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# ADVISORY COMMITTEE ON DANGEROUS PATHOGENS

# STATUS OF Q FEVER VACCINATION FOR HUMANS

## Introduction

A Q fever vaccine for humans is not currently licensed in the UK. Globally there are two broad types of vaccine currently in use or undergoing research: formalin-inactivated whole-cell vaccines such as the commercially available Q-vax in Australia, and acellular vaccines, such as trichloroacetic acid extracted (TCA) and chloroform-methanol residue (CMR) vaccines, developed in former Czechslovakia and USA.

However, due to the adverse local reactions that commonly develop as a result of vaccination with any of the currently available vaccines, recent developments have concentrated on the development of acellular vaccines using purified antigens.

A third type of vaccine, using live attenuated cells of the M-44 *C.burnetii* strain, was developed in Russia in the 1960s. Trials on experimental animals, however, produced lesions in the heart, spleen and liver following vaccination (Johnson 1977), and demonstrated considerable survival of the M-44 strain in the animals, raising concerns about reactivation of infection (Freylikhman 2003). Consequently this vaccine, although tested in some human volunteers, was not considered safe for use in humans. American researchers have conducted some limited human and animal trials using the Nine Mile strain EP88 attenuated vaccine.

## Q-vax

Q-vax, a whole cell vaccine, was developed by CSL Limited, Parkville, Victoria, Australia, and has been commercially available and used for human vaccination in occupational risk groups in Australia since March 1989. The vaccine comprises a purified killed suspension of *C.burnetii* prepared from phase I Henzerling strain of the organism – phase I vaccines have been shown to be 100-300 times more efficacious than phase II vaccines (Ormsbee 1964).

Developed in the early 1980s, it was initially trialled in four abattoirs in South Australia from 1981-1986, with promising results (Ormsbee 1990). A follow-up blind placebo-controlled trial in Queensland was undertaken using influenza and Q fever vaccines, and after 15 months the trial was terminated with all Q fever cases arising in the influenza vaccine group alone (Shapiro 1990). Investigations on abattoirs workers who were given Q-vax between 1985 and 1990 showed vaccine efficacy of '100%': no Q fever occurred in 2555 vaccinated abattoir employees, except two already with the disease at the time of vaccination (Marmion 1990; Shapiro 1990; Ackland 1994). This efficacy has been reduced to 'over 95%' in recent years (Marmion 2007), due to the few instances of laboratory proven Q fever that have arisen in vaccinated subjects in recent years. It is not clear what these apparent vaccine failures are due to.

Q-vax is a highly antigenic vaccine, prompting a serological response of predominantly IgM antibody to *C.burnetti* phase I antigen. The sero-conversion rate is reported to be only 50-80% (Worswick 1985), but development of long term cell mediated immunity following vaccination has been demonstrated (Izzo 1988). Protection has been reported to last for five years at least (Marmion 1990), although it is unknown whether this is due to the vaccination alone, or a combination of the vaccine and periodic occupational exposure.

Revaccination, or use of a booster dose, is currently not recommended due to the possibility of severe adverse effects; thus persons can only be given the vaccine once in their life. Following an outbreak of Q fever in an abattoir where a Q fever vaccination program was underway, it has been proved that Q-vax is effective if given in advance of likely Q fever exposure – post exposure vaccination is not protective (Gilroy 2001).

In Australia, Q-vax is recommended for use in persons from 15 years of age in the following occupational groups:

- Abattoir workers/meat processor workers
- Visitors to abattoirs
- Veterinary personnel
- Stockyard workers
- Farmers, farm hands
- Shearers and wool classers
- Livestock buyers, auctioneers and transporters
- Pelt and hide processors
- Others exposed to cattle, sheep or goats or their products

Laboratory workers handling veterinary specimens are also considered to be at risk, but vaccine is not recommended for this group.

Due to the highly immunogenic nature of the vaccine, and the possibility of severe reactions to the vaccine in previously exposed individuals, pre-vaccination screening is essential seven days before administration of the vaccine. Screening includes the taking of a full patient history to determine possible exposure to *C.burnetii* or any previous Q fever episodes, a serological test and a skin test. Self-reported patient history has been shown to be a poor predictor of immunity, however (Greig 2005). In addition, information on the vaccine is provided, including risk/benefit information which outlines any potential reactions to Q fever vaccination versus the effect of the disease itself.

Reactions to the vaccine can include:

Common (mild) reactions:

- Localised redness or tenderness at the injection site
- General mild influenza like symptoms

Rare reactions (moderate/severe):

- Fever, chills, sweating
- Local induration at the injection site
- Oedema
- Local abscess formation
- Vaccine-associated chronic fatigue syndrome

Recently in 2001, Australian authorities launched the National Q fever Management Program, aimed at reducing the incidence of Q fever in Australia. This program ran until 2004 in most states, but was extended in some jurisdictions until this year. State immunisation teams vaccinated abattoir workers primarily, followed by rural and other at risk groups in the second phase of the program. As well as reducing the number of cases of Q fever steadily between 2003 and 2006, it has also raised awareness of the disease nationally.

**Acellular vaccines**

Alternatives to the whole cell vaccine has been under development for some time. A vaccine is sought that does not require extensive pre-screening, and can be administered to all those at risk of acquiring the disease, rather than only those without prior exposure.

Chemovaccine, developed in former Czechoslovakia, is a TCA vaccine produced from the Nine Mile Phase I strain in the 1970s. Trials so far have demonstrated the vaccine's ability to prevent individuals from contracting Q fever for many years, by inducing both humoral and cellular responses (Brezina 1974; Kazar 1982). However, adverse reactions have occurred in previously infected persons, as has been found with whole-cell vaccines. It has been used in laboratory

workers and some industrial groups on a small scale. Reactions post-vaccination are thought to be similar to that of the whole cell vaccines, but comparative trials are needed (Marmion 2007).

CMR vaccine, developed from Phase I Henzerling strain in the US, has been tested on humans and animals. A comparison of the efficacy and immunogenicity of CMR vaccine versus Q-vax in cynomologous monkeys found that both vaccines gave equal protection against Q fever. Antibodies against both phase I and II antigens were also detected following use of the CMR vaccine (Fries 1993), but declined to baseline levels within 17 weeks of vaccination (Waag 2002). In addition, 30 and 60µg doses of CMR caused minimal adverse reactions in human volunteers, but higher doses gave reactions that were similar to those seen following the usual 30µg dose of Q-vax (Fries 1993).

Acellular vaccines have thus been shown to be as effective as whole cell vaccines, but with generally fewer side effects. However, trials are needed on the scale of those undertaken with Q-vax, to fully describe their potential.

**Other vaccine targets**

Neither Q-vax nor any of the acellular vaccines developed so far have eliminated the need for pre-screening, and thus a vaccine is sought that can be administered to all individuals within risk groups, regardless of previous exposure to *C.burnetii*.

Recent studies have concentrated on identifying protective antigens. Challenge studies with individual *C.burnetii* antigens have so far not been effective at inducing a protective immune response (Tyczka 2005). However, experiments by Li et al (2005), using combinations of recombinant protein to immunise mice, have demonstrated good immunogenic responses. Once effective protective antigens have been identified, development of DNA vaccines will be the next step (Zhang 2004). Likely vaccine candidates may also arise from an investigation of *C.burnetii*'s genome.

**Action**

Members are asked for their views on whether the use of vaccine in certain occupational groups against Q fever (a) as a matter of routine and (b) in an outbreak situation only should be referred to the Joint Committee on Vaccination and Immunisation (JCVI) for consideration.

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**September 2007**