Q fever queries and answers

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Acute Q fever is usually asymptomatic or flu-like, but chronic Q fever can cause life-threatening endocarditis. Animal reservoirs of the infection include sheep, cows, goats and possibly cats and dogs.

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Q fever is a zoonotic infection caused by the bacterium *Coxiella burnetii*. Short for 'query' fever, it was first described in 1937 among Brisbane abattoir workers but was soon recognised to occur worldwide.[1,2] It has a range of nonspecific clinical manifestations and causes both acute and chronic disease. Untreated, chronic disease has a high mortality rate. Although aspects of Q fever remain enigmatic, there have been recent advances in our understanding and management of this infection.

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Q FEVER TRANSMISSION

The causative bacterium *C. burnetii* is typically acquired by humans through inhalation or direct contact with contaminated dust, aerosols, animal products or the environment.[3-5] The infective dose is extremely low – fewer than 10 organisms by the respiratory route.

The main reservoirs for human infection in Australia are domestic ruminants: cattle, sheep and goats. The bacteria multiply in particular in the placenta and fetal fluids of these animals, resulting in environmental contamination. They are also shed in faeces, urine, milk and other body fluids, such as vaginal secretions, mucus and saliva. As *C. burnetii* is resistant to desiccation, it can persist for long periods in the environment. In a recent Q fever outbreak in the Netherlands, people living within 2 km of infected goat farms had a 30 times higher risk of infection than those living more than 5 km away.[6]

C. burnetii can infect a large variety of other animals, including mammals (dogs, cats, bats, horses, small rodents and marsupials), birds, fish, reptiles and arthropods. The role of companion animals and wild animals in human infection is being investigated, particularly as cases have been reported among people with no classic zoonotic risk factors.[7-11]

Ticks have a role in the transmission of *C. burnetii* between wildlife and birds and its spread to livestock and companion animals, but are not thought to be involved in significant human transmission to humans.[12]

Ingestion of unpasteurised milk containing *C. burnetii* is a possible route of transmission to humans. Human-to-human transmission of *C. burnetii* is extremely rare.

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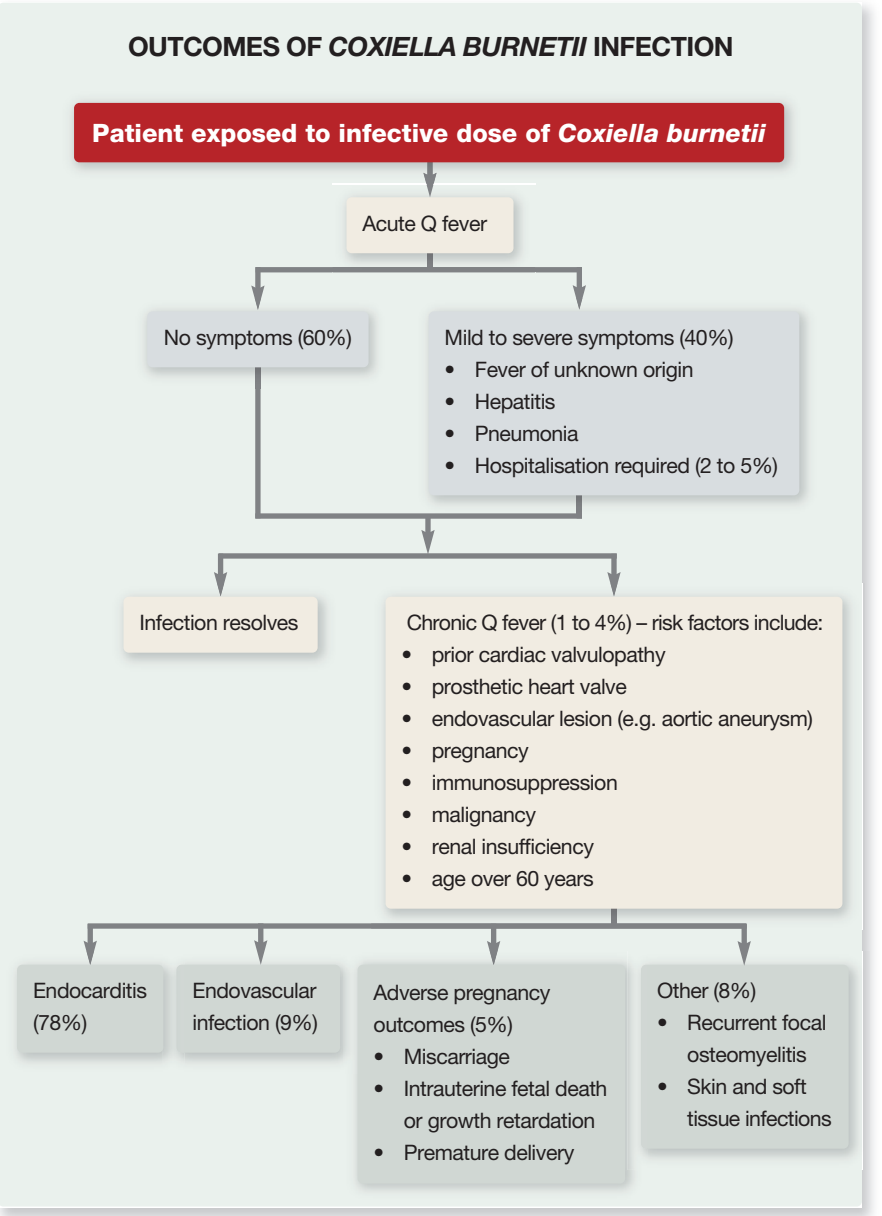
EPIDEMIOLOGY

Q fever has a worldwide distribution with the exception of New Zealand and possibly Tasmania. In Australia, around 300 cases are reported annually, mainly from NSW and Queensland. National notification rates varied between 2.5 and 4.9 per 100,000 population over the decade 1991 to 2001, but dropped to 1.5 per 100,000 population in 2011.[13] This decline is attributed partly to the Q fever vaccination program (see below) and partly to environmental factors such as the ending of drought conditions.[13]

Before the introduction of vaccination programs in Australia, approximately half of all cases of Q fever were among male abattoir workers aged between 20 and 59 years. Other at-risk populations include farm workers, veterinarians and animal transporters. Cases in Australia are generally sporadic, but outbreaks also occur. These may be small, involving a few people with a common exposure, such as delivery of an infected animal, or medium sized, such as in abattoirs. Large outbreaks have occurred overseas, such as the Netherlands outbreak, where more than 4000 human cases of Q fever were notified over three years, after the introduction of high-intensity dairy goat farming.[14]

CLINICAL FEATURES

The possible outcomes of infection with *C. burnetii* are summarised in the flowchart on this page. Q fever can be broadly divided into acute and chronic forms.[3,15]



Acute Q fever

Acute infection is asymptomatic in 50 to 60% of cases. When symptoms occur, there are two common presentations, as described below, each following an incubation period of two to three and a half weeks.

- A self-limiting flu-like illness that is often thought 'viral'. Onset is characteristically rapid, with high fever, rigors, profuse sweats, extreme fatigue, muscle and joint pain, severe headache and photophobia. There is usually evidence of hepatitis, ranging from an isolated increase in serum transaminase levels to clinically apparent hepatomegaly, mostly without jaundice.
- Pneumonia that manifests as interstitial pneumonitis with a nonproductive cough, minimal auscultatory findings and possible pleural effusions. The illness ranges from mild to severe, and may lead to acute respiratory distress syndrome. Pneumonia is the major manifestation of infection in North America and Europe but is less common in Australia.

Rare manifestations of Q fever include a maculopapular rash, pericarditis, myocarditis, aseptic meningitis, acalculous cholecystitis and mesangioproliferative glomerulonephritis.

Chronic Q fever

Chronic Q fever develops in 1 to 4% of cases. Most (75%) cases of chronic Q fever are thought to develop within six months of acute infection, whether symptomatic or asymptomatic, but may manifest years later. Untreated, chronic Q fever leads to

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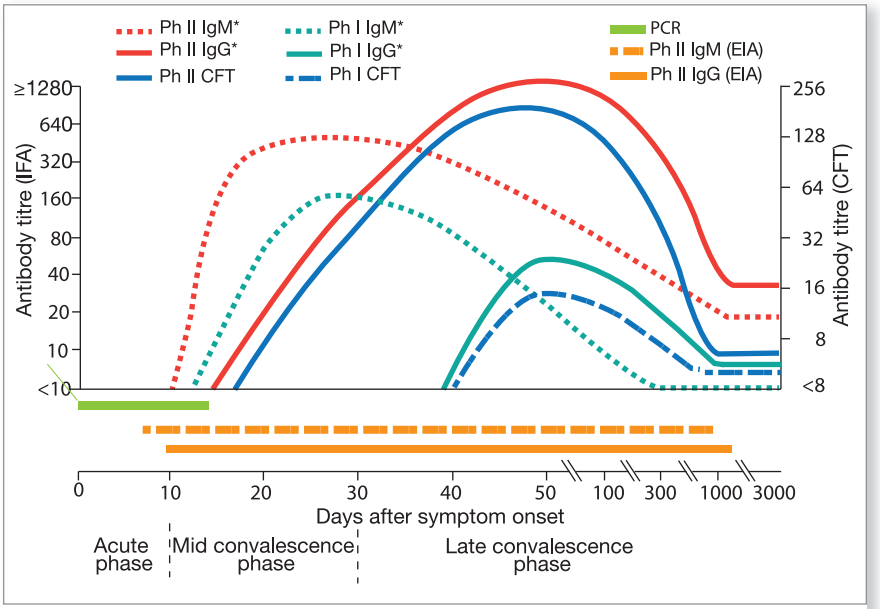

Figure. Typical serological response in acute resolving Q fever. IgM and then IgG antibodies develop to phase II antigens in 10 to 14 days from symptom onset. Seroconversion or a fourfold rise in phase II IgG or CFT titre in convalescent serum is diagnostic of acute Q fever.

ABBREVIATIONS: CFT = complement fixation test; EIA = enzyme immunoassay; IFA = immunofluorescence assay; PCR = polymerase chain reaction; Ph = phase. * By IFA.

considerable morbidity and a mortality rate of up to 60%.[5,16]

Endocarditis is considered the most common complication of chronic Q fever, usually occurring in patients with pre-existing cardiac valvulopathy. The risk of patients with valvulopathy developing chronic Q fever has been reported to be as high as 40%.[17] Men aged over 45 years are at particular risk.

Endovascular infections also occur in chronic Q fever, and after the Netherlands outbreak, equalled endocarditis in incidence.[18] Independent risk factors for chronic disease identified after the Netherlands outbreak were valvular surgery, vascular prosthesis, aneurysm, renal insufficiency and older age.[18] Immunosuppression (cancer, lymphoma) and pregnancy are also significant risk factors for chronic Q fever.[15]

Post-Q fever fatigue syndrome

Although relatively few patients with acute infection develop chronic Q fever, a much larger group suffers from persistent fatigue and other long-term effects. Unlike chronic Q fever, post-Q fever fatigue syndrome is not life-threatening, but it can be debilitating and seriously affect quality of life. After the Netherlands outbreak, 50% of patients reported being fatigued after one year compared with 26% in the control group.[19]

Post-Q fever fatigue syndrome has been attributed to dysregulation of cytokine production induced by persistent antigens, including lipopolysaccharide and proteins, rather than to persistent latent *C. burnetii* infection.[20,21]

Q fever in pregnant women

The risks of Q fever in pregnancy are not clear and may vary between *C. burnetii* strains found in different countries. Retrospective case series from France and Canada found that acute infection during pregnancy, particularly the first trimester, was associated with adverse outcomes, including spontaneous abortion, intrauterine fetal death or growth retardation and premature delivery, similar to the effects seen in animals.[22,23] Pregnancy has also been considered a risk factor for reactivation of infection, with a potential risk to the fetus and maternal chronic disease in subsequent pregnancies.[22]

In contrast, no adverse effect of Q fever on pregnancy was documented in a population-based study of the Netherlands outbreak.[24] Furthermore, a small uncontrolled study in pregnant women from Queensland postcode areas with high endemicity found no adverse events in previous pregnancies or in the early follow up of current pregnancies.[25] Seroprevalence rates in this antenatal population were around 6%.

Until more evidence becomes available, routine screening for *C. burnetii* infection during pregnancy is not recommended, even in high-risk populations. However, monthly serological monitoring is recommended for pregnant women with diagnosed acute Q fever to identify evolving chronic infection.

Q fever in children

Q fever was considered uncommon in children, but seropositivity in children younger than 15 years from south west Queensland is around 2.5%, increasing to 11.4% in those aged between 15 and 24 years.[26,27] There are also Australian reports of children with manifestations of chronic Q fever, including recurrent subcutaneous skin and soft tissue infections and recurrent chronic multifocal osteomyelitis.[28] The predisposing factors are not clear. The children are usually not systemically unwell, and the diagnosis is confirmed by biopsy of involved lesions showing a granulomatous tissue response, a positive result for *C. burnetii* on polymerase chain reaction (PCR) testing of affected tissue and serological results compatible with chronic disease.

DIAGNOSIS

Acute Q fever

The clinical diagnosis of acute Q fever is challenging because of its nonspecific

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manifestations. Consequently, laboratory confirmation is important.

Nonspecific blood tests

Thrombocytopenia, the presence of atypical lymphocytes and moderately raised serum levels of hepatic transaminases suggest the diagnosis of Q fever. Hyponatraemia due to inappropriate secretion of antidiuretic hormone, hypocholesterolaemia and a raised C-reactive protein level are also commonly noted nonspecific laboratory features but have poor predictive value.

Serological tests

Specific antibodies are often absent during the first 10 to 14 days after symptom onset, making early serological diagnosis difficult. Gold-standard laboratory diagnosis relies on paired serological testing of acute and convalescent sera.[29] *C. burnetii* displays biphasic variation of its cell wall antigens, resulting in different degrees of virulence. These variations are termed phase I and phase II. Counterintuitively, after acute infection, antibodies develop first to phase II antigens, followed by phase I antigens (see the Figure for a typical serological response in acute Q fever). Thus, the presence of phase II IgM with phase II IgG seroconversion (measured by enzyme immunoassay [EIA] or immunofluorescence assay [IFA]) is diagnostic of acute Q fever, as is a fourfold rise in titre of phase II IgG (IFA) or phase II complement-fixing (CFT) antibody (which comprises IgM and IgG) in convalescent serum.

Polymerase chain reaction testing

The development of serum PCR tests for *C. burnetii* DNA has allowed earlier diagnosis of acute Q fever.[30] The sensitivity of PCR testing depends on the time of serum collection in relation to symptoms and such testing is most reliable in the first seven to 10 days (sensitivity, 70 to 80%). Thus, although PCR testing may be helpful, it does not replace serological testing.[31]

Chronic Q fever

The diagnosis of chronic Q fever is controversial. Traditionally it has relied on serological tests showing persistently high or increasing levels of phase I IgG. A phase I IgG titre (IFA) greater than 800 has been considered diagnostic of chronic Q fever. However, results of this test vary depending on the specific assay used by the testing laboratory, and the cut-off titre of 800 is not definitive but an attempt to balance sensitivity and specificity.

Persistent or rising phase I IgG titres (IFA) of 1024 or more or a phase I CFT titre of 200 or more six months after infection have a reasonable positive predictive value for development of chronic disease, but may be found in recovering patients in 2% of cases.[24,29,32]

Consequently, the diagnosis of chronic Q fever should not rely on serological criteria alone but requires further evidence, summarised in the box on this page. The presence of long-term symptoms in a patient with a persistently elevated phase I IgG or CFT antibody titre is an indication for specialist referral or further investigation. This may include serial echocardiography (including transoesophageal echocardiography), positron emission tomography (PET), repeated serological tests, PCR testing and biopsy (e.g. in osteomyelitis).

EVIDENCE SUPPORTING A CHRONIC Q FEVER DIAGNOSIS

- Compatible clinical picture (differentiated from post-Q fever fatigue syndrome)
- Very high levels of phase I IgG, usually associated with high levels of phase II IgG:
  - phase I IgG titre ≥ 1024 (IFA)
  - phase I CFT titre ≥ 200 is supportive but not definitive
- Echocardiographic abnormalities, including cardiac valve vegetations, fibrosis or calcification
  - transthoracic imaging may not detect vegetations, which are mostly small in Q fever endocarditis
  - transoesophageal imaging is more sensitive but may still fail to detect vegetations and show only fibrosis, +/– calcifications
- Positive *Coxiella burnetii* PCR test result on blood (serum) or tissue (e.g. explanted valve or bone biopsy specimen)
- FDG-positron emission tomography and CT findings suggesting chronic infection (e.g. infected vascular aneurysm)

ABBREVIATIONS: IFA = immunofluorescence assay; CFT = complement fixation test; PCR = polymerase chain reaction; FDG = fluorodeoxyglucose.

MANAGEMENT

Acute Q fever

Acute Q fever is often asymptomatic or mild and self-limiting, with symptoms resolving within two weeks. The value of antibiotics in the absence of symptoms is not clear, but a recently published case-control study in the Netherlands outbreak suggests that antimicrobial drug treatment might reduce the risk of chronic disease.[18] For this reason, it seems reasonable to recommend treatment, even when symptoms have spontaneously resolved. Treatment is also recommended in acute symptomatic illness to hasten resolution. The current recommendation is oral doxycycline 100 mg twice a day for 14 days.[33]

A suggested management algorithm for acute Q fever is shown in the flowchart on page 58. Identification of valvular abnormalities warrants specialist advice to discuss either prophylactic long-term doxycycline therapy (for 12 months) or close follow up to detect chronic Q fever endocarditis.

The value of screening echocardiography for patients diagnosed with acute Q fever is debated. The high reported risk of chronic Q fever in patients with cardiac valvulopathy led to a French recommendation for routine echocardiography for all patients with acute Q fever to detect previously undiagnosed valvulopathy (e.g. congenital bicuspid aortic valve or mitral valve prolapse) and initiate preemptive

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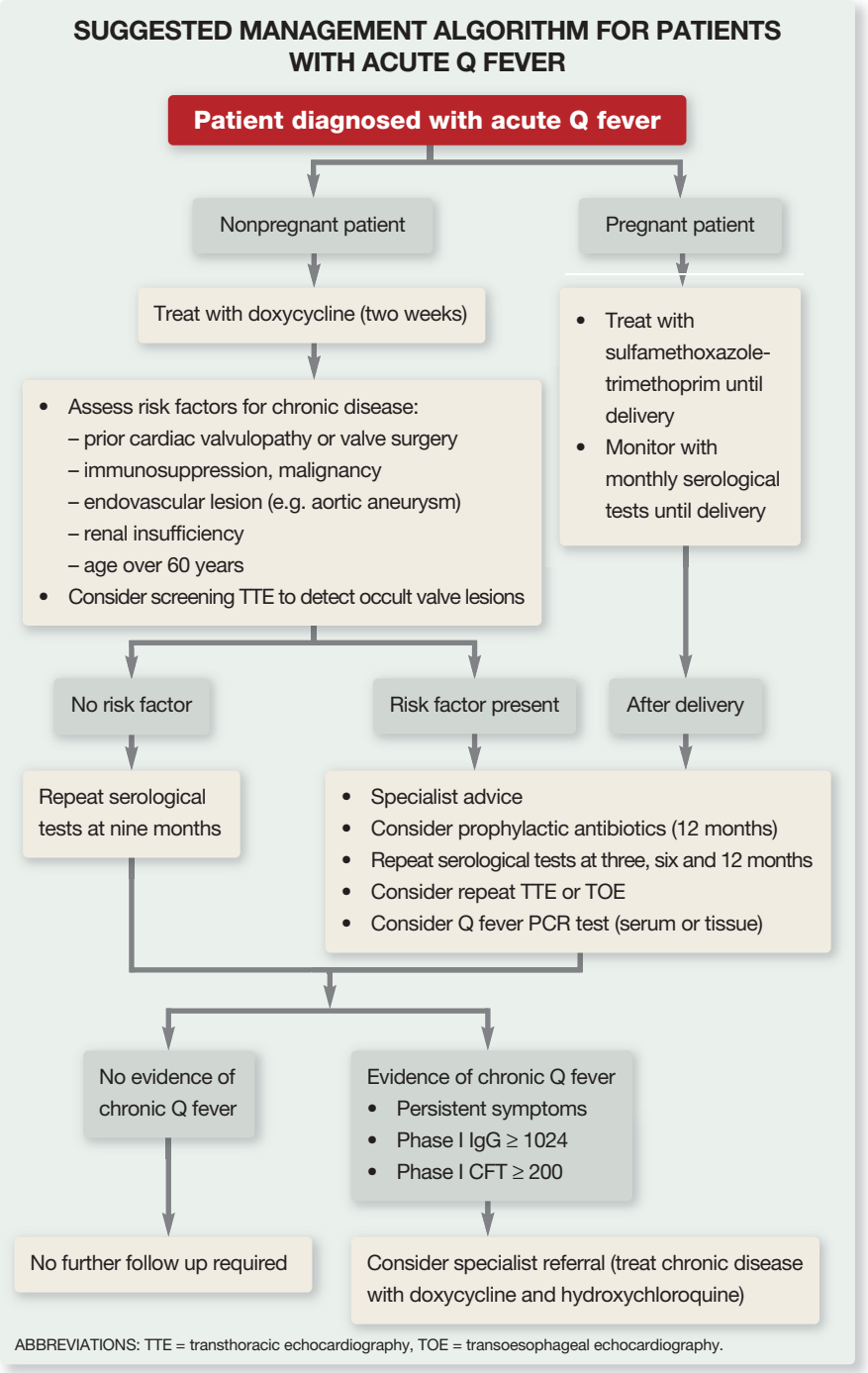

treatment.[34] This was considered particularly crucial for men older than 45 years, who have an increased risk of endocarditis.

Screening echocardiography was also adopted for Q fever patients in the Netherlands but is no longer standard as 59% of patients were found to have cardiac valvulopathy but none of these developed chronic Q fever.[24] Debate about the value of routine echocardiography has focused on the short duration of follow up to date and the possibility of geographic variation between *C. burnetii* strains.[32,35]

Current recommended follow up of patients with acute Q fever depends on the patient's identified risk factors. Serological testing is generally recommended at nine months or, if risk factors are identified, at three, six and 12 months, with optional PCR testing and echocardiography as indicated. Transoesophageal echocardiography is considered more sensitive than transthoracic echocardiography for the detection of valvular abnormalities as fibrosis without overt vegetations is common.

Q fever in pregnancy

Until the risks of Q fever in pregnancy are clarified it seems reasonable that pregnant women who are diagnosed with Q fever, particularly during the first trimester, receive treatment with combination sulfamethoxazole and trimethoprim until the end of the pregnancy, together with monthly serological monitoring.[22,23] Breast feeding is not contraindicated in mothers with *C. burnetii* infection, unless they develop chronic disease requiring long-term doxycycline treatment.

Chronic Q fever

Chronic Q fever is treated with a combination of oral doxycycline and hydroxychloroquine for a minimum of 18 months.[36] Surgical valve replacement may be indicated for patients with endocarditis, particularly for haemodynamic problems.

Clinical and serological monitoring helps determine the response to, and duration of, treatment. Patients have been known to require antibiotic therapy indefinitely because of a lack of serological response or relapsing infection.

Post-Q fever fatigue syndrome

Specialist opinion is helpful for patients who develop chronic symptoms characterised by fatigue, to help distinguish chronic *C. burnetii* infection(which warrants treatment) from post-Q fever fatigue (a noninfective complication with no specific treatment).

PREVENTION

Vaccination

Australia is the only country with a licensed Q fever vaccine. This is a single-dose

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RISK GROUPS TO CONSIDER FOR Q FEVER VACCINATION

- Workers in abattoirs (with the exception of pig abattoirs)
- Cattle, sheep and dairy farmers and their families
- Farm workers, including shearers and workers in stockyards and dairy farms
- Veterinary personnel
- Livestock transporters
- Others exposed to cattle, camels, sheep, goats and kangaroos or their products (including products of conception)
- Agricultural college staff and students
- Laboratory personnel handling veterinary specimens or working with *Coxiella burnetii*
- Visitors to at-risk environments (e.g. electricians and plumbers visiting abattoirs)
- Dog and cat breeders*

* Not currently included as a target group in the *Australian Immunisation Handbook* (9th ed.)[41]

PRACTICE POINTS

- Q fever is an important zoonotic infection; rural and abattoir workers exposed to cattle, sheep and goats are most at risk but exposure to cats, dogs and native animals may account for sporadic urban cases without classic risk factors.
- Acute infection is usually mild and self-limiting, but around 1 to 4% of infected patients develop chronic disease, which has high morbidity and mortality if untreated.
- Diagnosis of acute Q fever has relied on serological tests but polymerase chain reaction (PCR) testing can allow earlier diagnosis; diagnosis of chronic Q fever relies on a combination of clinical parameters, serological results (particularly elevated phase I IgG levels) and imaging.
- Antibiotic treatment is recommended even after spontaneous recovery from acute Q fever as it may reduce the risk of developing chronic infection.
- Serological monitoring after acute Q fever is generally recommended at nine months or, if risk factors for chronic infection are present, at three, six and 12 months, with optional PCR testing and imaging.
- GPs have a role in prevention by promoting Q fever vaccination.

subcutaneous vaccine comprising a killed suspension of phase I *C. burnetii* cells grown in egg yolks. The vaccine was trialled in South Australia and Queensland abattoirs in the 1980s and found to have a protective efficacy of over 95%.[37,38]

Widespread introduction of the vaccine for Australian abattoir workers from 1993 led to a significant reduction in their workers compensation claims and stabilisation of Q fever notifications in Australia at around 500 to 600 per year.[39] The focus for vaccination was then switched to include the at-risk rural community during the government-subsidised National Q Fever Management Program, 2001–2003/2004.[40] This program has now ended and it is up to individuals at risk to seek vaccination.

Risk groups to consider for Q fever vaccination are listed in the box on this page. In addition to the groups recommended by the current *Australian Immunisation Handbook* (9th ed.), it seems reasonable, in view of two recent outbreaks in small urban veterinary practices, to consider vaccination for dog and cat breeders.[8,9,41] The vaccine is currently registered for use only in people older than 15 years. No information is available on its paediatric use but anecdotal reports suggest there are no problems. The Australian Government has secured the supply of vaccine through to 2016.

Pre-vaccination screening

People with previous exposure to Q fever may rarely have severe local or systemic reactions to Q fever vaccine caused by prior sensitisation. Pre-vaccination screening is thus essential. This involves a skin test (to detect cell-mediated immunity) and a serological test (to detect phase II IgG as evidence of humoral immunity). It is important to specify to the pathology laboratory that a pre-vaccination screen is required so the appropriate test is performed. Only people with both a negative skin result and a negative serological result should be vaccinated.

More information

A useful video for GPs considering administering Q fever vaccine is available on the website of the manufacturer CSL Ltd (http://www.csl.com.au/s1/cs/auhq/1196562765747/Web_Product_C/1196562634452/ProductDetail.htm). GPs may also wish to register their patients on the Australian Q Fever Register (http://www.qfever.org), which currently includes more than 93,000 patients.

CONCLUSION

It is important that GPs, particularly those in rural areas, have a high level of suspicion for Q fever among patients who work with livestock, especially farmers, abattoir workers and veterinarians. With its non-specific symptoms, Q fever may present as a viral-like illness, hepatitis or atypical pneumonia. Although animal exposure is a clue to diagnosis, infection can occur without direct animal contact, and sporadic cases occur among people in urban areas. In a small proportion of cases, the infection may become chronic, leading to considerable morbidity and mortality. Some practice points for Q fever are summarised in the box on this page. MT

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