Q FEVER

GUIDELINES FOR ACTION IN THE EVENT OF A DELIBERATE RELEASE

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Note: Comments are welcome from healthcare, laboratory and public health professionals, and should be sent to DRcomments@hpa.org.uk. These guidelines may be subject to changes as comments are received, so please ensure that you have the latest version, which is available through the HPA website.
http://www.hpa.org.uk/deliberate_accidental_releases/biological

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1. BACKGROUND

These guidelines are intended for healthcare, laboratory and public health professionals to guide clinical and public health action in the event of a deliberate release of *Coxiella burnetii* the causative organism of Q Fever.

1.1 Introduction

Q fever is a highly infectious zoonosis caused by the organism *Coxiella burnetii*, which is widespread globally among livestock. Domestic ruminants (sheep, cattle and goats) are the most frequent source of human infection, though dogs, cats, and arthropods may also be a source. Infection in animals is usually asymptomatic, but in ruminants can cause abortions and stillbirths. In infected animals particularly high concentrations of organisms are found in the mammary glands, placental tissue and milk, and to a lesser extent in urine and faeces. The peak incidence of infection in humans in the UK is associated with the spring/early summer lambing season. Infection is commonest in rural areas. Outbreaks are rare, but may be large and their origin difficult to trace. Acute human infection is usually characterised by an influenza-like-illness or pneumonia, after which chronic infection such as endocarditis may develop. The clinical diagnosis of Q fever is difficult due to the variety of presentations ranging from non-specific illness to community-acquired pneumonia, hepatitis or endocarditis. Antibiotics are available for acute infection but are less effective in chronic disease. Vaccination and prophylactic antibiotics may be used in selected exposed individuals.

1.1.1 Deliberate release of *Coxiella burnetii*

C. burnetii could be used as a biological weapon in an aerosolised form or as a contaminant of food, water or potentially mail or other items. An aerosol would be the most efficient form of release; a single organism can cause disease if inhaled by a susceptible individual, and there is good evidence as to the role of wind transmission. Its ability to form resistant spore-like forms, remain viable in the environment for years after release, and its stability under production, storage and transport conditions also make it a suitable biological weapon. Environmental contamination would produce re-aerosolisation. Although an aerosolised release would not cause high mortality, it would result in large numbers of acute and chronically ill people.

1.2 Epidemiology

C. burnetii has a worldwide distribution with cattle, sheep and goats as the primary reservoir, but infection has been found in a wide variety of other animals. In humans Q fever is strongly associated with certain occupations e.g. farmers, abattoir and meat packing workers. People who come into contact with contaminated hay or stables occupied by livestock are also at risk, as are laboratory workers.

Around 50 sporadic cases of Q fever are reported in the UK each year, though this is may be a considerable underestimate of the true incidence because many of cases are asymptomatic or mild (~60% are asymptomatic and of those with symptoms, 40% will have mild disease). Reported cases in children are rare. However, outbreaks have been reported in industrial settings and sero-prevalence studies in the UK have found that 27% of farmers and 10% of the general population show signs of previous exposure.

1.2.1 Transmission

Aerosols are the major route of transmission to man either from direct exposure to infected tissues or indirectly through contaminated dust. Close contact with animals is not always required, although one of the highest risks of infection appears to be from parturient animals, especially sheep. The animal placenta may contain 10^9 organisms per gram of tissue. Humans are at greatest risk of exposure at parturition of livestock because primary aerosols containing large numbers of *C. burnetii* are shed at that time. Outbreaks have occurred where transmission is

thought to have been though wind-borne aerosol distribution, particularly during the lambing season. Van Woerden (2004) reported another outbreak that may have originated from boards made of straw that were being used as building materials. *C. burnetii* may also be inoculated through cuts in the skin, or by thorns entangled in the wool of sheep. The largest known outbreak of Q fever has been on-going in The Netherlands since 2007, with more than 2300 human cases reported in 2009 (Schimmer *et al* 2009; Enserink 2010; van der Hoeck *et al* 2010). The outbreak appears to be associated primarily with infected goat farms, especially with abortion waves on large dairy goat farms, and with aerosol transmission.

C. burnetii is also found in cattle, however pasteurisation has virtually eliminated milk as a potential route of infection. Person-to-person spread is thought to occur rarely, but has been documented *via* sexual contact, following contact with an infected parturient woman and through vertical transmission. Rare cases of nosocomial transmission have been reported following contact with contaminated clothes and items, via intradermal injections or blood transfusions and by aerosols produced during post mortem examination.

1.2.2 Infectious dose
Human volunteer studies have shown that inhalation of a single organism can produce infection in a susceptible person.

1.2.3 Incubation period
- In acute infections the incubation period is between 7 and 30 days, depending on the infecting dose, route of exposure and age of the patient.
- Chronic infections can present 6 months to several years after the initial infection. Patients developing chronic infections, such as endocarditis, may remain infected without manifesting symptoms; however relapses may occur in the future. *C. burnetii* has been demonstrated in the bone marrow of symptom free individuals up to 5 years after an acute infection.

1.2.4 Period of communicability
Person-to-person spread is not generally recognised. Although rare, documented cases of nosocomial transmission have occurred as the likely result of aerosol generation or percutaneous exposure.

1.3 Clinical features
Q fever causes both acute and chronic forms of disease in humans.

1.3.1 Acute infection
Only about half of people infected with *C. burnetii* become symptomatic. The most typical manifestation of acute Q fever is influenza-like illness; other common presentations include atypical pneumonia and hepatitis. Fever and fatigue are the most prominent manifestations and headache is common. Only about 5% of symptomatic patients require hospitalisation. Since Q fever presents as an undifferentiated febrile illness or an atypical pneumonia it may be difficult to distinguish it clinically from viral illnesses or other causes of atypical pneumonia.

Influenza-like-illness
- Usually presents as a self-limiting febrile illness lasting 2-14 days. Onset may be sudden.
- This may be accompanied by high fever, nausea, fatigue, severe headache (often frontal), myalgia, sweats, photophobia and significant weight loss.
- Untreated the fever may be prolonged (up to 57 days has been reported), treated with antibiotics the fever usually resolves in 24 – 48 hours.
- Cough and chest pains occur in approximately 25% of patients.
- May be associated with significant weight loss

- Acute symptoms usually resolve after approximately 10 days, but chronic malaise and fatigue may persist for months.

Pneumonia

- Pneumonia is usually mild with a dry cough, fever, and pleuritic chest pain with few clinical signs on examination.
- Chest x-ray usually shows infiltrates, most commonly in the lower lobes; single or multiple opacities are reported in 52% of cases and 12% develop a pleural effusion. X-ray findings may take 6 months or longer to resolve. The chest x-ray is normal in 10% of cases.
- 5% of cases develop splenomegaly.

Hepatitis

- May be asymptomatic, only being demonstrated on finding abnormal liver function tests. Patients with only mild chemical abnormalities, however may have significant histological changes including focal hepato-cellular necrosis and, in severe cases, granulomata.
- Hepatomegaly may occur but jaundice is rare.
- Extensive destruction of liver tissue leading to hepatic coma and death has occasionally been reported.

Neurological syndromes

- Neurological symptoms have been reported in 0.5% to 22% (mean 4%) of cases.
- Most common are meningoencephalitis, meningitis and myelitis.
- Patients may present with behavioural abnormalities, confusion, seizures or focal neurological signs. Other presentations include Guillain-Barré syndrome (including Miller Fisher variant), cerebellar ataxia, extra-pyramidal disease, optic neuritis or cranial nerve palsies.
- Most patients (66%) make a complete recovery and death is rare.

Other atypical presentations include thyroiditis, haemolytic anaemia, gastroenteritis, pancreatitis, maculopapular or purpuric rashes, and glomerulonephritis.

1.3.2 Chronic infection

Most people make an uneventful recovery from acute Q fever, however in some cases the infection becomes chronic leading to endocarditis, chronic hepatitis, chronic fatigue, osteomyelitis, septic arthritis, chronic interstitial lung disease or infection of aneurysms and vascular grafts. Onset of chronic disease usually occurs about 6 months following acute infection (with a range from 1 month to several years).

Endocarditis

- Patients with previous cardiac valve defects are at significant risk
- Accounts for 60 to 70% of all chronic Q fever, and 3% of all cases of reported endocarditis in England and Wales
- Intermittent fever, cardiac failure, hepatosplenomegaly, purpuric rash and clubbing have also been reported.
- Cardiac vegetations are visible on echocardiograph in only 12% of cases. Embolic manifestations occur in 20%.
- Q fever endocarditis develops more slowly than other forms of endocarditis and is associated with frequent relapses, despite antibiotic treatment.

Hepatitis

- Involvement of the liver in chronic Q fever is usually in conjunction with endocarditis, however, in a few rare instances chronic hepatitis without endocarditis has been described.

Chronic fatigue syndrome

- Characterised by fatigue, myalgia, arthralgia, breathlessness on exertion, blurred vision, night sweats, enlarged painful lymph nodes and changes in mood and sleeping patterns.
- Up to 20% of Q fever patients may have persistent symptoms, associated with chronic fatigue syndrome, three months after their acute episode.

1.4 Mortality

Death is rare in acute infection but was historically high in chronic infection due to endocarditis. With effective antibiotic therapy for endocarditis, life expectancy has significantly improved. Mortality from Q fever endocarditis is less than 10% when treated with appropriate antibiotic therapy; however, relapse rates of over 50% after cessation of antibiotic therapy can occur. Delay in diagnosis has an important effect on the prognosis of chronic Q fever.

1.5 Organism survival

C. burnetii is a highly pleomorphic coccobacillus with a Gram-negative cell wall. It is an intracellular organism, which can remain in infected cells without affecting their viability, living in the cell's phagolysosomes. This effectively allows the organism to "hide" from the immunological response. During bacterial replication *C. burnetii* may undergo sporogenesis. This spore-like form can withstand environmental extremes and is able to disseminate for miles when blown by the wind. The spore survives 7-10 months on surfaces at 15-20^{o}C, and for weeks on fresh meat in cold storage. *C. burnetii* is difficult to decontaminate from environmental surfaces since it is resistant to UV light, disinfectants and high temperatures. However, 2% formaldehyde, 1% Lysol, 5% hydrogen peroxide, 70% ethanol or 5% chloroform are thought to be effective.

1.6 Antibiotic susceptibilities

The treatment of choice for acute Q fever pneumonia is tetracycline or doxycycline. Despite erythromycin being ineffective *in vitro,* it is clinically effective, though less so than doxycycline. Erythromycin has been reported to have failed in the treatment of patients with severe pneumonia, which brings into question its use as an empirical treatment for atypical pneumonias. Doxycycline is also more effective than other macrolides, including clarithromycin and roxithromycin, which have been suggested as alternative therapies. Quinolones, chloramphenicol, rifampicin and co-trimoxazole have been shown to be effective against Q fever but data are sparse. Antimicrobial resistance is rare but it has been described, particularly with quinolones.

An *in vitro* study of the activity of fluoroquinolones against *C.burnetii*, suggest that the newer fluoroquinolones, particularly gatifloxacin, show more promise *in vitro* compared with the established fluoroquinolone ciprofloxacin (Lever *et al*. 2004). Clinical data suggest that clarithromycin or moxifloxacin may be safe and effective treatment for Q fever (Morovic 2005; Kuzman *et al*. 2005).

2. CLINICAL PROCEDURES

2.1 Diagnosis and collection of samples

Since clinical diagnosis and culture are difficult, diagnosis is usually made by serological methods.

2.1.1 Serology

In culture, *C. burnetii* undergoes phase variation from virulent "wildtype" phase I (as isolated from recent natural infections or maintained by passage in laboratory animals) to avirulent phase II after a (varying) number of passages in embryonated eggs. The antibody response to these different cell wall lipopolysaccharide antigens forms the basis of serological diagnosis.

In acute self-limited Q fever infections, antibodies to phase II antigens appear first, dominate the humoral immune response and are at higher titre than the anti-phase I titre. An initial rise in IgM antibody to phase II antigen is followed by an IgG response to the same antigen. IgM may persist at low levels for long periods following acute infection and does not necessarily indicate currently active disease. In chronic Q fever infections there is a response to both phase I and phase II antigens, with IgG and IgA antibodies to phase I being diagnostically useful (high IgA and IgG titres are indicative of chronic disease (endocarditis)). Phase I titres eventually equal or exceed phase II titres. The ratio of phase II to phase I antibodies can be a useful indicator for distinguishing acute from chronic Q fever infections (Peacock *et al* 1983).

Indirect immunofluorescence is the most accurate and readily available serological test for Q fever. Antibodies may be detected 2 – 3 weeks after the onset of the disease, and tests should be performed on both acute and convalescent samples. In the event of a deliberate release, ELISA tests may be better suited to population screening. Complement fixation tests are also available but are less specific and sensitive. PCR tests are being evaluated to detect *C. burnetii* in blood, urine and tissues samples.

2.1.2 Precautions for sampling

The samples outlined below should be taken to confirm the diagnosis. **These must be taken using Universal Precautions and with the utmost care to avoid inhalation or inoculation injuries**. The receiving laboratory should be telephoned to expect arrival. Chain of evidence documentation should also accompany all specimens; however in larger incidents this would only be required for several of the initial cases.

2.1.3 Samples to be taken from acutely ill humans

- Serum – acute and convalescent
- EDTA blood samples for PCR

2.1.4 Post mortem specimens

Samples may be taken dead humans to assist diagnosis, including:

- Tissue material from lung, spleen and lymph nodes
- Samples of body fluids if appropriate

2.1.5 Samples to be taken from the environment

Samples should be taken from any material (soil, dust, clothing, swabbing etc) in the environmental area thought to have been exposed to *C. burnetii* spores. Further advice on environmental sampling methods will be provided if a release is suspected.

2.1.6 Transport of samples

Strict procedures should be followed for the transport of samples of suspected Q fever, both from the clinical environment to the laboratory, and from local laboratories onto the reference laboratory. These are outlined in section 3.5. *C. burnetii* cultures fall into Category A for the purposes of transport. All samples should be transported as per UN 602 as described in "Appendix

1.2 Transport of infectious substances" in "Biological agents: Managing the risks in laboratories and healthcare premises." Advisory Committee on Dangerous Pathogens (ACDP), Health and Safety Executive (HSE) May 2005 accessed at http://www.advisorybodies.doh.gov.uk/acdp/managingtherisks.pdf

2.2 Treatment and follow-up

Many cases of Q fever go unrecognised or are diagnosed retrospectively. Most clinicians agree that antibiotics should be used in all cases of acute infection but some argue that antibiotics should be reserved for severe cases. Treatment is most effective when started within three days of acute illness. Possible or proven Q fever in pregnant women or in children should be discussed with an Infectious Disease physician on a case-by-case basis.

Expert advice should be sought for patients with the following 'high risk' conditions;

- Heart murmur or known valvular pathology
- Prosthetic heart valves
- Prosthetic vascular material
- Immuno-compromised

2.2.1 Acute Infection

Tetracycline or doxycycline is the treatment of choice in acute Q fever. **Seek expert advice**.

Table 1. Treatment for acute Q fever

	Antimicrobial agent	**Duration**
Adults	Tetracycline 500 mg four times daily or Doxycycline 100 mg twice daily	7-14 days. Continue treatment for at least 3 days after remission of fever.
Women who are pregnant or breast-feeding	Co-trimoxazole 960mg (800mg sulfamethoxazole/160mg trimethoprim) oral twice daily	Until term/ delivery
Children under 12	Co-trimoxazole (sulfamethoxazole 40mg/kg and trimethoprim 8mg/kg) Oral daily	14 days

Doxycycline or tetracycline should not be given to children under 12 years of age or to pregnant or breast-feeding women.

Fluoroquinolones should be used for patients with neurological symptoms because of their better penetration of the central nervous system.

Treatment options for hepatitis are as above with the addition that corticosteroids (prednisolone 0.5mg/kg/day) have been used successfully in cases that have shown a poor response to antibiotics.

2.2.2 Chronic Infection

There are no published data on controlled clinical trials for the treatment of Q fever endocarditis. Even after apparently successful treatment relapse of Q fever endocarditis can occur once antibiotics are stopped, thus some clinicians recommend that treatment be continued indefinitely. Combination antibiotic therapy (which has included; clindamycin with tetracycline, tetracycline with

co-trimoxazole, rifampicin and doxycycline and doxycycline and fluoroquinolones) are now used. Despite improved results with combination therapy relapse rates of over 50% are still seen and a minimum of 3 years treatment is recommended. A combination of doxycycline and chloroquine has been shown to reduce relapse rates if continued for at least 3 years. This may be due to improved antimicrobial activity through increased alkalinisation of the phagolysosome. Patients treated with the combined doxycyline and chloroquine regimen may have photosensitivity, and regular heart and eye examinations are required.

Antibody titres to *C. burnetii* phase 1 and phase 2 should be monitored every 3-6 months during treatment of chronic Q fever infections. Successful treatment is accompanied by a steady decline in phase 1 titres.

2.3 Infection control practice

2.3.1 Decontamination of exposed persons.

In the event of a known exposure to *C. burnetii*, the risk for re-aerosolisation is uncertain and is likely to depend on a number of variables, including the quantity of the organism on the surface; the type of surface and host factors. However, even low numbers (a single organism) of *C. burnetii* could potentially lead to infection in any person breathing in the organism. An incident specific risk assessment will be required.

In situations where the threat of exposure to *C. burnetii* exists, cleansing of skin and potentially contaminated fomites such as clothing, personal possessions or environmental surfaces should take place. Decontamination of exposed persons includes:

- Removal of contaminated clothing and possessions – should be stored in labelled double plastic bags until exposure has been ruled out.
- If *C. burnetii* is confirmed, all contaminated material must be incinerated or autoclaved.
- Minimal handling of clothing and fomites to avoid agitation.
- Instructing exposed persons to shower thoroughly with soap and water- appropriate facilities will be provided at the scene as necessary.
- Instructing attending personnel to wear full PPE when handling contaminated clothing and other fomites.

2.3.2 Isolation of patients

Person-to-person spread is thought to occur very rarely, if at all, and cases of pneumonia or endocarditis can be nursed in an open ward. Standard precautions are recommended for those managing Q fever cases in hospital. Gloves, gowns and facemasks should be worn within 3 feet of patients where there is possibility of droplet splashes from secretions of body fluids, such as during obstetric procedures.

2.3.3 Cleaning, disinfection and waste disposal

Spills of potentially contaminated material should be dealt with immediately using hypochlorite (5000 ppm available chlorine), 5% peroxide or phenol based solutions. Biohazardous waste should be autoclaved. The spore-like form of *C. burnetii* is resistant to normal disinfection, dilute bleach, UV radiation, heat and desiccation. Whilst it may be tempting to decontaminate large areas using pressure washing equipment, this practice should only be undertaken if appropriate precautions are taken as *C. burnetii* may be further spread by aerosols created by use of such equipment.

2.3.4 Post-mortem Procedures

Autopsy

The risk of acquiring Q fever following contact with the body of a person who has died from the disease is low, because although person-to-person transmission is rare, there is evidence in rare cases of transmission following autopsy.

Autopsy examinations may be carried out with appropriate precautions. Infected tissues may represent an aerosol hazard and respiratory precautions should be worn. The same procedures should be followed as for open pulmonary tuberculosis. The pathologist must be informed of the known or suspected diagnosis. Standard precautions for post-mortem examinations on patients infected with Containment Level 3 organisms are appropriate. Limiting the production of aerosols from the respiratory tract and the use of high efficiency facemasks (FFP3) will reduce risk. Instruments should be autoclaved.

Similarly, body preparation should be carried out with normal control of infection procedures. Standard precautions for the disposal of bodies infected with Containment Level 3 pathogens should be observed, and the undertaker should be informed. **Cremation** is the preferred method for disposal of the deceased. **Embalming** of bodies should not be undertaken because the body fluids are likely to contain large numbers of the causative bacteria and therefore the process of embalming exposes the embalmer to an unacceptable risk.

Pacemaker removal
Pacemaker removal is permitted. Pacemaker should be treated with hypochlorite solution (10,000ppm available chlorine), bagged and disposed of appropriately (not by incineration).

2.4 Post-exposure prophylaxis for persons exposed to Q fever

Post-exposure prophylaxis should be considered for essential personnel or those considered to be at high risk from a release. **However, chemoprophylaxis is not effective and may prolong the onset of disease if given within 7 days of exposure.**

Table 2. Post-exposure prophylaxis for Q fever

	Antimicrobial agent	**Duration**
Adults	Doxycycline 100mg twice daily **Start 8-12 days post exposure**	7 days
Pregnant women	Co-trimoxazole 960mg (800mg sulfamethoxazole/160mg trimethoprim) twice daily **Start 8-12 days post exposure**	7 days
Children under 12 yrs	Co-trimoxazole (sulfamethoxazole 40mg/kg and trimethoprim 8mg/kg) oral daily **Start 8-12 days post exposure**	7 days

Doxycycline should not be given to children under 12 years of age or to pregnant or breast-feeding women.

In a major incident information on how to access stocks of antibiotics for initial treatment or prophylaxis can be found on the DH website at:
http://www.dh.gov.uk/assetRoot/04/13/53/71/04135371.pdf

2.4.1 Immunisation
Vaccine is not available in the UK.

2.4.2 Contacts of cases
Chemoprophylaxis for those exposed to infected individuals is unnecessary.

2.4.3 Monitoring of exposed persons
Acute and convalescent serum samples should be collected from exposed individuals and tested for *C. burnetii* specific antibody responses. All individuals with evidence of recent infection should be referred for cardiac assessment.

2.5 Environmental decontamination

The greatest risk to human health following a release of Q fever occurs during the period in which the spores are airborne. The duration and scale of the infectious risk depends on the duration for which spores remain airborne and the distance they travel before they fall to the ground. This depends on meteorological conditions and aerobiological properties of the dispersed aerosol. There is likely to be a significant risk of re-aerosolisation; dust contaminated with *C. burnetii* is a common source of human infections and wind-borne cases are known to occur in endemic areas. A number of outbreaks have demonstrated the possibility of spread on fomites such as clothing, hay, straw, contaminated shoes and building materials. Fomites are likely to continue to pose a risk, even when they are not heavily contaminated. In the event of a known release, an **exposed zone** will be defined according to the time and place of release in order to identify all persons exposed to primary aerosolisation. Expert advice will be provided to determine the time after release for which spores are likely to remain airborne.

It is impossible to de-contaminate large areas of a potentially contaminated environment.

2.6 Protection of frontline workers

This includes all emergency staff involved in management at the scene of a release, as well as those involved in treating patients.

2.6.1 Protective clothing

Following an overt release of *C. burnetii,* the area affected by primary aerosolisation will depend on the time and place of release. This **exposed zone** presents the highest risk of infection. Any personnel entering this zone should wear a biologically-resistant suit with outer gloves and boots (for example a CR1, PRPS or gas-tight suit), and a correctly fitting high-efficacy particulate respirator of FFP3 standard **AT ALL TIMES**.

Healthcare workers will not normally be asked to enter this zone but may be called into it to treat casualties, for example if an explosive device has accompanied the release of biological agent. In this case the appropriate protective clothing and equipment should be worn.

Exposed persons will normally be moved from the exposed zone, through decontamination, to a place of safety (see section 4.3.1) for medical assessment. Frontline workers involved in decontamination, and others who have any contact with contaminated clothing and fomites should wear the appropriate protective clothing and equipment. Emergency staff who attend exposed persons after decontamination has been completed do not need to take any special precautions.

For healthcare workers involved in the management of hospitalised patients with all forms of Q fever, Universal Precautions (gloves, gowns, masks and hand washing) provide sufficient protection, and mortuary staff should use similar barrier protection. More sophisticated countermeasures for airborne protection such as high-efficacy air filter masks airborne protection are **not** required.

2.6.2 Antibiotic prophylaxis

Frontline workers entering the exposed zone, and others in the exposed area should be offered antibiotic prophylaxis as in Table 2. Prophylactic treatment may also be considered for frontline workers involved in the decontamination of exposed persons.

Decisions about who should receive prophylaxis should be taken on an individual basis according to duration and degree of potential exposure, and taking into account the availability and side effects of prophylactic treatments.

3. LABORATORY PROCEDURES

3.1 Risk assessment

C. burnetii is a Hazard Group 3 pathogen, and should thus be covered by existing risk assessments for handling such organisms in diagnostic microbiological laboratories. Note that blood samples from Q fever patients for serological testing, clinical chemistry or haematology pose no special risk and can be handled according to normal procedures. Laboratory staff handling samples suspected of containing *C. burnetii* must wear masks, gloves and gowns.

3.1.1 Receipt of samples

Samples should have been labeled as 'High risk' by the submitting staff, and should be handled according to local protocols for such samples. All laboratory procedures should be performed, by experienced BMS or scientists, in a containment level 3 facility using a Class 1 protective safety cabinet. Chain-of-evidence documentation should accompany specimens. In larger incidents, this would only be required for several of the initial cases.

3.2 Isolation and Identification

C. burnetii is a strictly intracellular organism and therefore cannot be grown on standard laboratory media. It has been successfully isolated in guinea pigs, mice and embryonated eggs but this has largely been abandoned because these methods are more hazardous than *in vitro* cell culture. A number of cell lines are suitable for *in vitro* culture. Although culture is not always successful it remains useful for identifying strains and ascertaining antibiotic sensitivities. PCR tests have been developed to detect *C. burnetii* in blood, urine and tissues samples.

The diagnosis of Q fever is usually confirmed by serological methods at reference facilities. Antibodies may be detected 2 – 3 weeks after the onset of the disease, and tests should be performed on both acute and convalescent samples. Indirect immunofluorescence assay is the usual reference method for detecting antibodies and for distinguishing between acute Q fever (characterised by a higher level of antibodies to phase II antigen) and chronic Q fever (where antibodies to phase I are increased).

3.3 Waste disposal

In the laboratory, hypochlorite (5,000ppm) disinfection is necessary for decontaminating surfaces that may have been exposed to *C. burnetii* spores. All other waste containers should be autoclaved. Note that the sporulated form of *C. burnetii* is resistant to normal disinfection, dilute bleach, UV radiation, heat and desiccation.

3.4 Reference laboratory

All samples for serological testing should be sent to the reference laboratory. All samples must be packaged appropriately, taking care to observe the procedures outlined in section 3.5. The sender's name and address should be clearly marked. The reference laboratory should be telephoned prior to sending to expect the sample. **Samples should be forwarded urgently to:**

Dr Robert C Spencer
HPA South West
Bristol Royal Infirmary
Marlborough Street
Bristol BS2 8HW
Tel: (+44) 0117 342 3242

OR

Dr Tim Brooks
Special Pathogens Reference Unit
HPA Centre for Emergency Preparedness and Response
Porton Down, Salisbury, Wiltshire, SP4 0JG
Tel: (+44) 01980 612774
Tel: (+44) 01980 612100 (24hours)

3.5 Transportation of samples with suspicion of *C. burnetii*

Strict procedures apply for transport of samples to the laboratory. Biological agents, or materials that contain or may contain them, are allocated to UN Division 6.2 – infectious substances. Infectious substances are divided into Category A or Category B. Full details are given in Appendix 1.2 Transport of infectious substances in *Biological agents: Managing the risks in laboratories and healthcare premises*. ACDP HSE May 2005 available at http://www.advisorybodies.doh.gov.uk/acdp/managingtherisks.pdf and in the Department of Health's guidance, available at http://www.dh.gov.uk/assetRoot/04/11/48/13/04114813.pdf

Cultures of *C. burnettii* are Category A infectious substances capable of causing disease in humans or animals and are therefore assigned to UN2814 and must be packaged in accordance with UN Packaging Instructions PI620 (road/rail) /PI602 (air). P620 and P602 are identical specifications but given different codes in ADR and ICAO regulations respectively (for a full description of PI see http://www.unece.org/). Category A transfers should be individually requested through an approved courier. The service will be a next day, tracked door-to-door delivery, which must be signed for at collection and receipt.

Clinical samples are generally classified as Category B and are assigned to UN3373 (Diagnostic and Clinical specimens) and should be packaged in accordance with UN PI650. Clinical samples may be posted.

Packaging must meet with UN performance requirements i.e. UN-type approved packaging for Class 6.2 substances. The packaging should consist of an inner package (watertight receptacle, watertight secondary packaging, an absorbent material in sufficient quantity to absorb the entire contents placed between the receptacle and the secondary packaging) and a rigid outer package of adequate strength for capacity, mass and intended use. Packages should be marked with the proper shipping name (i.e. UN 2814), and the appropriate warning label (i.e. the danger sign for infectious substances).

The following procedures should be adopted for the transport of all specimens, and also all cultures for confirmation. These apply within hospitals and laboratories as well as for specimens sent to the reference laboratory:

- The primary container (bijoux or similar) should be screwed tight, labeled and placed in an intact plastic bag.
- A 'High Risk' label should be affixed to both specimen and request form. The latter should include any other relevant information and include adequate clinical details to indicate level of suspicion.
- Under no circumstances should the request form be placed in the same bag as the specimen.
- The bag should be sealed, using tape or heat sealer. Pins, staples and metal clips should not be used. A separate bag should be used for each specimen.
- Each specimen must then be placed in a leak-proof secondary container with sufficient absorbent material to absorb all the contents should leakage occur.
- Each specimen must be packaged individually - i.e. three specimens, three separate packages.
- The secondary container should be externally disinfected – e.g. by wiping with hypochlorite (1,000 ppm available chlorine).

3.5.1 Samples sent to the reference laboratory

Samples should be transported according to local arrangements for High Risk specimens. Precautions should include:

- Secondary containers should be placed within a final outer tertiary packaging.

- This packaging **must** comply with the UN-type approved packaging for the transport of infectious substances.
- The package should be certified to this standard and carry the appropriate UN certification numbers on the tertiary packaging along with the following information:
  1 BIOHAZARD – danger of infection symbol Class UN 6.2.
  2 Instructions not to open if found.
  3 Telephone number of a responsible person - e.g. Consultant Microbiologist, Laboratory Manager.
- The container should be transported either by an approved courier for cultures (UN 2814) or by post for clinical samples (UN 3373), without delay, directly to the reference laboratory.

3.5.2 Samples sent within hospitals and laboratories

- Secondary containers should be placed in a good quality box, which is well taped up and clearly labeled "Pathological Specimen – Open only in Laboratory".
- Specimens should be transported by hand by a responsible person using the above packaging.
- Vacuum-tube systems should **not** be used for transportation of specimens within hospitals or laboratories.
- Extra care should be taken to ensure that laboratory records are kept to a high standard.

3.6 Protection of laboratory staff

All laboratory procedures must be performed in a Containment Level 3 facility using a Class 1 biological safety cabinet. Under these circumstances there is no indication for antibiotic prophylaxis for laboratory staff unless there is an inoculation injury or a spillage releasing aerosols.

Any member of laboratory staff, working with specimens or cultures of Q fever, who develops a febrile / respiratory illness, should seek urgent medical attention.

4. PUBLIC HEALTH PROCEDURES

4.1 Surveillance and detection of deliberate releases of Q fever

A deliberate release may be overt with an announcement and/or confirmation by environmental sampling. However, it is also possible that a deliberate release may be covert and will not be identified until the first cases of disease arise.

Q fever occurs naturally in the UK, though is an uncommon disease. There are about 70 cases of Q fever reported in England and Wales each year. Clusters do occur naturally, especially in agricultural areas. However, when investigating such events, deliberate release should be considered. If a release occurs, it is most likely to be detected by an increase in acute cases first; and chronic cases may follow later.

Close co-ordination with veterinary colleagues is essential. Disease in animals is usually asymptomatic, but it can lead to abortion and stillbirths; infected animals could act as an ongoing source of potential human infection. Incident managers should ensure that appropriate veterinary advice is taken.

4.2 Case Definitions

4.2.1 Suspected case

A patient with a consistent clinical illness: a high fever, influenza-like illness, an atypical pneumonia or hepatitis, and for which no explanation has been found.

If Q fever is suspected, microbiological specimens should be sent to the reference laboratory, and consideration should be given to initiating empirical treatment pending results. Obviously the level of suspicion depends on local circumstances at the time – in the event of a known or suspected deliberate release the threshold for diagnosing Q fever should be lower.

4.2.2 Confirmed case

A case that clinically fits the criteria for suspected Q fever, and in addition, definitive positive results are obtained on one or more pathological specimens by the reference laboratory.

4.3 Public Health Action

4.3.1 Procedure for handling exposed persons

Depending on the site and method of release, *C. burnetii* spores may be dispersed over a wide area. Expert advice will be provided to define an exposed zone in time and space. All individuals who have been present in the exposed zone need to be identified. In the event of an overt release, some of them will still be at the scene when emergency services respond to the incident. This group will be decontaminated and then referred to health workers at a nearby place of safety for assessment (this will be a clinical area just outside the exposed zone and within the cordon that will be established at the scene of the incident). Others will have left the scene before emergency services arrive and will be identified later when they approach GPs and A&E departments after details of the incident have been made public. Procedures need to ensure that these individuals are appropriately decontaminated, receive appropriate advice including that about prophylaxis, and have their details collected for follow up.

4.3.2 Post-exposure prophylaxis

Individuals for whom prophylaxis is indicated:

- Individuals who have been present in the exposed zone should be offered post-exposure prophylaxis as outlined in Table 2. **Prophylaxis should commence 8-12 days after exposure, and not before.** It is not effective and may only prolong the onset of disease if given within 7 days of exposure (USAMRIID 2004).

If suspected or confirmed cases of Q fever arise among persons who have been outside but in close proximity to the exposed zone in time or space, the defined parameters of the exposed zone should be reviewed with a view to extending post-exposure prophylaxis.

- Prophylaxis for other groups may be considered in the event of an incident. However, it is not advisable to give antibiotics to people who do not have a clear history of having been present at the time and site of release. It is inappropriate to provide antibiotics to large numbers of people who have not been exposed, but who are generally concerned or have non-specific mild illnesses. Rather than prophylaxis, increased surveillance, prompt investigation and treatment are encouraged.

4.3.3 Follow-up of exposed persons

After an overt release, a basic set of personal details needs to be collected from all persons present in the exposed zone.

4.3.4 Case finding

Once cases of Q fever have been detected and a release is suspected, there should be immediate advice to health care workers and other individuals, and enhanced surveillance for other cases.

4.3.5 Preventing secondary spread

Person-to-person spread of *C. burnetii* is negligible, and therefore there is no specific treatment or advice is required for secondary contacts. There is no requirement for quarantine of infected patients. However those contaminated with *C. burnetii* spores will need to be decontaminated as described in section 2.3.1

4.4 Epidemiological investigation

If cases are strongly suspected or confirmed and show increased numbers or unusual presentations, the HPA Centre for Infections should be notified immediately (020 8200 6868, 24 hours).

If cases arise due to a covert release, or following an overt release but in people who have not been present in the exposed zone, it is important to collect some epidemiological details in addition to a basic set of personal details. This is in order to define or redefine the exposed zone and aid identification of others at risk of infection. Details should be as thorough as possible, whilst recognising that in the event of a large release with multiple exposed persons or cases, it may not be possible to collect comprehensive information from everyone.

The aim of epidemiological investigations may be:

- Following a covert release, to assist definition and ongoing review of the temporal and spatial parameters of the exposed zone so that post exposure prophylaxis can be distributed appropriately.
- Following an overt release, to guide review of the exposed zone if cases arise in persons who were not present within it.

4.4.1 Epidemiological sampling

Microbiological samples will be taken from the environment by the police. These will be tested in designated laboratories.

5. LIST OF NATIONAL EXPERTS

Advice on any aspect of *C. burnetii* including diagnosis, management and public health aspects can be obtained from:

Clinical advice

Dr Robert C Spencer
Health Protection Agency South West
Level 8
Bristol Royal Infirmary
Marlborough Street
Bristol BS2 8HW
Tel: (+44) 0117 342 3242
e-mail: robert.spencer@UHBristol.nhs.uk

Prof Nigel F Lightfoot
Tel: (+44) 01912815671
Mobile: (+44) 07785232398
e-mail: nigel.lightfoot@mac.com

Diagnostic laboratory and Environmental

Dr Tim Brooks
HPA Centre for Emergency Preparedness and Response
Special Pathogens Reference Unit
Porton Down
Salisbury SP4 0JG
Tel: (+44) 01980 612774 (direct)
(+44) 01980 612100 (24hours)
e-mail: tim.brooks@hpa.org.uk

Public Health or Out of hours

Contact details are held at HPA Centre for Infections by the 24 hour on call duty doctor;
Tel: (+44) 020 8200 6868

6. REFERENCES

Arricau-Bouvery N, Rodolakis A. Is Q fever an emerging or re-emerging zoonosis? *Vet Res* 2005; **36**: 327-349.

Cutler SJ, Paiba GA, Howells J, Kenton LM. Q fever – a forgotten disease? *Lancet Infect Dis* 2002; **2**:717-718.

Cutler SJ, Bouzid M, Cutler RR. Q fever. *J Infect* 2007; **54**: 313-318.

Donaghy M, Prempeh H, Macdonald N. Outbreak of Q fever in workers at a meat processing plant in Scotland, July 2006. *Eurosurveillance Weekly*, 24 August 2006. Accessed at: http://www.eurosurveillance.org/ew/2006/060824.asp#2

Enserink M. Questions abound in Q-fever explosion in the Netherlands. *Science* 2010; **327**:266-267.

Fournier P-E, Marrie TJ, Raoult D. Diagnosis of Q fever. *J Clin Microbiol* 1998; **36**(2):1823-1834.

Hawker JI, Ayres JG, Blair I, Evans MR, Smith DL, Smith EG. *et al*. A large outbreak of Q fever in the West Midlands: windborne spread into metropolitan area? *Comm Dis Pub Health* 1998;**1**(3):180-187.

Kagawa F. K, Wehner J. H, Mohindra V. (2003) Q fever as a biological weapon. *Sem Resp Infect* **18**(3):183-195.

Klaassen CHW, Nabuurs-Franssen MH, Tilburg JJHC, Hamans AWM, Horrevorts AM. Multigenotype Q fever outbreak, the Netherlands. *Emerg Infect Dis* 2009; **15**: 613-614.

Kuzman I, Puljiz I, Ethakovic-Rode O. Cure of Q fever pneumonia with moxifloxacin: a case report. *Scand J Infect Dis* 2005; **37**: 778-780.

Lever MS, Bewley KR, Dowsett B, Lloyd G. *In vitro* susceptibility of *Coxiella burnetii* to azithromycin, doxycycline, ciprofloxacin and a range of newer fluoroquinolones. *Int J Antimicrob Agents* 2004; **24**:194-196.

Madariaga M, Rezai K, Tenholme G M, Weinstein RA. Q fever: a biological weapon in your backyard. *Lancet Infect Dis* 2003; **3**:709-721.

Marrie TJ. Q fever pneumonia. *Curr Opinion Infect Dis* 2004; **17**:137-142.

Maurin M, Rauolt D. Q Fever. *Clin Microbiol Rev* 1999 ; **12**(4):518-553.

Moodie CE, Thompson HA, Meltzer MI, Swerdlow DL. Prophylaxis after exposure to *Coxiella burnetii*. *Emerg Infect Dis* 2008; **14**: 1558-1566.

Morovic M. Q fever pneumonia: are clarithromycin and moxifloxacin alternative treatments only? *Am J Trop Med Hyg* 2005; **73**: 947-948.

Parker NR, Barralet JH, Morton Bell A. Q fever. *Lancet* 2006; **367**:679-688.

Peacock MG, Phillip RN, Williams JC, Faulkner RS. Serological evaluation of Q fever in humans: enhanced phase I titres of immunoglobulins G and A are diagnostic for Q fever endocarditis. *Infect Immun* 1983; **41**:1089-1098.

Schimmer B, Dijkstra F, Vellema P, Schneeberger PM, Hackert V, ter Schegget R, Wijkmans C, van Duynhoven Y, van der Hoek W. Sustained intensive transmission of Q fever in the south of the Netherlands, 2009. *Euro Surveill* 2009;**14**(19):pii=19210. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19210

Tissot-Dupont H, Amedei M, Nezri M, Raoult D. Wind in November, Q fever in December. *Emerg Infect Dis* 2004; **10**(7):1264-1269.

USAMRIID: Darling RG, Woods JB, eds. Medical Management of Biological Casualties Handbook 2004, 5th edition. p45-51.

Van Woerden HC, Mason BW, Nehaul LK, Smith R, Salmon RL, Healy B. Q fever outbreak in industrial setting. *Emerg Infect Dis* 2004; **10**(7):1282-1289.

Van der Hoek W, Dijkstra F, Schwimmer B, Schneeberger PM, Vellema P, Wijkmans C, ter Schegget R, Hackert V, van Duynhoven Y. Q fever in the Netherlands: an update on the epidemiology and control measures. *Euro Surveill* 2010; **15**(12):pii=19520. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19520

Waag DM. *Coxiella burnetii*: Host and bacterial responses to infection. *Vaccine* 2007; **25**: 7288-7295.

Woldehiwet Z. Q fever (coxiellosis): epidemiology and pathogenesis. *Res Vet Sci* 2004; **77**:93-100.