Abattoir-associated Q fever: a Q fever outbreak during a Q fever vaccination program

Abstract

Objectives: To investigate an abattoir outbreak of Q fever in southern New South Wales with reference to the protective effect and safety of the formalin-inactivated Q fever vaccine (Q Vax) administered before and during the outbreak.

Methods: In September 1998, after notification of four Q fever cases in the abattoir, a cohort investigation of 103 workers was undertaken. Data on age, sex, immune status, vaccination status and main work area were obtained from the medical officer administering the vaccination program and abattoir records. Symptoms and occupational risk factors for illness were obtained from interview of 63 (61%) employees.

Results: Of 103 abattoir employees, 16 (16%) had immunity from previous Q fever exposure and 19 (18 %) had been vaccinated at least six weeks before the first case of Q fever exposure in the abattoir. Of the remaining 68 workers who were susceptible to primary infection, 29 (43%) had laboratory confirmed acute primary Q fever and eight were suspected cases. No workers vaccinated before the likely period of exposure developed Q fever. Of 32 workers vaccinated post-exposure, four developed laboratory-confirmed Q fever within eight days of vaccination. Vaccination administered 10 or more days after the likely period of exposure showed no significant protective effect (RR=0.57; 95% CI 0.13-2.57; p=0.60).

Conclusions: Q-Vax was highly effective when administered in advance of the likely period of Q fever exposure. Post exposure vaccination was not shown to be protective.

Implications: This study reinforces meat industry vaccination guidelines for abattoir employees. The optimal time to vaccinate workers is before they are put at occupational risk.

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Derrick first described acute primary Q fever in 1935. He studied fevers in Queensland abattoir and agricultural workers and also isolated the causative organism in guinea pigs.[1] Burnet and Freeman subsequently identified the isolates as rickettsia-like.[2] They now constitute a separate genus, *Coxiella burnetii,* unrelated to rickettsiae and are phylogenetically closer to *Legionella sp.*[3] *C. burnetii* is an intracellular bacterium. It has a complex intracellular replication cycle in macrophages and other cells, which results in the liberation of a small, compact, highly resistant cell with a fine structure resembling that of an enterobacterium.[3,4]

Q fever is endemic in most countries. In brief, cattle, sheep and goats are the most important zoonotic sources of human infection. Milk, urine, excreta and the products of conception from infected animals are another source of infection and environmental contamination. Occupational groups with direct animal contact such as farmers, abattoir workers, veterinarians, animal transporters and other animal handlers, such as shearers, are particularly at risk of contracting the disease.

Exposure to *C. burnetii* may result in a broad spectrum of clinical outcomes.[5,6] Infection may be asymptomatic or present as an acute febrile illness characterised by fever, sweats, myalgias, arthralgias, headache and weight loss. Acute complications such as atypical pneumonia, hepatitis, aseptic meningitis and encephalitis may occur. In most cases the symptoms of Q fever are self-limited, though endocarditis, osteitis, hepatitis and chronic fatigue may develop as chronic sequelae.[5,7-9] Reactivation of Q fever occurs in animals and humans during pregnancy, and aerosols from the products of conception in animals are highly infectious by the respiratory route. The slaughtering of pregnant, infected animals therefore places abattoir workers at high risk of infection.

The stimulus to vaccinate against Q fever followed outbreaks of disease in laboratory workers in the 1940s. The first effective vaccines to be developed were formalin-inactivated whole cell vaccines.[10] Subsequently, more highly purified vaccines strictly in the Phase I antigenic state were used together with prevaccination testing for immunity. These proved to be safe and highly protective.[11] Other vaccines comprising solvent extracted complexes of protein and lipopolysaccharide or extracted cell residues,

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although immunogenic and protective in laboratory animals have not been field tested in humans on a scale that allows a comparative evaluation of their reactogenicity or duration of protection.[11]

An effective whole cell, formalin inactivated Phase I antigen vaccine against Q fever (Q-Vax, CSL Ltd) was licensed for marketing in 1989.[12-15] In the same year, a Ministerial Working Party on zoonoses in the meat industry recommended vaccinating against Q fever.[16] These recommendations were conveyed to the meat industry and later reinforced by meat industry guidelines.[17] The standard protocol for Q fever vaccination includes pretesting by serological examination and skin test. This avoids the administration of Q fever vaccine to subjects previously infected clinically or subclinically with *C. burnetii.* Once sensitised to *C.burnetii,* these subjects are at increased risk of adverse reaction to Q fever vaccination (for details see CSL Ltd booklet *Q fever, Your Questions Answered*).

During the clinical trials of Q Vax in the 1980s, which involved approximately 2,500 abattoir workers,[14] there were no confirmed Q fever cases in the vaccinees once sufficient time (more than 20 days) had elapsed after vaccination for cellular immunity to develop. Since then, with vaccination of a much larger number (more than 65,000) of subjects, a few cases – around 14 – of primary Q fever or Q fever-like illness have been detected in vaccinees within a year or two after inoculation (B. Marmion, unpublished data). Serological analysis suggests that about half of the patients had not responded to the vaccine antigen and developed a primary infection. The remainder had been primed by the vaccine but (presumably) not protected against a heavy exposure.

In both the 1980s clinical trials, and during the 12 years since marketing approval, coincidences of occupationally acquired Q fever and vaccine inoculation have been observed.[11] The onset of Q fever in these instances ranged from a day or so before inoculation up to 15 days afterwards but not subsequently, reflecting the time at which cell-mediated immunity is fully developed after vaccination. In some circumstances the temporal association between skin testing (i.e. intradermal inoculation of 0.02ug of vaccine on to the volar surface of the forearm), or vaccination on the one hand and the development of primary Q fever infection on the other, has been misinterpreted as infection from the vaccine. This is particularly so when there are no cases of Q fever in untested or unvaccinated individuals in the abattoir.

In the present outbreak, the timing and prolonged nature of the vaccine program and of the introduction of Q fever into the abattoir offered a unique opportunity to define the interaction of the two processes.

Background

In early September 1998, four cases of laboratory-confirmed Q fever were notified to the Southern New South Wales (NSW) Public Health Unit (PHU). The cases were employees of an abattoir in southern NSW. These were the first notifications of Q fever in the district for the year. The abattoir had commenced operations in early April, 1998. Adult cattle, including old dairy cows, were the only livestock to be slaughtered on the premises. The abattoir had started a vaccination program in April 1998 when 19 of the total 103 workforce were vaccinated without adverse effects. A second phase of the vaccine program for 1998 was in progress at the time of notification of the four Q fever cases. As these cases happened to be related in time to pretesting and vaccination, the abattoir management raised concerns about the safety of the skin test reagents and vaccine. This investigation aimed to describe the outbreak of Q fever in time and to determine the safety and effectiveness of Q fever vaccination when given before and after the likely period of Q fever exposure.

Methods

Outbreak investigation

To determine the date of onset of symptoms for cases and the timing and nature of possible exposures to *C burnetii,* a list of all employees, their telephone numbers and main work areas were obtained from the abattoir. Abattoir management were informed that this was a public health investigation to ascertain extent of morbidity in affected workers, to describe vaccine safety and effectiveness and to prevent further cases from occurring.

Employees were interviewed by telephone with a detailed questionnaire that sought additional information on possible exposure to *C. burnetii*. Verbal consent for interview was obtained and the aims of the outbreak investigation explained to each interviewee.

Adverse events were explored, including post Q fever fatigue syndrome, which may have resulted from vaccination.

Active surveillance

The regional public health unit instituted active surveillance for determination of further cases. Local general practitioners were encouraged to consider Q fever in any patient who presented with symptoms of a Q fever-like illness and to obtain laboratory confirmation. They were asked to notify any cases that were suspected or confirmed as required by the *NSW Public Health Act 1991*.

Case definitions for acute primary Q fever

Confirmed case

A serologically confirmed case of Q fever was one with a fourfold or greater increase in antibody titre to phase II antigen by Complement Fixation Test (CFT) or a positive IgM titre (≥80) to phase II antigen by Immunofluorescence (IF) Test. These criteria were applied to persons in the abattoir or local community after June 1998.

Suspected case

A suspected case was defined as one in which at least four of the following symptoms were reported, after June 1998, in an abattoir or local community member: fever, sweats, rigours,

fatigue, headache, myalgia, arthralgia, or cough but for whom serological tests were negative or not available.

Vaccination and pretesting for immune hypersensitivity

Pre-vaccination skin testing had been done in conformity with the Q Vax product information. The skin test is a an intradermal injection of 0.1 mL of diluted Q fever vaccine containing 0.02μg of purified organisms on the volar aspect of the forearm. Subjects who tested negative on skin test after seven days and who were non-immune on Q fever specific serology, were vaccinated with Q-Vax, a whole-cell formalin inactivated Henzerling strain of *C burnetii* phase I.[13]

To determine the safety of the vaccine, we obtained all available vaccination records for abattoir workers from the local medical officer responsible for the abattoir Q fever vaccination program. We requested dates and results for pre-vaccination skin testing and serology, and dates of vaccination for both the pre-outbreak program in April and the September program conducted during the outbreak. Results of serological tests were obtained from the reference laboratory to which all specimens had been sent. Additional demographic information regarding age and sex was obtained if available.

Immunity

Workers susceptible to primary Q fever infection in this outbreak were defined as having either no evidence of post-infection immunity from a previous Q fever exposure, or had not been vaccinated at least two weeks before the period during which Q fever exposure was likely to have occurred. Onset of exposure in this outbreak was the two-to-four-week period prior to symptom onset in the index case.

Post-infection immunity was shown by the following parameters:

- A positive skin test defined as any erythema or induration at the site of injection after five to seven days. (i.e. post-infection immunity secondary to past Q fever exposure); and/or
- Positive screening serology defined as a baseline Complement Fixation antibody Titre (CFT) to Phase II antigen of ≥1 in 2.5.

Additionally, we considered that a clinical history of Q fever prior to June 1998 with or without screening test results probably indicated post-infection immunity, provided that work history included high-risk exposures including animal husbandry and slaughtering.

Analysis

We calculated Vaccine Efficacy (VE) for the abattoir cohort comparing the attack rate in those vaccinated in April, pre-outbreak, with the attack rate in those determined to be susceptible to primary infection prior to the outbreak. Analysis of results was performed using Epi-info version 6.04.[18]

Results

The outbreak

Of 103 employees employed at the abattoir since it started operations in April 1998, 82 (80%) were male and 21 (20%) were female. Age was determined in 82 (80%) workers. The median age was 33.5 years (range: 17-62 years). Twenty-nine (28%) of 103 employees met the case definition of confirmed Q fever and 8 (8%) had suspected Q fever. Active surveillance did not identify any cases outside the abattoir. The date of onset for the first confirmed case of Q fever was 18 July 1998, eight weeks after the first vaccination campaign had ended (see Figure 1). The epidemic peaked in the first week of September 1998.This was coincident with the commencement of the second screening and vaccination campaign. Date of onset of illness was not available for one case.

Sixteen workers (16%) had post-infection immunity on the basis of skin or serological tests and 19 (18%) had received vaccine at least two weeks in advance of the estimated exposure period of the

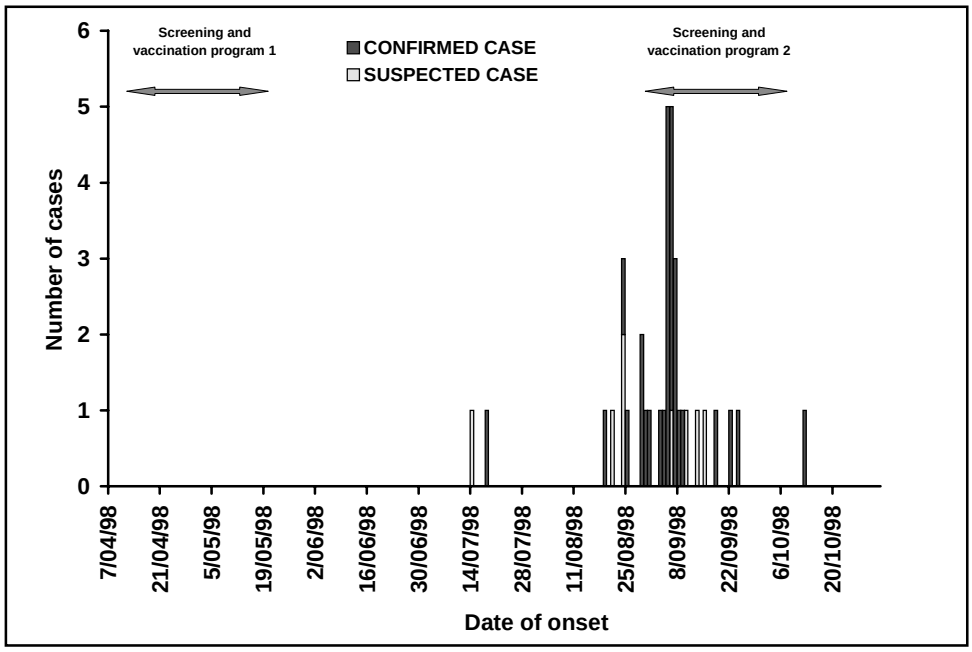

Figure 1: Date of onset of illness in laboratory-confirmed and suspected cases of Q fever, southern NSW, 1998

Table 1: Symptoms reported by 24 laboratory-confirmed Q fever cases and eight cases of suspected Q fever.

Symptom	Number of confirmed and suspected cases interviewed with symptoms n=32 (interviewed)	% with symptoms out of 32 cases interviewed
Headache	32	100
Sweats	30	94
Fever	29	91
Fatigue	29	91
Myalgia	29	91
Arthralgia	28	88
Rigors	25	78
Cough	22	69
Photophobia	21	66
Shortness of breath	15	47
Chest pain	10	31
Jaundice	4	13
Weight loss	4	13

index case. Post-infection immunity was confirmed in only 10 (26%) of those with previous abattoir experience. Sixty-eight (66%) employees were considered susceptible to primary infection.

The attack rate in the susceptible workforce of 68 was 43% (29) for confirmed cases and 54% (37) for confirmed and suspected cases combined. The eight suspected cases reported symptoms resembling Q fever-like illness. Four of the cases remained negative for IgG and IgM antibodies to *C. burnetii* Phase I and II antigens and were also negative on serological tests for other respiratory pathogens (Legionella, influenza A and B, adenovirus, parainfluenza, chlamydia and mycoplasma). The other four suspected cases provided only one serum sample for testing and IF tests for Q fever antibody were negative.

Sixty-three employees (61%) were interviewed by telephone: 32 Q fever cases and 31 non-cases. Of the remaining 40 workers, 19 had no contact phone number, 19 could not be contacted after at least three attempts at calling their number, and two refused interview. Of the 40 not interviewed, five had Q fever-like illness as determined from GP records.

Impact of Q fever-like illness

The most common symptoms reported by cases in this outbreak are given in Table 1. One confirmed case was admitted to hospital for a period of four days. Twenty-three (96%) confirmed cases reported taking time off work on account of illness as compared with five (62%) suspected cases. The median number of sick days for ill workers was seven (range 1-23).

Exposure period

Although the onset date of the index case was mid-July, we estimated from the epidemic curve that the likely period of intense exposure for most cases in this outbreak was August 1998. This encompassed the known two-to-four-week incubation period for *C. burnetii* and was based on date of symptom onset for most (97%) cases (see Figure 2). Two cases of Q fever (one confirmed and one suspected) had a likely period of exposure in June, eight weeks after the abattoir started operations and eight weeks after the initial vaccination program. Another case had illness onset in October, and could have been exposed after the month of August, or had a longer than usual incubation period.

Nature of exposures

High-risk exposures were defined as those that involved the handling of stock (stockyard) or processing of meat (slaughterline, by-product/condemned areas, boning and packing rooms).

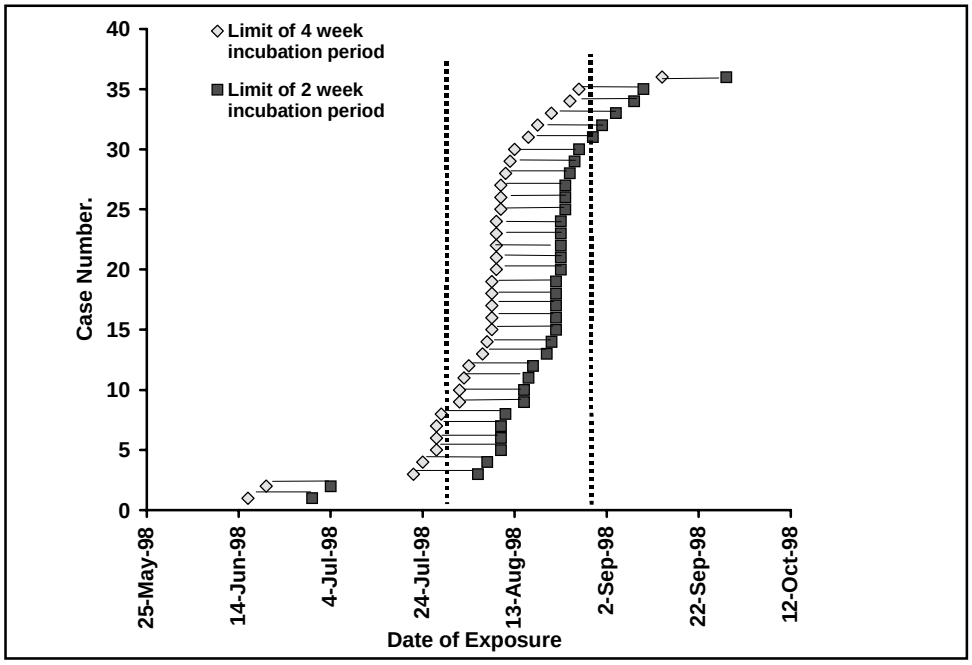

Figure 2: Estimated dates of exposure for cases of Q fever (confirmed and suspected) based on a two-to-four-week incubation period.

Table 2: Vaccination and illness in vaccinated and unvaccinated workers before Q fever exposure.

	Ill	Not ill	Total
Vaccinated pre-exposure	0	19	19
Not vaccinated pre-exposure	37	31	68
Total	**37**	**50**	**87**

Notes:
Relative risk (RR) of illness in vaccinated (0/19) versus non vaccinated (37/68) =0
*VE= (1-RR)*100= (1-0)*100=100%*

Table 3: Illness in relation to timing of skin testing and vaccination.

Skin test and illness onset	
Ill after skin test	19/25
Ill < 10 days post skin test	15
Ill 10-13 days post skin test	2
Ill ≥14 days post skin test	2
Ill before skin test	**6/25**
Ill ≤48 hours before skin test	0
Ill >48 hours before skin test	6
Vaccination and illness onset	
Ill after vaccination	**4/7**
Ill < 10 days post vaccination	4
Ill 10-14 days post vaccination	0
Ill >14 days post vaccination	**0**
Ill before vaccination	**3/7**
Ill ≤48 hours before vaccination	1
Ill >48 hours before vaccination	2

The freezer/load-out area was also considered high risk as staff from this area took delivery of packaged meat that was held in a carton room that was contiguous with the boning room. Maintenance workers and cleaners were a less well-defined group, as their allocated work areas were not known. On the basis of these workers having no regular direct contact with livestock or meat processing they, together with administration staff, were categorised as being at low risk.

Vaccine efficacy

From Figure 2, the estimated period of exposure for most cases of Q fever-like illness was the month of August. Vaccination and screening had taken place in two phases: 19 workers were vaccinated before and 32 after the likely period of Q fever exposure.

There was no significant difference between exposure potential for the 19 employees vaccinated in April/May 1998 before the outbreak and the 68 susceptible employees who were eligible for vaccination at the time of the outbreak. Twelve of 19 workers in this vaccinated group (63%) versus 50 of 68 (73%) susceptible were categorised as working in high-risk areas (RR=0.89; 95% CI 0.59-1.25, p=0.55). There were no cases of Q fever in this vaccinated group and 37 cases in the susceptible workers. Therefore the calculated VE for this group is 100% (see Table 2).

Vaccine safety

No adverse reactions occurred in the 19 workers vaccinated prior to the outbreak. Between 4 September and 6 October 1998, 32 susceptible employees who had been potentially exposed to Q fever in the abattoir were vaccinated. Q fever-like illness was reported in seven (22%) vaccinated employees compared with 30 (83%) of 36 non-vaccinated workers. Thirty-one (97%) of all vaccinated workers were inoculated on or after 10 September. Twenty-eight of these had no symptoms before vaccination whereas three reported illness onset prior to the date of vaccination. Only two mild local reactions following vaccination were reported.

The relative risk of Q fever-like illness in workers, who were vaccinated on or after 10 September, assuming all were exposed, was not significantly different to those who remained unvaccinated after this time (RR= 0.57; 95% CI 0.13-2.57; p=0.60).

The timing of skin testing and vaccination in relation to symptom onset in skin tested and vaccinated workers is shown in Table 3. In the 25 subjects who were skin tested and who were ill, symptom onset in 19 occurred after skin testing, and in six cases before. In only two skin-tested subjects did illness develop after a period of 14 days. Of the seven vaccinated cases, three developed suspected Q fever before vaccination. The four remaining cases developed Q fever after skin testing and vaccination. Symptoms developed in these cases at two, four, six and eight days after vaccination.

Discussion

We did not find any evidence that this abattoir-related outbreak of Q fever in southern New South Wales resulted from a Q-Vax skin testing or vaccination program. It is clear that unscreened, unvaccinated, non-immune workers developed Q fever after exposure to *C. burnetii* in the abattoir. Workers vaccinated prior to the exposure remained well. At the time of the outbreak two-thirds of the workforce were susceptible to primary infection. The high attack rate (54%) in susceptible workers suggested a significant exposure to *C.burnetii*.The nature of the contaminating event is unknown but it is possible that the source of the outbreak was infected pregnant cattle that originated from a Q fever endemic area.

Q fever infection is known to occur in 30% to 70% of susceptible exposed persons,[19] although between 33% to 54% of serologically diagnosed cases in the outbreak setting may be asymptomatic.[20,21] In this outbreak investigation, only workers with symptoms were tested for disease and therefore no asymptomatic infections were identified.

The effectiveness, safety and longevity of Q fever vaccination have been assessed in several vaccination challenge trials of abattoir workers[15,12] and a retrospective cohort survey of employees at three abattoirs over a five-year period.[14] The few cases of Q fever in vaccinated workers reported in any of these studies occurred when the dose of vaccine was given during the incubation period of a natural infection, with no cases occurring after 13 days of vaccination. This same observation occurred in this

outbreak investigation, with all four cases of Q fever occurring within eight days of vaccination. Moreover, of 19 workers who developed illness after skin testing, 17 did so within 14 days of inoculation. *In vitro* measures of cell mediated and antibody induced immunity are positive after two weeks of vaccination[22] which supports the observation that the vaccine is clinically effective after this period of time and not protective against natural infection beforehand. Only two workers reported mild self-limiting local reactions to the vaccine. In larger published vaccination series,[11] where subjects were screened for immunity before vaccination, mild reactions such as tenderness and erythema at the injection site occurred in 48% and 33% of vaccinees respectively, with symptoms enduring from one to three days. Severe reactions consisting of sterile abscesses have been reported in only two of 5,000 subjects vaccinated in the years 1981 to 1989. One of these subjects had equivocal pre-vaccine immunity.

The optimal time to vaccinate workers is at least two weeks in advance of occupational exposure. In this outbreak the vaccine was highly effective when given in advance of exposure, with no illness reported in vaccinated subjects. By contrast, post-exposure vaccination did not confer any significant protection. Post-exposure vaccination was instituted late in the natural history of this outbreak (at least 10 days after the likely period of exposure) when most cases had already progressed to illness or were in the late stages of their incubation period.

Increased efforts to promote vaccine utilisation in the work place need to be considered. Discounts on insurance premiums paid by industries that vaccinate their workforce could alleviate the costs to industry of vaccination. Maintaining vaccination standards by regular audits, streamlining screening and vaccination by the maintenance of a central register, and making Q fever vaccination protocols a part of standard occupational health and safety manuals would serve to lift the profile of vaccination in at-risk occupational groups.

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