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Q fever: the long journey to control by vaccination

Barrie Marmion

The current whole-cell vaccine and protocol for Q fever prophylaxis are effective

At the end of 2006, the Australian Ministers for Health and Agriculture announced funding for an upgraded facility to allow CSL Limited to recommence production of the Q fever vaccine (Q-Vax) and comply with changed biocontainment regulations.¹ Production of the vaccine had ceased at the end of 2005 because of inability to meet these new regulations and other production pressures. Federal government support is a welcome step forward in the control of a major infective disease in Australia, and comes as a substantial relief to the rural community and meat processors. In addition, it keeps faith with the considerable efforts by state health department immunisation teams and medical practitioners to extend the use of the vaccine from abattoirs to the at-risk rural community during the government-subsidised National Q Fever Management Program, 2001–2003/2004 (<http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/q-fever-man>).

Attempts to control Q fever by vaccination have a long history.² After the discovery of clinical Q fever and isolation of the causative organism by Edward Derrick in Queensland in the 1930s, and the subsequent identification of the isolates (an obligate intracellular bacterium) by Macfarlane Burnet, the disease emerged as an important “campaign” infection (Balkan grippé) for armies in the Mediterranean arena during World War II. At the time, various vaccine formulations were prepared from the coxiella grown abundantly in chick embryo yolk sacs, as devised by H R Cox at the National Institutes of Health/National Institute of Allergy and Infectious Diseases, Rocky Mountain Laboratory, Montana, USA. Suspensions of infected yolk sac were inactivated with formalin and ether (eg, by Smadel and colleagues).² These were protective in animals and in human volunteer and challenge trials. But use in humans produced unpredictable, severe local reactions.

Derrick expressed a common view of these early Q fever vaccines in his 1964 Elkington Oration: “What of the future; there is an effective vaccine but it produces unacceptable reactions”.³ His assessment is still repeated uncritically in the medical literature.

The experience in Australia from 1980 to 2005 with the present generation of whole-cell vaccines (eg, Q-Vax [CSL Limited]) and a different vaccination protocol has been quite the reverse. The contemporary whole-cell, formalin-inactivated Q fever vaccine has also sometimes been dismissed as “old-fashioned”—ignoring a protective efficacy of over 95%. In fact, the formulation is appropriate for the complex immunopathology of acute Q fever.

Insight into the critical components for an improved whole-cell vaccine started in Cambridge in the 1950s with Stoker and Fiset’s⁴ discovery of the antigenic phase variation of *Coxiella burnetii*. Concurrent studies, also in Cambridge, by Abinanti and Marmion⁵ showed that antibody to the Phase I antigen (ie, the lipopolysaccharide of coxiella cells with a complete set of sugar residues in its O-chains) was protective in a mouse spleen model of Q fever infection. On the other hand, protection was not conferred by antibody to Phase II antigens (ie, from coxiella with a full complement of proteins, but with genetically driven or other

variations in the level of synthesis of complete lipopolysaccharide O-chains — recent research reports^{6,7} give a more detailed explanation of the chemistry of phase variation).

Subsequently, Ormsbee et al⁸ at Rocky Mountain Laboratory extended these observations to show that a formalin-inactivated vaccine made from coxiella predominantly in the Phase I antigenic state was significantly more protective in a guinea pig model of Q fever on a weight-for-weight basis than one made from cells predominantly in Phase II. The latter preparation, and indeed the earlier vaccines developed by Smadel, probably owed their partial protective properties to residual Phase I cells in a population of Phase II variants. The importance of Phase I lipopolysaccharide as a protective immunogen is supported by the finding that a Phase I Q fever vaccine loses its protective efficacy in mice when treated with potassium periodate to ablate the sugar residues in the lipopolysaccharide (unpublished data).

The major host cells for *C. burnetii* in animals and humans are in the monocyte–macrophage lineage. The interactions of coxiella with this key regulatory cell series for the cellular immune system underlie both the immunopathogenesis of Q fever and the prophylaxis afforded by the vaccine. The coxiella proteins (as peptides) stimulate T-lymphocyte immunity and memory, with the generation of interferon- γ and other cytokines that control intracellular replication of coxiella.² On the other hand, interactions of coxiella and monocyte–macrophage cells produce mediators that down-regulate the cellular immune system and the formation of interferon- γ by T lymphocytes.^{9,10} A possible explanation for the central requirement of the Phase I determinant in a vaccine is that antibody to it blocks interaction of coxiella and the monocyte–macrophage cells. Consequently, down-regulation of the cellular immune system does not occur and coxiella growth is restricted.

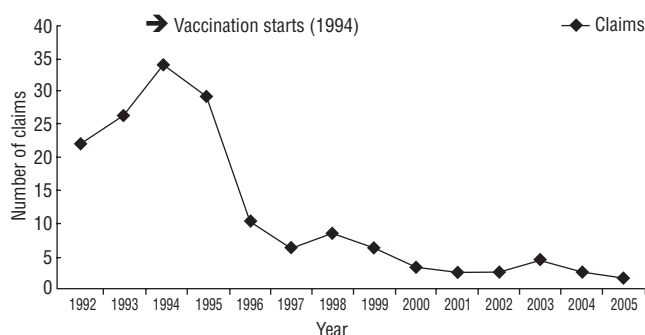
A contributory component for vaccine efficacy may be the slow biodegradability of the small-cell variant of coxiella. This displays both Phase I lipopolysaccharide and protein antigens, thus providing continuing antigenic stimulation and protection.

An important step in the development of the current protocol for vaccination was the finding by Lackman and colleagues² at Rocky Mountain Laboratory that adverse reactions to whole-cell vaccine could be minimised by intradermal skin testing of potential vaccinees with a dilute vaccine to detect prior cellular immune sensitisation.

In the early 1980s, 50 years after Derrick’s discovery — and probably after some 40 000 overt cases of Q fever — Dick Ormsbee and I asked CSL Limited to make Ormsbee’s highly purified version² of Q fever vaccine with its negligible residual yolk protein. At the time we knew that Hornick, Fiset and colleagues,² under the auspices of the Commission on Rickettsial Diseases (US Armed Forces), had vaccinated volunteers with whole-cell vaccine and challenged them with aerosols of living *C. burnetii*. Even small doses (1–10 μ g) of vaccine were protective.

Open clinical trials of the Ormsbee-type vaccine (Q-Vax) (produced by CSL) at a dose of 30 μ g as a subcutaneous injection were

1 Control of abattoir-associated Q fever in a major Queensland abattoir complex



Claims per annum for compensation for clinically and laboratory-proven, occupationally acquired Q fever. (Data supplied by and reproduced with permission of Australian Meat Holdings, Queensland.)

3 Efforts to produce less reactogenic, alternative vaccines without the need for pretesting

Extracts of coxiella containing lipopolysaccharides and protein (eg, chemovaccine)² or delipidated coxiella cell residues² are protective in animals. Chemovaccine has been used in Eastern Europe in laboratory workers and some industrial groups. It is protective, but about as reactogenic as whole-cell vaccine. To establish efficacy, duration of protection and reactogenicity (severe adverse incidents are rare and idiosyncratic), comparative trials are needed of these vaccines versus whole-cell vaccine in larger numbers of subjects.

There is also active research into simpler vaccines of coxiella proteins prepared by recombinant DNA methods.¹² So far, coxiella proteins alone appear not to be protective,¹³ although a recombinant fusion protein given with Freund's complete adjuvant (a potent macrophage activator) protected in a mouse model.¹⁴

The quest for a simpler vaccine should continue; whether successful or not, it is yielding valuable insights into the immunobiology of Q fever. But the three-component nature of the existing vaccine and the roles in protection of lipopolysaccharides, macrophages and antibody need to be taken into account.

performed in workers at four abattoirs in South Australia in the 1980s.² These established the vaccine's safety in an industrial environment in which prior clinical or subclinical infection and immune sensitisation were common. As in the US volunteer trials, the vaccine was protective.

A formal "blind" comparison of Q-Vax and influenza virus vaccine performed at three Queensland abattoirs also showed complete protection.²

Box 1 shows the practical value of vaccine prophylaxis in a large abattoir group in Queensland, 1992–2005. Occupationally acquired, laboratory-proven Q fever is compensable. Compensation claims — a significant expense for the industry — declined steadily after the vaccination program started. Box 2 shows the number of Q fever cases notified to the National Notifiable Diseases Surveillance System across Australia, 1991–2006. The yearly totals include Q fever cases both in and outside abattoirs.

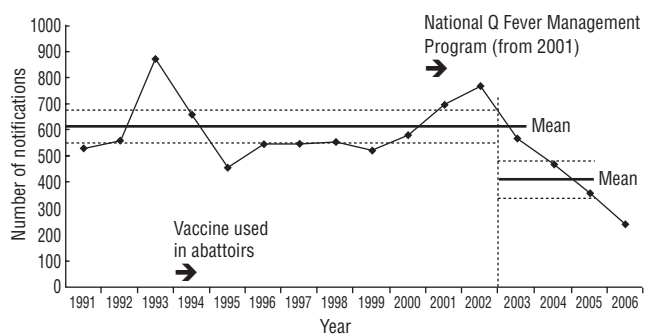
Abattoirs across the country gradually took up vaccination from 1993–1994, greatly aided by CSL's vaccine consultants. During the period 1994–2000, although the number of Q fever notifications stabilised at around 500–600 per year, probably reflecting fewer cases in abattoirs, an unambiguous downward trend in Q fever notifications for the country as a whole did not occur. This is not

surprising, as it has been apparent since the 1930s that only a variable proportion of Q fever cases occurs in abattoirs (eg, 68% of Derrick's series of 273 cases¹¹).

During the National Q Fever Management Program, state immunisation teams worked intensely to vaccinate abattoir workers, and rural and other at-risk groups in the population. Evaluation continues, but Box 2 shows an encouraging and significant decline in case numbers from 2003 to 2006.

What of the future? Further refinement of existing vaccine protocols is needed as problems surface from wider use. Efforts to produce less reactogenic vaccines for use without pretesting are summarised in Box 3.² Balanced against the continuing and substantial Q fever problem in Australia, the current whole-cell vaccine and protocol are effective, they have been tested in over 150 000 subjects, and prophylaxis for this disease is available now.

2 Vaccination and changing trends in the numbers of notified cases of Q fever across Australia, 1991–2006



Means (SEs) for 1991–2002 and 2003–2006; P = 0.01 for comparison of means. (Yearly totals for Q fever notifications and the basic curve are from the National Notifiable Diseases Surveillance System.)

Acknowledgements

Dedicated to the memory of RA (Dick) Ormsbee, who with Paul Fiset developed an improved whole-cell Q fever vaccine (1960–1970) and saw its protective efficacy and licensing in 1989 before his untimely death in an accident in 1991.

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