmission risk in both field and veterinary facilities.

**KEYWORDS**

abortion, *Coxiella burnetii*, coxiellosis, Q fever, shedding, zoonotic

## 1 | INTRODUCTION

Query fever, (Q fever) was first described as a febrile illness of abattoir workers in Australia in 1937.[1] Subsequently, the causative agent was identified as *Coxiella burnetii*, a ubiquitous, small, pleomorphic,

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intracellular Gram-negative bacterium.[2,3] Infections principally occur through inhalation or ingestion, although infection by blood transfusion occurs.[4,5] Infections in animals are termed coxiellosis. Coxiellosis occurs in a variety of species, with domestic ruminants serving as the most important reservoir for human infection. Coxiellosis is frequently subclinical, with clinical disease manifesting most commonly in small ruminants as late-term abortion, stillbirth, and birth of weak offspring and rarely as abortion or reproductive failure in cattle. Placental membranes, fetuses, and uterine fluids from clinically affected animals can contain massive numbers of *C. burnetii*; however, the agent can be shed in large numbers during parturition in clinically unaffected animals.[6] The organism replicates within the trophoblasts of the placenta and after the logarithmic growth phase, produces a spore-like bacterial form termed a small cell variant (SCV)[7]; these SCVs are responsible for persistence of the organism in dust, manure, and the air of farms.[8–13] Aerosols originating from infected farms can act as a source of infection for humans.[12,14,15]

In this document, we define coxiellosis-positive herds as those with evidence of infection (identification of *C. burnetii* or its DNA in biological samples obtained from livestock), which might or might not result in clinical disease and shedding in individual animals. While serologic testing cannot rule-out infection, in most cases it alone is not sufficient to document coxiellosis at the herd level, and additional testing focused on documenting the presence of the organism is warranted. At the individual animal level, evidence of infection with the organism, with or without clinical disease would be considered coxiellosis; however, the extent and duration of shedding is unpredictable in affected animals.

Query fever and coxiellosis are considered to be re-emerging diseases in many countries. Recently, outbreaks of abortion in sheep and goats with concurrent human illness have occured worldwide.[16–20] Although human infections are often asymptomatic or mild, debilitating complications can occur.

There are several relevant publications available for human and veterinary health professionals, which provide guidance for livestock and public health concerns related to *C. burnetii*. These are summarized in Table 1. The objective of this consensus statement is to complement these documents and to provide more focused recommendations—based on the literature and expert opinion—regarding the clinical management of animals on premises with confirmed or suspected coxiellosis. These recommendations focus primarily on ruminants; however, pertinent discussions are also included related to companion animals, horses, and wildlife. Specific questions addressed in this statement include:

1. How can coxiellosis be most accurately diagnosed at the herd/flock level with consideration of the individual animal level?
2. How can infected herds and flocks be managed to control clinical and subclinical disease, including shedding of the agent and transmission to other herds and flocks?
3. How can the zoonotic risks be mitigated?

## 2 | DIAGNOSIS OF *C. BURNETII* IN INDIVIDUAL ANIMALS

To determine the presence or freedom of infection because of *C. burnetii* in livestock operations, the strengths and limitations of diagnostic tests in various clinical scenarios must be understood. Diagnostic tests detect either the agent (Table 2) or immunological evidence of previous exposure (Table 3) to *C. burnetii*.

A number of commercial PCR kits are available for *C. burnetii* DNA detection. A commonly used target gene is *IS1111*, which is present in multiple copies on the genome, but varies in the exact copy number by genotype.[28,29] A commercial European kit uses the *GAPDH* gene target.[26] When warranted, molecular based bacterial genotyping can be performed to gain insights into the epidemiology and pathogenicity of the isolate.

A positive antibody titer is evidence of current or previous infection with *C. burnetii*, but is not necessarily indicative of current or prior shedding or disease. Importantly, seronegative animals (regardless of test used) can be actively shedding the organism.[30] Serologic tests evaluate antibodies to two distinct antigenic forms of *C. burnetii* called phase I and phase II.[31] Most commercially available antibody tests for livestock detect the summative titer to phase I and phase II antibodies. Data in humans suggest that when independently analyzed, phase II antibodies indicate an acute infection when found in higher titers than phase I antibodies.[22] However, phase-specific antibody testing in livestock remains poorly characterized at present.

Enzyme linked immunosorbent assay (ELISA) is preferred for large-scale screening of the infection status livestock.[24] The CHEKIT Q Fever Antibody ELISA, (IDEXX Laboratories, Inc) is based on *C. burnetii* purified antigens of the 9-Mile tick-sourced strain.[32] It can be used on serum, plasma and milk of ruminants. The manufacturer claims 100% sensitivity and 100% specificity based on tests performed on 81 samples of animals with known infection status. In Europe, the LSIVET Ruminant Milk/Serum Q fever (Laboratoire Service International, Lissieu, France) is an ELISA test using an ovine-derived antigen.[33] Sensitivity is estimated to be 85% and specificity at

**TABLE 1** Publications that augment and synergize with this consensus statement

| Focus | Title | Affiliation |
|---|---|---|
| Guidance for a Coordinated Public Health and Animal Health Response | Prevention and Control of *Coxiella burnetii* Infection among Humans and Animals: Guidance for a Coordinated Public Health and Animal Health Response, 2013[21] | National Association of State Public Health Veterinarians and the National Assembly of State Animal Health Officials |
| Human Q Fever Diagnosis and Epidemiology | Diagnosis and Management of Q Fever — United States, 2013 Recommendations from CDC and the Q Fever Working Group[22] | US Centers for Disease Control and its affiliate Q Fever Working Group |
| US Risk Assessment of Large-Scale Outbreak in Goats | Evaluation of Factors that Would Initiate or Propagate Epidemic Coxiellosis in the United States. Domesticated Goat Population[23] | USDA Centers for Epidemiology and Animal Health |

**TABLE 2**  Summary of diagnostic test used for detection of evidence of infection with *C. burnetii*

| Test | Diagnostic specimen | Considerations[aa] |
|---|---|---|
| Direct Observation of Bacteria | Placental membranes with at least 1–2 cotyledons, fetal tissues, and vaginal mucous | • Pinkish red coccobacillary; usually intracellular bacteria on modified Ziehl-Neelsen, Giminez, and Giemsa stains.[24]<br>• Confirm by immunohistochemistry testing[24] |
| Polymerase Chain Reaction | Abortive tissues, individual and BTM and milk products, feces, vaginal mucus, and environmental samples | • PCR generally indicates presence of DNA from live or bacteria, from infection or contamination.[25]<br>• qPCR allows for better interpretation of the significance of results: < 1000 gene copies of IS1111/μL is not generally considered a significant result.[26,27]<br>• Sensitivity and specificity of the test depend on the gene target of the assay.<br>• PCR on blood may augment, but should not replace other methods of testing as sensitivity is not known. |
| Bacterial culture | Abortive tissues, individual and BTM and milk products, fecal material, vaginal mucus, and environmental samples | • Rarely performed because of human health risk and fastidious growth requirements of the organism.<br>• Must be done in Biosafety Level 3 laboratory.<br>• Requires relatively high levels of shedding to be reliably cultured. |

[a] Positive results may need to be reported to local public and/or animal health officials.

95%.[34] Phase-specific ELISAs have been developed but are not widely available for clinical application.[31]

Although infection with *C. burnetii* does stimulate cell mediated immunity (CMI), diagnostic testing of CMI is not commercially available. In one study, the interferon-gamma assay did not differentiate between exposed and non-exposed goats.[28] Additional research regarding CMI testing for diagnosis of coxiella infections is needed.

# 3 | DIAGNOSIS OF *C. BURNETII* INFECTED HERDS AND FLOCKS

Subclinical infection with *C. burnetii* in ruminants is far more common than clinical infection. This creates a challenge in arriving at the correct diagnosis when investigating abortion outbreaks, trying to assess zoonotic risk, or determining freedom from infection in individuals or groups of animals. Most animals that abort because of *C. burnetii* infections are not systemically ill.[6] Coxiella-associated abortion outbreaks with >10% attack rates during the lambing/kidding season of a flock or herd are not uncommonly reported in small ruminants. Neonates can also be born alive but weak during abortion outbreaks.[6] In cattle, abortion is uncommon, although it has been hypothesized that there is an association between reproductive failure and infection.[35]

## 3.1 | Investigating *C. burnetii* as the cause of abortion

When investigating the cause of abortion, both the placenta and the aborted fetuses should be examined. Severe placentitis is frequently present in small ruminants affected by *C. burnetii* infections. Extracellular and intracellular organisms are usually visible in large numbers when direct smears of cotyledon tissues and histopathological sections are examined microscopically.[24,36,37] Lesions in the placenta of cows that abort because of *C. burnetii* infections are typically much milder.[26] Quantitative PCR (qPCR) results can be helpful when determining if *C. burnetii* is the most likely cause of the abortion in small ruminants, rather than simply being concurrently shed or representing environmental contamination. Animals with abortion caused by *C. burnetii* tend to have qPCR Ct values that correspond to several orders of magnitude greater quantities of organisms (eg, $10^9$-$10^{10}$ copies/μL) than those associated with asymptomatic long-term shedding or environmental contamination.[38,39] In cases of abortion with *C. burnetii*, fetal tissues (liver, abomasal fluid, and lung) can also be PCR-positive. High numbers of organisms as evidenced by qPCR values combined with histopathologic placental lesions provide strong evidence that the abortion is caused by *C. burnetii*. However, identification of PCR-positive samples regardless of the quantity of organisms detected should trigger a discussion of the zoonotic implications of the findings and evaluation of the biological risk it entails.

**TABLE 3**  Summary of diagnostic test used for detection of evidence of exposure to *C. burnetii*

| Test | Diagnostic specimen | Considerations[a] |
|---|---|---|
| ELISA | Serum | • Preferred for large scale screening of livestock.[24]<br>• Good agreement with IFA results. |
| Immunofluorescence Assay (IFA) | Serum | • Definitive serological test in human medicine.<br>• Less widely utilized in veterinary medicine due technical requirements.<br>• Very good agreement with ELISA. |
| Complement Fixation Test (CFT) | Serum | • Less sensitive than most ELISA (as low as 10% in aborting animals); good specificity (>98%).[17-19]<br>• Negative ELISA samples may show low CFT titres, possibly detecting IgM.[15]<br>• Limited utility in livestock. |

[a]With all serological tests listed, seronegative animals may shed the organism.

## 3.2 | Patterns of shedding in aborting herds/flocks

Before aborting, shedding of bacteria in vaginal fluids is absent or minimal, even when bacterial counts *in utero* are substantial.[6] This limits the utility of using PCR as a prepartum assessment of an animal's risk of abortion or post-partum shedding. However, bacterial shedding patterns change dramatically at abortion or parturition. After aborting, bacterial shedding can be detected by PCR in vaginal mucus, feces, and milk, but patterns of shedding are different among species. In cattle, vaginal shedding of *C. burnetii* is typically very short (<14 days) while shedding in milk occurs for much longer periods.[40] Among infected goats during the first month postpartum, the proportion of does shedding in milk, feces or vaginal mucus is similar for individuals that abort and those that kid normally (30%–50%).[41] Milk shedding patterns in goats are similar to vaginal shedding but with lower numbers of pathogens and for longer periods (8 weeks or more).[6,41–43] The level of vaginal shedding typically decreases by 2–3 weeks postkidding.[31]

## 3.3 | Abortion, serological response, and shedding

Sheep and goats that abort are usually seropositive at the time of abortion, although titers can decrease with time.[31,44] However, infected, seropositive herd-mates can undergo normal parturition and deliver healthy offspring.[32] Additionally, seronegative small ruminants can have PCR-positive vaginal swabs after parturition.[44] During outbreaks of coxiellosis, aerosol contamination of sampling supplies because of high environmental load can occur and lead to false positive test in pathogen detection.

## 3.4 | Herds or flocks infected with *C. burnetii* in the absence of abortions—shedding patterns

It is common to encounter herds or flocks where bacteria are being shed without any history of abortion or other abnormal reproductive events.[30,45–47] In such cases, the numbers of organisms being shed is typically much lower than is seen in aborting animals, but the proportion of animals shedding can still be as high as 90%–100%.[30] Shedding is common in birth fluids, vaginal mucus, milk, and feces but the relative quantity of bacteria shed in these bodily fluids differs by species in a pattern similar to that of aborting herds/flocks.[30,45–47]

## 3.5 | Serological status and shedding

In dairy cattle, seroconversion tends to occur within the first ninety days of lactation, with young multiparous cattle being the most likely to seroconvert.[35,48] Serologic status of individual cows is moderately predictive of shedding status. Approximately 65% of cows with PCR-positive milk samples remain seronegative.[30]

Similarly, in small ruminants, there is poor correlation between risk of bacterial shedding and serological status. Among sheep and goats that shed *C. burnetii* by any route, the proportion of seropositive sheep is low (<10%) and moderate in goats (~50%).[30] A high proportion of goats shedding at parturition will be seronegative one month later and in contrast, a high proportion of non-shedding goats are frequently seropositive.[39,47,49–51]

## 3.6 | Bulk tank milk (BTM) testing and herd/flock status

Immunological testing of BTM has been evaluated as a means to evaluate the likelihood of previous infection and the risk shedding bacteria in healthy dairy herds. In dairy cattle, PCR based BTM testing results for a given herd generally provide consistent results over time.[26] BTM antibody concentrations in that species is strongly predictive of within-herd seroprevalence; detection of a within-herd prevalence of >20% is possible with a BTM ELISA.[52] There appears to be good agreement between seroprevalence and BTM antibody concentration in dairy sheep flocks.[53] As such, BTM ELISA is a useful test for large-scale screening programs to detect flocks that have been previously infected, although BTM PCR may be more sensitive for detection of actively infected/shedding flocks.[53] In dairy goat herds, BTM ELISA also is similarly predictive of shedding status when measured with BTM PCR (cut-off 100 bacteria/mL milk) and also for detecting previously infected herds with seroprevalence of >15% (SP ratio of 43%).[54] Bulk tank milk containing >$10^5$ *C. burnetii*/mL as estimated by qPCR is associated with herd seroprevalence of ≥50% in dairy cattle.[35]

## 4 | LOW-RISK HERD/FLOCK STATUS FOR *C. BURNETII* INFECTION

It is often important to evaluate whether individuals or groups of animals have a low risk for shedding *C. burnetii*, such as when animals are used for teaching, research or when planning obstetrical procedures in clinical veterinary practice. As previously stated, serological testing of individual animals does not reliably predicting the likelihood of shedding in any species[47] Detection of shedding by PCR can be used to determine current status; however, that shedding status can change rapidly.[30,41] For example, a pregnant goat can be PCR-negative and seronegative immediately before parturition, but still shed bacteria during a normal parturition.[30,41] The following recommendations are based on first principles of disease surveillance, the epidemiology of coxiellosis, and the accuracy of available diagnostic tests.

The infection status of the population is often used to make inferences regarding the status of individuals. Unfortunately, the best method for determining whether flocks or herds have a low likelihood of current or previous infection has not been well established. It is much easier to detect evidence of infection than it is to determine freedom from infection.[55] Given the zoonotic nature of coxiellosis, the practitioner needs to determine the level of risk that they are willing to assume with regard to their efforts to determine infection status. This decision process might differ because of the highly infectious and zoonotic nature of this organism. Flock-level status with *C. burnetii* is often subject to more rigorous proof of low to no risk of infection than other disease agents. Online calculators can be used to determine the percentage of the herd that needs to be sampled to achieve a reasonable confidence of detecting infection. (See the sample size and FreeCalc calculators at AusVet: http://epitools.ausvet.com.au). This resource also provides a calculator for estimating true prevalence when using imperfect tests. Also, see the sample size calculators for risk-based sampling and representative sampling.

If a small number of serologically positive animals (eg, <1%) are found in a herd where definitive determination of the herd level infection status is necessary because of regulatory or marketing requirements, further nonserologic testing can be performed to confirm the population's status. PCR may be performed on vaginal mucus, feces, environmental samples, or milk. Additionally, adult animals that are euthanized can be evaluated for *C. burnetii* by conducting PCR testing on female reproductive organs, liver, spleen, kidney, and lung.

As an alternative to serology, PCR can be used as a screening test. This can be done at the herd-level in dairy herds using BTM or in samples collected from individual animals. Data suggest that a single dairy goat shedding organisms in milk that is mixed with that from up to 25 000 other animals can be detected; as such, it is likely that low herd prevalence (eg, <0.001%) can be detected using this methodology.[56] However, use of repeated testing is always advisable in situations where knowing the status is critical. PCR is most sensitive on vaginal mucus in the first week postpartum.[6,42] The possible role of *C. burnetii* in all abnormal parturient events, particularly those that are abortions or when stillbirth and weak neonates are present, should also be thoroughly investigated in herds/flocks that are trying to achieve or document a low-risk status. Abortions should be submitted to a diagnostic laboratory for routine investigation that includes qPCR of placental and fetal tissues, as well as histopathology of placenta. The veterinarian or owner might also want to submit randomly selected placental samples from normal parturitions for qPCR. Evaluation of blood by qPCR is not recommended as a screening test, as the magnitude and duration of bacteremia in ruminants are not well characterized.[57]

Introduction of new animals to a herd, or movement of animals between different management groups of a farm can represent an important biosecurity risk to maintaining a low-risk herd status. Detection of infected animals with absolute certainty before their introduction to a herd or flock is not currently possible; however appropriate diagnostic screening, as discussed earlier, decreases the risk of disease introduction. New introductions should only come from herds where testing indicates a low risk of *C. burnetii* infection. Since *C. burnetii* can infect any species including all livestock, domestic animals and wildlife, the interface of the herd with these animals should be minimized to the extent possible. Location of the farm is critical; as organisms can be transmitted in airborne particles for 5 km or more, so it is suggested that a herd with low-risk status be located at least that far from other small ruminant operations.[14,58] Strategies to mitigate spread of infection within and among farms and to humans are discussed later in this statement. Unfortunately, even when precautions are put in place to promote achieving or maintenance of low infection risk in a population, because of the ubiquitous nature of the organism, coxiellosis or detection of the organism during surveillance can still be warranted. A combination of good biosecurity, vaccination (where available), and early detection of shedding with appropriate management of infected animals appears to be the most appropriate way to maintain a low-risk population.

## 5 | SURVEILLANCE OF COXIELLOSIS IN CATTLE, SHEEP, AND GOAT FARMS

The main aim of surveillance for shedding of *C. burnetii* is to detect shedding in an early stage, so that environmental contamination and human exposure can be prevented or minimized. Based on the characteristics of the different tests, several PCR techniques seem most applicable for routine surveillance of shedding of *C. burnetii* in samples of different origin from domestic ruminants. Surveillance of shedding in dairy ruminants can be performed using BTM samples. Further research on testing of environmental and air samples is necessary before they are implemented into surveillance programs.[29,59–62]

After a large human Q fever outbreak in the Netherlands, several compulsory disease control measures were implemented nationwide. A compulsory vaccination program in dairy goat herds was initiated, and its efficacy monitored using BTM PCR and surveillance for abortion. This control program allowed officials to certify individual herds as having a low-risk of coxiellosis, and to provide early detection of any change in herd status.[63]

## 6 | CONTROL OF COXIELLOSIS

Several studies have investigated risk factors of coxiellosis in ruminants in the past decade.[20,64–67] Factors that were associated with lower risk of seropositivity in ruminants in these studies included quarantine of new animals entering the farm, use of stringent hygiene measures for visitors, limited introduction of new animals, prompt removal of birth materials immediately postpartum, and frequent cleaning or changing of bedding. When attempting to control coxiellosis, the primary goal should be the reduction of zoonotic risk associated with shedding during an abortion event, during normal parturition, or through shedding in the milk and manure. The following control measures can be considered for achieving these goals.

### 6.1 | Vaccination

In portions the European Union, vaccination using a phase I killed *C burnetii* vaccine (Coxevac, Ceva Sante Animale) is recommended for use in goats for reduction of abortion risk and shedding of *C. burnetii* in vaginal fluids, feces, and milk and in cattle for reduction of shedding. It has proven to be effective at reducing bacterial shedding levels (<200 organisms per vaginal sample in 24% of vaccinated animals) under experimental conditions, as well under field circumstances.[3,68–71] The vaccine instructions are to administer to nonpregnant animals at least 3 weeks before breeding; ideally animals are initially vaccinated when young (goats at 3 months of age), 3 weeks later, and then followed by an annual booster vaccination. The effect on bacterial shedding is most pronounced in goats when vaccinated before their first pregnancy.[68] In contrast, vaccines developed from killed phase II (SCV) organisms did not affect the course of the disease or excretion.[3] Reduced shedding in sheep after vaccination with a phase 1 vaccine during pregnancy has been reported.[72] However, no reduced shedding was observed after vaccination during pregnancy in goats.[68] At the time of writing of this

consensus statement, there is not a commercially available phase I vaccine licensed and available in the US. The Canadian Food Inspection Agency has stated it will issue a biologic import permit allowing provisional use of a commercial phase I vaccine in Canadian herds and flocks when the need is demonstrated (personal communication P. Menzies).

## 6.2 | Antibiotic treatment to control abortion and shedding of *C. burnetii*

Overall, there is a lack of scientific evidence of efficacy of antimicrobial drugs when used in attempts to control abortion or shedding of *C. burnetii*. Because of this lack of evidence and the need to promote antimicrobial stewardship, it is the opinion of this consensus panel that antimicrobial drugs should not be used for control or treatment of coxiellosis. In vitro, *C. burnetii* is sensitive to several antimicrobial drugs, including tetracycline. In-feed administration of antimicrobial drugs do not reach target concentrations in reproductive tissues or the fetus.[73,74] In the face of an outbreak, treatment with two successive injections of oxytetracycline during the last month of pregnancy has been proposed for use in goats.[3,75] But to date, there are no well-controlled field trials demonstrating an evidence-based benefit of this intervention in goats.[76] The same treatment regimen has been evaluated in sheep, but our study also implemented concurrent vaccination and suffered from low statistical power, making interpretation of results difficult.[77] In cattle, antimicrobial treatment with injectable oxytetracycline was not associated with decreased shedding in milk.[71] Another study suggested that a single treatment with oxytetracycline, administered at drying off, had no effect on the bacterial load.[78]

## 6.3 | Expected clinical course at the herd-level

The most beneficial tool that has been described for management of clinical disease is the implementation of vaccination using phase I form of the killed bacteria.[79] Once coxiellosis is confirmed on a premises, infections should be considered endemic in the population.[80] Animal infection and shedding should generally be expected for multiple years to come, even in the face of intervention measures, including vaccination.[56] In cases of coxiellosis abortion storms, the rate of coxiellosis related abortions is likely to decrease after initial introduction, but shedding during normal parturition will continue.[41,81] Despite the difficulty in eliminating the presence of the organism it is critical that measures are to decrease the environmental load and the related zoonotic infection risk.

## 6.4 | Controlling environmental contamination and transmission

The SCV of *C. burnetii* is profoundly resistant to environmental stress, desiccation, and most commonly used disinfectants. It can survive in the environment for prolonged periods of times (years to decades), and is readily aerosolized in dust.[8,82,83] Based on epidemiologic data collected during the outbreak in the Netherlands, wind dispersion aerosols can result in dissemination of the disease for up to 5 km downwind of infected facilities.[14,58] The greatest risk of aerosol

formation and subsequent human transmission appears to be linked with parturition of animals, especially sheep and goats.[20,84] When small ruminant farms are endemically infected, measures should be taken to minimize the potential aerosol formation from highly infected materials. The presence of an abortion storm may increase this risk because of a higher proportion of animals shedding and should be addressed appropriately as described below.[6,44,85]

Measures that can be implemented to control transmission, environmental contamination and consequently minimize zoonotic risk include:

- Segregate periparturient animals from other high-risk animals (gestating and young). This may decrease exposure to the high level or organisms in aborted fluids.
- Manage parturient animals in an enclosed environment with controlled airflow to lower risk for down-wind transmission. This may increase risk of seroconversion for animals housed within the same environment.
- Eliminate land application of fresh manure.
- Compost manure for 90 days before land application and transport manure and apply only on damp low-wind days.[86–88]
- Promptly remove and dispose of aborted fetus and uterine fluids either by closed composting or burning.
- Move naïve or gestating animals to areas of the farm that are upwind of aborting animals.
- Minimize development of excessively dry and dusty environments in animal housing areas (mist or gently wetting down dusty environments) and around barns.

Mammals, both wild and domestic, birds, and ticks can act as reservoirs of infection and also potential mechanisms of transmission.[89,90] *Coxiella burnetii* shedding occurs from all domesticated species.[91–93] Farm dogs and farm cats commonly scavenge on and might disseminate the organism in the local environment. These non-livestock species also experience clinical abortion associated with this organism and, zoonotic disease has ensued.[94–97] Infected horses, mules and donkeys in rare cases can abort.[98] *C. burnetii* shedding has been described in many species of wild animals commonly encountered on farms, including wild migratory and nonmigratory birds.[99–101] Methods to reduce risk from these species, particularly those that are reproductively active, have not been shown yet to be effective; however, it might be prudent to restrict their access to livestock whenever feasible.[97,102,103]

## 6.5 | Quarantine

In many US states and other animal health jurisdictions, coxiellosis is a reportable disease. If infection and disease is documented in these jurisdictions, state animal health officials ultimately have control of regulatory actions that may be required. According to the National Association of State Public Health Veterinarians and National Assembly of State Animal Health Officials guidance document, quarantine of infected herds is "generally not recommended."[21]

**TABLE 4** Characteristic of individuals that have an increased risk of zoonotic infections of *C. burnetii*[22]

| Condition | General principles |
| --- | --- |
| Occupations with the highest risk of exposure | |
| • Livestock producers, their families and employees<br>• Slaughterhouse employees<br>• Research laboratory animal workers handling pregnant sheep<br>• Veterinarians<br>• Animal health technicians<br>• Veterinary students<br>• Livestock service providers (nutritionist, AI technicians, shearers, livestock truckers) | Any individual in contact with parturient or early post-partum small ruminants or cats. Longer and closer exposure = higher risk. However, the public can also be at risk of exposure under specific circumstances. Some examples:<br>• Individuals attending agricultural exhibitions or petting zoos especially if parturient or early postpartum animals are present.<br>• Living in close proximity to a livestock operation, particularly if sheep or goats and even more likely if parturient. Close proximity can mean up to several kilometers away.<br>• Consumption of raw milk or raw milk cheeses cured for < 90 days. The low pH of hard cheeses will kill the bacteria. |
| Factors that increase risk for severe disease consequences if infected | |
| • Pre-existing cardiac valve disease<br>• Artificial heart valves or grafts<br>• Arterial aneurisms<br>• Immunosuppression (including HIV, chemotherapy, or concurrent disease)<br>• Pregnancy (*see comment)<br>• Extremes of age (infants and geriatric) | Individuals with these factors should avoid or greatly limit contact with high-risk livestock (see Table 5)<br>Infection during pregnancy is a risk for the women to develop chronic Q fever later; however, the major concern is pregnant women with Q fever are at higher risk of miscarriage/stillbirth, premature parturition and intrauterine fetal growth retardation and should receive prompt medical treatment to avoid adverse outcomes.[16,107–111] |

## 6.6 | Using individual testing to eradicate infection from a herd/flock

Strategies focused on managing coxiellosis using an individual test and remove approach are unlikely to succeed and are not recommended because reliable, consistent identification of infected animals using the currently available diagnostic tests remains problematic. As discussed above, some serologically negative animals shed the organism, and shedding is often intermittent and inconsistent except during the parturient and immediately postparturient period making identifying all positive animals difficult by PCR. Further, the high level of environmental contamination combined with the extreme persistence of this organism in the environment allow for continued exposure and make eradication difficult.

## 6.7 | Depopulation and breeding ban

Facing an epidemic of human Q fever concurrent to small ruminant coxiellosis, the Netherlands utilized a multi-pronged approach to limit transmission to humans.[16] In addition to vaccination, the government initiated a program to depopulate all pregnant goats on infected farms and concurrently placed a permanent breeding ban on all non-pregnant animals on infected farms that were not vaccinated before their first pregnancy.[43] These measures were intended to reduce the likelihood of postparturient shedding of the bacterium either from abortion or normal kidding.[68] Together with vaccination, this approach did ultimately aid in stopping the epidemic; however, questions remain regarding the necessity of the depopulation efforts.[68] Based on the epidemiologic data and our current knowledge of vaccine efficacy, use of a depopulation approach is not appropriate in most farm management plans. In agreement with this assessment, the NASPHV and NASHO guidance document states "mass euthanasia of infected herds is never warranted."[21]

## 7 | ZOONOTIC RISKS AND MITIGATION STRATEGIES

Diagnostic testing strategies used to identify infections in humans have been defined and discussed in detail elsewhere.[22] Table 4 provides characteristics of people that have higher risks for exposure and infection. Most exposure to *C. burnetii* is via infection with the SCV form, usually through inhalation of aerosolized bacterium, although ingestion of contaminated milk products is also possible.[7] As few as 1–10 organisms are cable of causing an infection.[104] Approximately half of human infections with *C. burnetii* are asymptomatic.[105] Acute-onset clinical disease occurs 2–6 weeks postexposure in the other half.[106] Most acute clinical infections results in flu-like symptoms (fever, headache, chills, sweating, and fatigue)[22] Some people develop severe headaches that originate from the retro-orbital area.[22] Without treatment, the febrile episodes resolve in 10–14 days and most people fully recover, although there are some that develop a post Q fever fatigue syndrome.[22] However, some individuals require antibiotic treatment to recover and a small proportion of those can require hospitalization.[22] Because of the nonspecific clinical signs of acute Q fever and its self-limiting course in most people, it is probably vastly underreported.[22] This is supported by the high seroprevalence among people that have a high risk of infection, including veterinarians.[69–71] Approximately 30%–50% of patients with acute, symptomatic Q-fever develop pneumonia, while a small proportion of other develop acute hepatitis, myocarditis and meningoencephalitis.[22]

Clinical disease associated with the chronic form of Q-fever occurs in <5% of people that develop acute symptomatic infections, although chronic disease has been reported in people with no history of acute symptoms.[22] Chronic Q fever can develop months to years after the acute infection.[7,22] Endocarditis and other vascular infections are the most common manifestation of chronic Q fever but can also present as chronic hepatitis, osteomyelitis, septic arthritis, and chronic pneumonia.[22]

## 7.1 | How can people protect themselves from Q fever?

There are two approaches for protecting people from infection (in the absence of human vaccination, which is only available in Australia): avoiding situations that lead to exposure, and use of hygiene and personal protective equipment (PPE) to reduce the likelihood of infection. When possible, people with a higher risk of developing severe consequences from infection (eg, people with cardiac valvular disease, immunosuppression, and pregnancy) should consider avoiding situations associated with a higher likelihood of exposure. If this is not possible, then infection risks should be minimized by optimizing environmental hygiene, through optimal adherence to hand hygiene, and by using of PPE including gloves, protective outerwear, and respiratory protection. It is difficult to provide clear-cut recommendations regarding which people should use PPE and when and how rigorously the precautions should applied. This is because it is clear that infection and shedding prevalences are often high in ruminants, and the seroprevalence for *C. burnetii* is high among high-risk professions (as high as 60%), but the number of documented cases of Q fever in people is relatively small.[112] Further, most of these clinical Q fever cases are mild and self-limiting.[22] However, the severe health consequences in a small minority of clinically affected individuals means that the risks for zoonotic infections cannot be ignored. It is clear that when a documented case of Q fever in a person has epidemiological links to farm exposures, other personnel associated with that farm might have an increased risk of developing clinical Q fever in the same period, and higher levels of precautions are warranted.[21] Thus, the risk of serious health consequences for an individual that becomes infected needs to be considered in context with the exposure risk of the situation. Concern for these circumstances is not uniform because people have varying levels of risk-aversion regarding this disease problem. As a result, infection control practices that are employed for *C. burnetii* frequently vary depending among individuals and institutions. However, there is an ethical responsibility for employers and institutions to promote awareness and education regarding risks for zoonotic infection, and to facilitate the ability for individuals to protect themselves. Thus, employers have a responsibility to make it easy and acceptable for individuals to use infections control methods that fit their individual situation and their personal level of risk-aversion.

In situations described above where exposure is likely, such as during parturition of infected small ruminants, infection can occur through inhalation of small particle aerosols. Use of eye protection such as splash shields and high efficiency respiratory protection is needed to protect workers in these situations. Surgical masks or dust masks might be helpful in preventing inhalation of larger droplets, but they are not sufficient to prevent inhalation of small particle aerosols or fine dusts. Tight fitting respirators (eg, full- or half-face canister respirators) and N95 masks should only be used by trained personnel that are medically cleared to use this type of PPE. Alternatively, powered air-purifying respirators can be worn by trained individuals without the need for fit-testing, which can increase flexibility of management protocols. Use of gloves and rigorous adherence to hand hygiene practices will help to prevent inadvertent oral exposures.

Because of risks for infection with a variety of important zoonotic agents, including *C. burnetii*, personnel involved in obstetrical procedures should also prevent skin exposures by using appropriate barrier clothing. It has also been recommended that administrative personnel providing oversight for occupational safety might want to collect and store pre-exposure serum samples to aid in diagnosis of *C. burnetii* infections, should the need arise.[22]

It situations where previous testing and the health history of a flock or herd suggests that there is a low risk of *C. burnetii* infection, it might be considered reasonable to employ less rigorous infection prevention methods, especially when working on nonobstetrical health/disease problems. However, in situations where the infection status of individuals, or source flocks or herds, is unknown, it is advisable that more stringent precautions be applied because of the ubiquity of *C. burnetii*.

## 7.2 | Recommendations for management of animals in a veterinary hospital

Veterinary personnel caring for livestock cannot be protected from all risk of exposure to *C. burnetii*, regardless of the precautions that are employed. However, there are opportunities to mitigate risk, especially in veterinary hospital settings. As animals are admitted to a facility, the clinician should assess the risk of zoonotic exposure to *Coxiella* and should preemptively develop an individualized infection control plan for that patient. As discussed, periparturient sheep and goats have the highest risk for vaginal shedding of *C. burnetii*, especially from parturition until 2 weeks postpartum or longer. Small ruminants presenting with a history of dystocia, abortion, stillbirth or offspring that fail to thrive, have a particularly high likelihood of shedding, but these signs can also be caused by other infectious and noninfectious causes of abortion.[21] Ruminants with no history of individual or farm level reproductive disorders can shed the organism asymptomatically. It should also be noted that all domestic species have been documented to be capable of shedding the organism, so routine biosecurity measures including hand washing, eliminating storage or consumption of food and drink in animal care areas, and use of appropriate hospital-dedicated clothing should be advocated in all areas of the hospital (both large and small animal). Table 5 summarizes some characteristics that will assist veterinarians in assessing the zoonotic disease hazard posed by individual patients.

There are no published evaluations regarding the efficacy of coxiellosis management strategies in veterinary hospitals, but general principles of biosecurity and infection control should be employed in developing plans for management of this disease in hospital settings (Table 6).

## 7.3 | Recommendations for control of human exposures in the field

Some of the precautions that are recommended for control of exposure to *C. burnetii* in veterinary hospitals may be difficult or impossible to apply in field circumstances. Consideration of the likelihood of infection in herds/flocks, and in individual animals can provide a basis for appropriately adjusting the rigor of precautions commensurate

**TABLE 5** Characteristics used to aid in the assessment of the risk of zoonotic exposure to *C. burnetii*

| Risk category | Patient characteristics |
|---|---|
| Lower Risk | • Male ruminants.<br>• Nonpregnant female ruminants.<br>• Pregnant small ruminants that will be leaving the facility before parturition.<br>• Other parturient mammals. |
| Intermediate Risk | • Periparturient small ruminants without an individual or farm level history of recent dystocia, abortion, stillbirth, or offspring that are born weak and undersized.<br>• Periparturient cattle.<br>• Periparturient felines that have been confined to the indoors. |
| Highest Risk | • Periparturient small ruminants from a herd/flock with a known history of coxiellosis, or from a herd/flock with a history of recent dystocia, abortion, stillbirth, or offspring that are born weak and undersized.<br>• Periparturient felines if they have outdoor access.[94–96,103,113,114] |

with the risk of exposure. This will also facilitate easier management of animals in situations where the infection risk is low. Contact with flocks/herds that have a higher infection risk (known endemic infection status or during abortion outbreaks), and interaction with animals in key shedding circumstances (eg, contact during periparturient events) should trigger use of more rigorous prevention methods.

Frequent contact with animals or their environments increases the risk for a variety of zoonotic infections. As such, it is always advisable to use separate clothing for activities involving contact with livestock and to change out of this clothing before returning to a person's home, areas where food is prepared or consumed, and before contacting individuals that have increased risks for zoonotic infections (eg, young children, elderly, etc). Strict attention to hand hygiene will also decrease risks for zoonotic infections, particularly before any hand-to-face contact (eg, eating, smoking, etc), before and after animal contact, and before returning to vehicles or home.

Infection principally occurs through inhalation or ingestion. Prevention strategies should counter these types of exposures to prevent anthropogenic transmission to people and animals. Use of water impervious protective outer attire (ie, barrier gowns) that is disposable or facilitates cleaning and disinfection between contact with different animals will help to prevent transmission when working with periparturient animals. These items should be changed or cleaned and disinfected changed after working with periparturient animals or their environments (eg, cleaning) and when exiting the livestock-rearing facilities. As discussed previously, rigorous attention to hand hygiene and appropriate use of eye and respiratory protection are essential to prevent human infections in high infection risk circumstances. Veterinary personnel and producers should consult with an occupational health physician before employing any type of respirator.

Where possible, it is also important to dispose of the afterbirth and contaminated bedding shortly after parturition to minimize

**TABLE 6** Biosecurity measures that should be considered for inclusion based on the risk posed by different types of patients

| Risk category | Possible infection control and biosecurity measures that should be considered |
|---|---|
| **Lower Risk** | • Assurance of personnel training on clinical signs of Q fever and how to mitigate their risk. The NASPHV document provides some good materials for this process, especially Appendix 2: Q Fever Factsheet and Appendix 3: Personal Protective Actions & Equipment for Animal Owners, Caretakers.[21] In addition, these individuals should be instructed to immediately seek medical attention if they develop symptoms consistent with Q fever and that they should specifically notify their physician of a potential exposure.<br>• General best practice hospital biosecurity measures including: Use of dedicated clothing and footwear on the clinic floor that does not leave the hospital, use of standard barrier precautions at all times and frequent thorough hand washing after handling animals and excluding food and drink from animal housing areas. |
| **Intermediate Risk** | **Above precautions plus:**<br><br>• When performing procedures involving reproductive fluid and tissues, veterinary personnel should use disposable plastic sleeves and/or gloves and either a face shield or protective eyewear and respiratory protection (see discussion regarding use of respirators).<br>• All reproductive tissues (placenta) and bedding contaminated with amniotic and allantoic fluids should be removed as soon as possible, handling and disposing in a manner that prevents further exposure to humans or animals, as well as preventing environmental contamination.<br>• Personnel with known risk factors for Q fever should be excluded from exposure to these animal care situations.<br>• Personnel exposed to animals considered to have a greater risk of shedding *C. burnetii* should seek medical attention if they develop signs related to Q-fever (including fever or flu-like illness). |
| **Highest Risk** | **Above precautions plus:**<br><br>• Patients that have a high likelihood of shedding *C. burnetii* should be managed separately from other susceptible animals in areas of facilities that have separate ventilation and are easy to clean and disinfect. This might be easiest to achieve in a separate facility such as an isolation facility.<br>• Because human infection can result from exposure to contaminated droplets, small particle aerosols, and dusts, use of eye protection (eg, face shields) and respiratory protection should be facilitated and encouraged, if not required. Respirators must only be used after appropriate training, medical clearance, and fit testing.<br>• Personnel exposed to animals that should monitor themselves for signs of infection (eg, fever, flu-like illness, etc). Maintaining a daily log of body temperature may be recommended for people with highest likelihood of exposure and infection, especially if they have risk factors for severe Q-fever.[22] People that develop any signs of illness should seek advice from a healthcare professional. |

**TABLE 7** Disinfectants that have demonstrated at least some level of efficacy in deactivating *C. burnetii* and could be used in veterinary facilities or farms

| Product | Level of efficacy and reference |
|---|---|
| Quaternary ammonium/detergent (MicroChem-Plus) | Complete inactivation after a 30 minutes contact time.[22] |
| 70% Ethanol | Complete inactivation after a 30 minutes contact time, but requires frequent reapplication because of rapid evaporation.[116] |
| 1% Peroxygen (Virkon S) | >90% reduction in infectivity after a 30 minutes contact time.[118,119] |
| 1:100 dilution of hypchlorite | >90% reduction in infectivity after a 30 minutes contact time.[118,119] |

NOTE: All organic matter should be removed before cleaning, and proper PPE should be worn during cleaning.

environmental contamination and prevention of human and animal exposures. Even in situations where circumstances prevent complete cleaning, best efforts should be made to remove contaminated materials. When possible, cleaning with detergents and water, followed by use of disinfectants should be employed. Guidelines for cleaning and disinfection best practices have been previously published.[115] Recommendations regarding disinfection are described below. Routine cleaning and disinfection of lambing/kidding pens has been demonstrated to be associated with a lower risk of human seroconversion in producers.[64,65] During this cleaning on farms with documented coxiellosis it is recommended that a fit tested N95 mask be used, and essential if another individual developed Q fever. In addition, farm personnel that are pregnant or are otherwise at higher risk of developing Q fever based on the description above should consider taking a higher level of precautions, including using a fit tested N95 mask.

## 7.4 | Recommendations for management of animals used in veterinary teaching

For teaching laboratories involving small ruminants, use male and nonpregnant females that have not given birth in the previous 2 months.[22] Use of animals with impending parturition or early postpartum small ruminants for elective teaching exercises should be limited where possible.

## 7.5 | Disinfection

The SCV is highly resistant to many commercially available disinfectants as well as heat, pressure and drying.[116–119] Therefore, removal of contaminated materials (eg, bedding) through standard cleaning protocols likely provides the most immediate benefit and may lower the level of bacteria in the environment. Scrubbing with detergents and rinsing with copious amounts of water (when possible) should be emphasized whenever possible as a means to reduce the environmental load of infectious organisms. However, care should be taken to prevent aerosolization through use of high pressure washers or moving of bedding using leaf blowers and pressure washers, and personnel should use appropriate PPE during cleaning and disinfection. There is little published research regarding the efficacy of cleaning and disinfection processes, but Table 7 provides a list of some possible disinfectant options that may provide better efficacy.

## 8 | FUTURE DIRECTIONS

While scientists have made important strides during the last decade in improving our understanding of the animal and human health

implications related to *C. burnetii* infections, a number of issues still need to be addressed. The authors of this report believe that the following actions should be prioritized by scientists, regulators and other government officials.

- Considered the highest priority by this consensus panel is the need to develop, validate, and license an effective *C. burnetii* vaccine(s) for use in livestock as an aid for controlling coxiellosis in North America. To be useful, the vaccine should prevent reproductive losses, and very importantly minimize shedding of infectious organisms to the greatest extent possible. As described above, vaccines that use phase 1 antigens are the best tool (and in many cases the only reasonable tool) for managing coxiellosis in animals. The low efficacy of antibiotic treatment, coupled with the difficulty associated with providing effective biosecurity for a highly infectious airborne pathogen, severely limits the ability of veterinary and public health officials to effectively manage coxiellosis.

- Providing access to an effective and safe vaccine for humans is also important to prevent disease among people with a high risk of exposure or high risks for severe disease consequences. There are no vaccines approved for use in humans in North America, but there is a phase 1 strain whole cell *C. burnetii* vaccine that is commercially available in Australia (Q-Vax, CSL). It is routinely used for people working in high-risk occupations, including veterinarians and veterinary students. This vaccine has been shown to be effective in preventing Q fever disease when administered to people documented to be seronegative.[120,121] Importantly, people that have been exposed to *C. burnetii* before vaccination can suffer from local and occasionally severe systemic adverse effects.

- There is a need for additional research related to the role of antibiotics in the management and control of abortions and pathogen shedding in livestock. The human literature suggest that antibiotic treatment can be effective in control and eliminating pathogen shedding in humans; however, similar responses have not been observed in ruminants (see section above).

- To allow for improved disinfection of hospital facilities there is a need for additional work focused on the development of effective bacteriocidal products and applications.

- There is a critical need for the development of novel testing approaches that can identify animals that are subclinically infected with coxiella before parturition. At present, none of the available diagnostic assays allow the reliable pre-parturient detection of animals that will shed organism at parturition. This greatly hampers biosecurity control measures and increases human risk of exposure.

- While currently technically challenging and not widely available, genotyping of clinical coxiella isolates holds great potential to improve our understanding of coxiella epidemiology and transmission. Additional efforts in this area may improving our understanding of the role of genotypic similarity or differences in animal reservoirs of infection and continue to build our understanding of the difference in zoonotic risk associated with different genotypes.

## CONFLICT OF INTEREST DECLARATION

## OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

## INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

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