

## 3.17 Q FEVER

### Bacteriology

Q fever is caused by *Coxiella burnetii*, an obligate intracellular bacterium, classified in a separate genus, *Coxiella*. A near relative is *Legionella pneumophila*.<sup>1</sup> The organism is slightly more resistant to heat than other vegetative bacteria, but nevertheless is inactivated at pasteurisation temperatures. It survives well in air, soil, water and dust and may also be disseminated on fomites such as wool, hides, clothing, straw and packing materials.<sup>2,3</sup>

### Clinical features

Q fever can be acute or chronic, and there is increasing recognition of long-term sequelae. However, in many instances, infection can be asymptomatic.<sup>4,5</sup>

Acute Q fever usually has an incubation period of 2 to 3½ weeks, depending on the inoculum size and other variables<sup>6</sup> (range from 4 days up to 6 weeks). Clinical symptoms vary by country but in Australia it commonly presents with rapid onset of high fever, rigors, profuse sweats, extreme fatigue, muscle and joint pain, severe headache and photophobia.<sup>4,5</sup> As the attack progresses there is usually evidence of hepatitis, occasionally with frank jaundice; a proportion of patients may have pneumonia which is usually mild but can require mechanical ventilation. If untreated, the acute illness lasts 1 to 3 weeks and may be accompanied by substantial weight loss in the more severe cases.<sup>4,5</sup>

*C. burnetii* may cause chronic manifestations, the most commonly reported being subacute endocarditis. Less common presentations include granulomatous lesions in bone, joints, liver, lung, testis and soft tissues. Infection in early pregnancy, or even before conception, may recrudesce at term and cause fetal damage.<sup>7-9</sup>

Recent studies have also identified a late sequel to infection, post Q fever fatigue syndrome (QFS), which occurs in about 10 to 15% of patients with acute Q fever.<sup>10-13</sup> Laboratory research suggests that *C. burnetii* persists in most instances of acute Q fever, regardless of clinical status, and that immunogenic variation in the response to persistent infection leads to cytokine dysregulation and determines whether QFS occurs.<sup>11,14,15</sup>

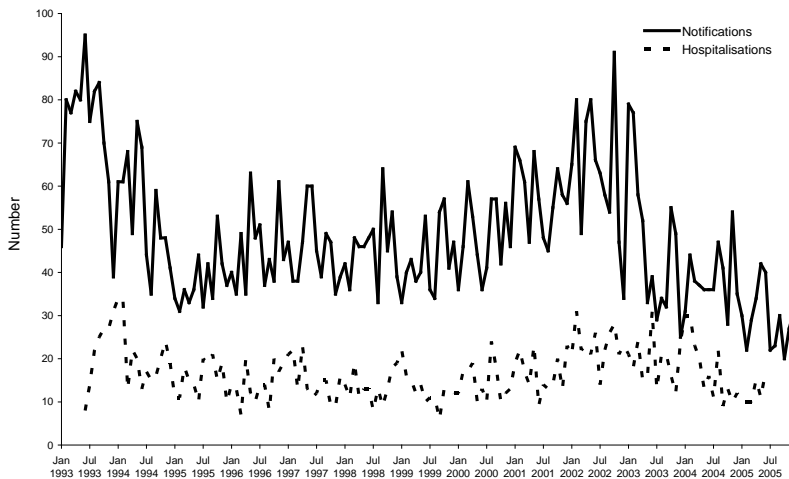
### Epidemiology

*C. burnetii* infects both wild and domestic animals and their ticks, with cattle, sheep and goats being the main source of human infection. Companion animals such as cats and dogs may also be infected. The animals shed *C. burnetii* into the environment through their products of conception (especially high numbers of coxiellas) but also in their milk, urine, and faeces. *C. burnetii* is highly infectious<sup>16</sup> and can survive in the environment. The organism is transmitted to humans via

the inhalation of infected aerosols or dust. Those most at risk include workers from the meat and livestock industries and shearers, with non-immune new employees or visitors being at highest risk of infection. Nevertheless, Q fever is not confined to occupationally exposed groups; there are numerous reports of sporadic cases or outbreaks in the general population in proximity to infected animals in stockyards, feedlots, processing plants or farms.

Use of Q fever vaccine in Australia can be considered in 3 periods. First, from 1991 to 1993 when vaccine was used in a limited number of abattoirs, then from 1994 to 2000 when vaccination steadily increased to cover large abattoirs in most states,<sup>17</sup> and finally from 2001 to 2006 during the period of the Australian Government sponsored Q fever Management Program.<sup>18</sup> This program extended vaccination to farmers, their families and employees in the livestock-rearing industry. With respect to abattoir workers, there has been a clear reduction in Q fever cases and associated insurance claims since 1994.<sup>17,19</sup> More widely, the numbers of Q fever cases reported to the National Notifiable Diseases Surveillance System (NNDSS) have declined over the period 1994 to 2005, during which there has been an increasing use of vaccine (see Figure 3.17.1). This decline is suggestive of an impact from vaccination among people not working in abattoirs but, as there are substantial variations in total numbers of cases from year to year, requires confirmation over a longer period.<sup>20</sup>

**Figure 3.17.1: Q fever notifications and hospitalisations, Australia, 1993 to 2005,\* by month of diagnosis or admission<sup>20</sup>**



\* Notifications where the month of diagnosis was between January 1993 and December 2005; hospitalisations where the month of admission was between 1 July 1993 and 30 June 2005.

## Vaccine<sup>4,21</sup>

- **Q-VAX** – CSL Biotherapies (Q fever vaccine). Each 0.5 mL pre-filled syringe contains 25 µg purified killed suspension of *Coxiella burnetii*; thiomersal 0.01% w/v. May contain egg proteins.
- **Q-VAX Skin Test** – CSL Biotherapies (Q fever skin test). Each 0.5 mL liquid vial when diluted in 15 mL of sodium chloride contains 16.6 ng of purified killed suspension of *Coxiella burnetii* in each diluted 0.1 mL dose; thiomersal 0.01% w/v before dilution. May contain egg proteins.

Q fever vaccine and skin test consist of a purified killed suspension of *C. burnetii*. It is prepared from the Phase I Henzerling strain of *C. burnetii* grown in the yolk sacs of embryonated eggs. The organisms are extracted, inactivated with formalin, and freed from excess egg proteins by fractionation and ultracentrifugation. Thiomersal 0.01% w/v is added as a preservative.

Phase I whole-cell vaccines have been shown to be highly antigenic and protective against challenge both in laboratory animals and in volunteer trials.<sup>22</sup> Serological response to the vaccine is chiefly IgM antibody to *C. burnetii* Phase I antigen. In subjects weakly seropositive before vaccination, the response is mainly IgG antibody to Phase I and Phase II antigens.<sup>23</sup> Although the seroconversion rate may be low, long-term cell-mediated immunity develops<sup>24</sup> and the vaccine has been shown to be protective in open and placebo-controlled trials, and in 2 post-licensing trials, to have a vaccine efficacy of 100%.<sup>25-28</sup> Lack of seroconversion is not a reliable marker of lack of vaccination.<sup>22</sup>

During recent years, with much larger numbers vaccinated, a few instances of laboratory proven Q fever have been observed in vaccinated subjects.<sup>21</sup> It is important that these apparent vaccine failures are fully investigated and that vaccination status is reported for all notified cases.

It should be noted that vaccination during the incubation period of a natural attack of Q fever does not prevent the development of the disease.<sup>22</sup>

A useful website for Q fever vaccine providers is <http://www.qfever.org/vaclist.php>.

## Transport, storage and handling

Transport the vaccine according to *National Vaccine Storage Guidelines: Strive for 5*.<sup>29</sup> Store at +2°C to +8°C, and do not freeze or store in direct contact with ice packs. If vaccine has been exposed to temperatures less than 0°C, do not use. Protect from light.

## Dosage and administration

A single dose of 0.5 mL of Q-VAX is given by SC injection after ascertaining that serological and skin testing have been performed and that both tests are negative (see 'Pre-vaccination testing' below).

## Recommendations

Q fever vaccine is recommended for those at risk of infection with *C. burnetii*. This includes abattoir workers, farmers, stockyard workers, shearers, animal transporters, and others exposed to cattle, camels, sheep, goats and kangaroos or their products (including products of conception). It also includes veterinarians, veterinary nurses, veterinary students, agricultural college staff and students (working with high-risk animals) and laboratory personnel handling veterinary specimens or working with the organism (see also Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.6 *Recommended vaccinations for those at risk of occupationally acquired vaccine-preventable diseases*).

Workers at pig abattoirs do *not* require Q fever vaccination.

### Pre-vaccination testing

(i) Before vaccination, people with a negative history of previous Q fever must have serum antibody estimations and skin tests to exclude those likely to have hypersensitivity reactions to the vaccine resulting from previous (possibly unrecognised) exposure to the organism.

(ii) If the person has a positive history of previous infection with Q fever, or has already been vaccinated for Q fever, skin testing and serology are *not* required and vaccination is *contraindicated*.

(iii) Note that a few subjects who have had verified Q fever in the past show no response to serological or skin testing. However, such subjects may experience serious reactions to administration of Q fever vaccine. Thus, it is vital to take a detailed history and to obtain documentation of previous Q fever vaccination or laboratory results confirming Q fever disease in all potential vaccinees; those who have worked for more than 10 years in the livestock or meat industries should be questioned particularly carefully. If there is any doubt about serological results or skin testing, they should be repeated 2 to 3 weeks later (see (vi) below for interpretation).

(iv) Antibody studies were originally done by complement fixation (CF) tests at serum dilutions of 1 in 2.5, 5 and 10 against the Phase II antigen of *C. burnetii*. Although this is generally satisfactory, many testing laboratories now use enzyme immunoassay (EIA) or immunofluorescent antibody (IFA) to detect IgG antibody to *C. burnetii* as an indicator of past exposure. Subjects CF antibody positive at 1 in 2.5, IFA positive at 1 in 10 or more, or with a definite positive absorbance value in the EIA, should *not* be vaccinated (see Table 3.17.1).

(v) Skin testing and interpretation should only be carried out by experienced personnel. For further information on training and accredited Q fever immunisation service providers, contact your State or Territory Health Department (see Appendix 1, *Contact details for Australian, State and Territory Government health authorities and communicable disease control*). Skin testing is performed by diluting 0.5 mL of the Q-VAX Skin Test in 15 mL of sodium chloride (injection grade). Diluted Q-VAX Skin Test should be freshly prepared, stored at +2°C to +8°C and used within 6 hours. 0.1 mL of the diluted Q-VAX Skin Test is injected intradermally into the volar surface of the forearm. Commercial isopropyl alcohol skin wipes should not be used. If the skin is not visibly clean, then methylated spirits may be used. A positive reaction is indicated by any induration at the site of injection after 7 days. Individuals giving such a reaction must *not* be vaccinated, because they may develop severe local reactions.

**Table 3.17.1: Interpretation and action for serological and skin test results (with modifications from *Q fever. Your questions answered* (CSL, 1999)<sup>a</sup>)**

Serology	Skin test	Interpretation/Action
Positive antibody test*	Positive <sup>†</sup>	Sensitised: do not vaccinate
	Borderline <sup>‡</sup>	Sensitised: do not vaccinate
	Negative <sup>§</sup>	Sensitised: do not vaccinate
Equivocal antibody test <sup>^</sup>	Positive	Sensitised: do not vaccinate
	Borderline	Indeterminate (see (vi) below)
	Negative	Indeterminate (see (vi) below)
Negative antibody test <sup>#</sup>	Positive	Sensitised: do not vaccinate
	Borderline	Indeterminate (see (vi) below)
	Negative	Non-immune: vaccinate

\* Positive antibody test: CF antibody or IFA positive (according to criteria used by diagnosing laboratory); or definite positive EIA absorbance value (according to manufacturer's instructions).

† Positive skin test: induration present.

‡ Borderline skin test: induration just palpable.

§ Negative skin test: no induration.

^ Equivocal antibody test: CF antibody or IFA equivocal (according to criteria used by diagnosing laboratory); or equivocal EIA absorbance value (according to manufacturer's instructions).

# Negative antibody test: CF antibody or IFA negative (according to criteria used by diagnosing laboratory); or definite negative EIA absorbance value (according to manufacturer's instructions).

(vi) Test results are indeterminate when skin test induration is just palpable *and/* or there is an equivocal level of antibodies in one or other of the serological tests.

An indeterminate result, which occurs in only a small proportion of subjects, may be the consequence of past infection with Q fever. It may also merely indicate the presence in the subject of antibodies to antigens shared between *C. burnetii* and other bacteria. Australian Q fever vaccine users have dealt with this finding in one of two ways:

- (a) Repeat the skin test and interpret as per the guidelines for initial testing. Collect serum 2 to 3 weeks later to look for a rise in titre of *C. burnetii* antibodies in the IFA test, using Phase I and Phase II antigens, and immunoglobulin class analysis. A significant increase (defined as a 4-fold rise in titre of paired sera) indicates previous Q fever infection and vaccination is then contraindicated.
- (b) Vaccinate the subject using SC injection of a 5 µg (0.1 mL) dose instead of a 25 µg (0.5 mL) dose of the vaccine. If there are no adverse effects (severe local induration or severe systemic effects, perhaps accompanied by fever) 48 hours after the injection, a further 0.4 mL (20 µg) dose of the vaccine is given within the next 2 to 3 weeks, ie. before the development of cell-mediated immunity to the first dose.

### Booster doses

Immunity produced by the vaccine appears to be long lasting (in excess of 5 years). Until further information becomes available, revaccination or booster doses of the vaccine are *not* recommended because of the risk of accentuated local adverse events.

## Contraindications

Q fever vaccine is contraindicated in the following:

- individuals with a history of an illness suggestive of or proved to be Q fever,
- those shown to be immune by either serological testing or sensitivity to the organism by skin testing,
- those who have been previously vaccinated against Q fever,
- those with known hypersensitivity to egg proteins or any component of the vaccine (Q-VAX may contain traces of egg protein, formalin, and sucrose).<sup>21</sup>

There is no information available on the accuracy of skin testing or the efficacy and safety of Q fever vaccine use in individuals with impaired immunity. In general, skin testing and Q fever vaccine should be avoided in such people.

The lower age limit for Q fever vaccine is not known. However, it is not recommended for use in those aged <15 years.

## Precautions

Vaccination of subjects already immune to *C. burnetii*, as a result of either previous infection or subjects being rendered hyperimmune by repeated vaccination, may result in severe local or systemic adverse events.

## Adverse events

Non-immune subjects very commonly show local tenderness (48%) and erythema (33%) at the vaccination site. Local induration or oedema is uncommon (<1%). General symptoms occur commonly in about 10% of vaccinees and may include mild influenza-like symptoms such as headache (9%), fever (up to 2%), chills and minor sweating.<sup>4,21</sup>

There are also 2 patterns of more significant adverse events among the estimated more than 130 000 individuals vaccinated from 1989–2004.<sup>5,17</sup>

The first and familiar pattern is the intensified local reaction at the injection site which may occur shortly after inoculation in individuals sensitised immunologically by previous infection or repeated vaccination. Rarely, an immune abscess develops and requires excision and drainage. The acute reactions may be accompanied by short-term systemic symptoms resembling the post Q fever fatigue syndrome. Note, however, that not all those with positive pre-vaccination skin and/or serological tests develop severe reactions. The introduction of the pre-vaccination skin test at NIH/NIAID Rocky Mountain Laboratory,<sup>30</sup> later combined with antibody testing in Australia, has largely eliminated reactions due to previous immune sensitisation. Despite this, the adverse experience from the earlier American trials<sup>22</sup> in which subjects were not pre-tested, were vaccinated repeatedly or were inoculated with vaccines of a different composition and larger bacterial mass, are still quoted in the general Q fever literature as representative of a whole cell vaccine.

The second, much less frequent, pattern has been reported in people who were skin and antibody test negative at the time of vaccination who did not have any immediate reaction. Some 1 to 8 months after vaccination, some vaccinees, predominately women, developed an indurated lesion at the inoculation site. At the time when the indurated lesion developed, the original skin test site often became positive, presumably indicating a late developing cellular immune response. These lesions were not fluctuant and did not progress to an abscess. Most gradually declined in size and resolved over some months without treatment. A few lesions were biopsied or excised and showed accumulations of macrophages and lymphocytes.<sup>31,32</sup>

## Use in pregnancy

Not recommended. Q fever vaccine contains inactivated products and inactivated bacterial vaccines are not considered to be harmful in pregnancy. However, safety of the vaccine in pregnancy has not been established. No information is available on the use of Q fever vaccine during breastfeeding.

## Variations from product information

The product information for Q-VAX does not include the use of the reduced dose of vaccine in individuals who have indeterminate results on either serological or skin testing. However, this option has been used successfully by experienced Q fever vaccinators.

## References

Full reference list available on the electronic *Handbook* or website <http://immunise.health.gov.au>.