4.15 Q FEVER

4.15.1 Bacteriology

Q fever is caused by *Coxiella burnetii*, an obligate intracellular bacterium. The organism 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. *C. burnetii* has been weaponised and is considered a Category B bioterrorism agent.

4.15.2 Clinical features

Q fever can be acute or chronic, and there is increasing recognition of long-term sequelae. Infection is asymptomatic in at least half of cases.

Acute Q fever usually has an incubation period of 2 to 3½ weeks, depending on the inoculum size and other variables (range from 4 days up to 6 weeks). Clinical symptoms vary by country, but, in Australia, the most common presentation is rapid onset of high fever, rigors, profuse sweats, extreme fatigue, muscle and joint pain, severe headache and photophobia. 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 more severe cases. Infection often results in time off work, lasting a few days to several weeks.

*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.

Studies have also identified a late sequela to infection, post Q fever fatigue syndrome (QFS), which occurs in about 10 to 15% of patients who have previously had acute Q fever. Research suggests that non-infective antigenic complexes of *C. burnetii* persist for many years after acute Q fever, and the maintenance of immune responses to these antigens might be the biological basis by which QFS occurs.

4.15.3 Epidemiology

*C. burnetii* infects both wild and domestic animals and their ticks, with cattle, sheep and goats being the main sources of human infection. Companion animals such as cats and dogs may also be infected, as well as native Australian animals such as kangaroos, and introduced animals such as feral cats and camels. The animals shed *C. burnetii* into the environment through their placental tissue or birth fluids, which contain exceptionally high numbers of *Coxiella* organisms, and also via their milk, urine and faeces. *C. burnetii* is highly infectious 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. Although most notifications occur among men from rural areas or with occupational exposure, a recent serosurvey from Queensland indicated a high rate of exposure among urban residents, including women and children.

Use of Q fever vaccine in Australia can be considered in 4 periods: from 1991 to 1993, when vaccine was used in a limited number of abattoirs; from 1994 to 2000, when vaccination steadily increased to cover large abattoirs in most states; from 2001 to 2006, during the period of the Australian Government sponsored National Q fever Management Program (NQFMP); and the period since 2007 after the NQFMP finished, where the vaccination remains available on the private market. The NQFMP funded screening and vaccination of abattoir workers and shearers and then extended vaccination to farmers, their families and employees in the livestock-rearing industry. Following introduction of the program, the number of Q fever cases reported to the National Notifiable Diseases Surveillance System declined by over 50% (see Figure 4.15.1), with the greatest reductions among young men aged 15–39 years, consistent with high documented vaccine uptake among abattoir workers. As a result, other occupational groups as well as non-occupational animal exposures appear to be accounting for an increasing proportion of notifications.
4.15.4 Vaccine

- **Q-Vax** – CSL Limited (Q fever vaccine). Each 0.5 mL pre-filled syringe contains 25 µg purified killed suspension of *Coxiella burnetii*; thiomersal 0.01% w/v. Traces of formalin. May contain egg proteins.

- **Q-Vax Skin Test** – CSL Limited (Q fever skin test). Each 0.5 mL liquid vial when diluted to 15 mL with sodium chloride contains 16.7 ng of purified killed suspension of *C. burnetii* in each diluted 0.1 mL dose; thiomersal 0.01% w/v before dilution. Traces of formalin. May contain egg proteins.

The 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. 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. Lack of seroconversion is not a reliable marker of lack of vaccination. Although the seroconversion rate may be low, long-term cell-mediated immunity develops and estimates of vaccine efficacy have ranged from 83 to 100%, based on the results of open and placebo-controlled trials, and post-marketing studies. It is important that vaccination status is reported for all notified cases and apparent vaccine failures are investigated.

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.

The Q fever vaccine and skin test are available for purchase in Australia through the private market. The Australian Government may fund the vaccine and skin test in emergency situations where there is a Q fever outbreak.

### 4.15.5 Transport, storage and handling

Transport the vaccine according to *National vaccine storage guidelines: Strive for 5.* Store at +2°C to +8°C. 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 it. Protect from light.

Diluted Q-Vax Skin Test should be freshly prepared, stored at +2°C to +8°C and used within 6 hours.
4.15.6 Dosage and administration

The dose of Q fever vaccine is 0.5 mL, to be 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).

Q fever vaccination and skin testing training is undertaken via an educational video available online. Please contact the manufacturer for access details.

4.15.7 Recommendations

Children aged <15 years

Q fever vaccine is not recommended in children aged <15 years. There are no data on the safety or efficacy of Q fever vaccine in this age group.

Adolescents aged ≥15 years and adults

Q fever vaccine is recommended for those at risk of infection with C. burnetii. This includes abattoir workers, farmers, stockyard workers, shearsers, 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, professional dog and cat breeders, agricultural college staff and students, wildlife and zoo workers (working with high-risk animals) and laboratory personnel handling veterinary specimens or working with the organism (see also 3.3 Vaccination of persons at occupational risk, Table 3.3.7 Recommended vaccinations for persons at increased risk of certain occupationally acquired vaccine-preventable diseases).

Workers at pig abattoirs do not require Q fever vaccination.

Pre-vaccination testing

- Before vaccination, persons with a negative history of previous infection with 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.

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

- It is essential 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. Some persons who have had verified Q fever disease in the past may show no response to serological or skin testing; however, they may still experience serious reactions to Q fever vaccine. Persons who have worked in the livestock or meat industries for some time should be questioned particularly carefully. The Australian Q Fever Register (www.qfever.org), established by Meat and Livestock Australia (MLA), has records of receipt of Q fever vaccination for some individuals, which can be accessed by registered users. If there is any doubt about serological or skin test results, testing should be repeated 2 to 3 weeks later (see below for interpretation).

- Serological and skin test results should be taken into account, according to Table 4.15.1, before vaccination. 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 who are 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.

- Skin testing and interpretation should only be carried out by experienced personnel. Details of immunisation service providers trained in the administration of Q fever skin testing can be obtained online from the Australian Q Fever Register (www.qfever.org). Skin testing is performed by diluting 0.5 mL of the Q-Vax Skin Test in 14.5 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. A 0.1 mL dose 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. Skin reactions are common 3 to 4 days after skin testing; however, these reactions generally resolve by day 7 when the skin test is read. 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.

- The result of testing is considered ‘indeterminate’ when skin test induration is just palpable and the antibody test is either equivocal or negative, or when there is no skin induration and an equivocal antibody test (see Table 4.15.1). 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 providers have dealt with this finding in one of two ways:
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.

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 events (e.g. 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, that is, before the development of cell-mediated immunity to the 1st dose.

<table>
<thead>
<tr>
<th>Serology</th>
<th>Skin test</th>
<th>Interpretation/Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive antibody test*</td>
<td>Any skin test result</td>
<td>Sensitised: do not vaccinate</td>
</tr>
<tr>
<td>Equivocal antibody test†</td>
<td>Positive† or Borderline§ or Negative¶</td>
<td>Sensitised: do not vaccinate Indeterminate (see above)</td>
</tr>
<tr>
<td>Negative antibody test#</td>
<td>Positive Borderline Negative</td>
<td>Sensitised: do not vaccinate Indeterminate (see above) Non-immune: vaccinate</td>
</tr>
</tbody>
</table>

* Positive antibody test: CF antibody or IFA positive (according to criteria used by diagnosing laboratory [see above]; or definite positive EIA absorbance value (according to manufacturer’s instructions)
† 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)
‡ Positive skin test: induration present
§ Borderline skin test: induration just palpable
¶ Negative skin test: no induration
# 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)

**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.

### 4.15.8 Pregnancy and breastfeeding

Q fever vaccine is not routinely recommended for pregnant or breastfeeding women. Q fever vaccine contains inactivated products; 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.

Refer to 3.3 *Groups with special vaccination requirements*, Table 3.3.1 *Recommendations for vaccination in pregnancy* for more information.

### 4.15.9 Contraindications

Q fever vaccine is contraindicated in the following groups:

- persons with a history of laboratory-confirmed Q fever, or with medical documentation that supports a previous diagnosis of Q fever
- persons shown to be immune by either serological testing or sensitivity to the organism by skin testing
- persons who have been previously vaccinated against Q fever
- persons with known hypersensitivity to egg proteins or any component of the vaccine (Q-Vax may contain traces of egg protein and formalin).40

There is no information available on the accuracy of skin testing or the efficacy and safety of Q fever vaccine use in persons who are immunocompromised. In general, skin testing and Q fever vaccine should be avoided in such persons.
There are no data on the safety or efficacy of Q fever vaccine in children. Q fever vaccine is not recommended for use in those aged <15 years.

4.15.10 Precautions

Vaccination of subjects already immune to C. burnetii as a result of either previous infection or vaccination may result in severe local or systemic adverse events. It is important that persons with a negative history of previous infection with Q fever must have serum antibody estimations and skin tests performed prior to vaccination (see ‘Pre-vaccination testing’ above).

4.15.11 Adverse events

Non-immune subjects very commonly show local tenderness (48%) and erythema (33%) at the vaccination site. Local induration or oedema is uncommon, occurring in <1% of recipients. General symptoms occur commonly in about 10% of vaccine recipients and may include mild influenza-like symptoms, such as headache (9%), fever (up to 0.2%), chills and minor sweating.6,40

Erythematous skin reactions are common 3 to 4 days after skin testing; however, these reactions generally resolve by day 7 when the skin test is read.

There were also two patterns of more significant adverse events among the estimated more than 130 000 persons vaccinated between 1989 and 2004.5,26 The first and familiar pattern is the intensified local reaction at the injection site, which may occur shortly after vaccination in individuals sensitised immunologically by previous infection or vaccination. Rarely, an abscess develops and requires excision and drainage. This acute reaction may be accompanied by short-term systemic symptoms resembling the post Q fever fatigue syndrome. However, not all those with positive pre-vaccination skin and/or serological tests develop severe reactions. The use of the pre-vaccination skin test developed by the US National Institute of Health and the National Institute of Allergy and Infectious Diseases,41 which was later combined with antibody testing in Australia, has largely eliminated reactions due to previous immune sensitisation. Despite this, the adverse experience from earlier American trials,21 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 the broader experience with whole-cell Q fever vaccines.

The second, much less frequent, pattern has been reported in people who are skin and antibody test-negative at the time of vaccination and who do not have any immediate reaction. Some 1 to 8 months after vaccination, some vaccine recipients, predominantly women, have developed an indurated lesion at the inoculation site. At the time when the indurated lesion develops, the original skin test site often becomes positive, presumably indicating a late developing cellular immune response. These lesions are not fluctuant and do not progress to an abscess. Most gradually decline in size and resolve over some months without treatment. A few lesions have been biopsied or excised and have shown accumulations of macrophages and lymphocytes.42,43

4.15.12 Public health management of Q fever

Q fever is a notifiable disease in all states and territories in Australia.

Further instructions about the public health management of Q fever, including management of cases of Q fever, should be obtained from state/territory public health authorities (see Appendix 1 Contact details for Australian, state and territory government health authorities and communicable disease control).

4.15.13 Variations from product information

The product information for Q-Vax does not include the use of a reduced dose of vaccine in persons who have indeterminate results on either serological or skin testing. The ATAGI recommends instead that experienced Q fever vaccinators may elect to give reduced vaccine doses in subjects who have indeterminate results on either serological or skin testing.

References

A full reference list is available on the electronic Handbook or website www.immunise.health.gov.au.


25. Tozer SJ, Lambert SB, Sloots TP, Nissen MD. Q fever seroprevalence in metropolitan samples is similar to rural/remote samples in Queensland, Australia. *European Journal of Clinical Microbiology and Infectious Diseases* 2011;30:1287-93.


