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ORIGINAL ARTICLE

Q fever vaccination of children in Australia: Limited experience to date

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Aim: Q fever is a zoonotic disease caused by the bacterium *Coxiella burnetii* and is associated with significant morbidity and mortality in both adults and children. Australia is the only country that has produced and registered a Q fever vaccine for human use, but this vaccine is licenced only for people aged over 15 years as data and experience in children are limited. This review describes the experience of Q fever vaccination of known paediatric cases in Australia to date.

Methods: Patients aged younger than 15 years who received the Q fever vaccination had data abstracted from medical records after consent was obtained from the relevant guardians. Data on risk factors for Q fever, skin testing procedure, dose of vaccination, adverse effects and follow-up assessment were obtained.

Results: Twelve children were identified as having received the Q fever vaccination. Vaccination was feasible, with empirical weight-based dose adjustment performed for younger children. There were no significant adverse effects.

Conclusions: Q fever vaccine may be safe in children and should be considered in children who are at significant risk of Q fever infection. Safe vaccine protocols with proven efficacy will allow children of all ages to be protected. Prospective studies of vaccination in children are indicated. Expanding available Q fever registries to include children would allow outcomes to be systematically followed.

Key words: Australia; bacterial vaccines; child; *Coxiella burnetii*; Q fever; vaccination.

What is already known on this topic

1 Q fever infection in children can result in significant morbidity and occasional mortality.
2 Australia is the only country in the world with a Q fever vaccine licenced for use in humans.
3 Vaccination is effective in preventing Q fever in adults, but limited data exist for children.

What this paper adds

1 Q fever vaccination may be indicated in children with a high likelihood of Q fever exposure.
2 This small report indicates that Q fever vaccination in children is feasible and is likely to be safe.
3 Prospective studies of the safety and efficacy of Q fever vaccination of children are indicated.

Q fever is a zoonotic disease caused by the bacterium *Coxiella burnetii*. It is associated with significant morbidity and mortality, with increasing recognition of serious disease in children.[1,2] The need for a vaccine for children has been recognised for many years.[3] Q fever in children is likely underdiagnosed as it is frequently associated with asymptomatic infection or a mild and transient acute illness, and clinicians are unlikely to specifically request Q fever investigations in these cases. Focal persistent disease is serious, manifesting as endocarditis, endovascular infection, lymphadenitis and osteomyelitis.[4–6] Q fever is recognised in a wide range of host species, with multiple potential sources of exposure.[7] *C. burnetii* is excreted in milk, faeces, urine and birth by-products, facilitating its dissemination in the environment.[3] This is also suggested by sero-prevalence studies, showing significant prevalence in paediatric populations. Q fever exposure was detected in 19% of children aged younger than 15 years in a study undertaken in Switzerland during an outbreak.[8] Two sero-prevalence studies have been conducted in Queensland, Australia, in children aged younger than 15 years. One from South West Queensland (2002) using a convenience sample from routine laboratory samples identified past exposure in 2.5% of 237 children tested,[9] and the other reported sero-prevalence of 1.3% in samples from 844 children (2009).[10] Another study among residents of the Hunter New England region in New South Wales, Australia, reported sero-prevalence of 1% in the

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0–9 age group and 5% in the 10–19 years old age group, taken from routine blood samples obtained in 2006–2009.[11]

Australia is the only country to have produced and registered a Q fever vaccination for human use.[12] Other countries have a registered veterinary vaccine, although this is not available in Australia.[13] Australia has a high rate of Q fever notifications, with Queensland having a rate of 11.9 per 100 000 in 2001, prior to the widespread use of Q fever vaccination.[14] A total of 116 Q fever notifications were made for children aged 0–14 years in Australia from 2007 to 2016.[15] Vaccination for adults with potential occupational exposure to Q fever was offered as part of the National Q Fever Management Program, which included funded vaccine between 2001 and 2006. This programme had a significant impact on Q fever notification rates, with a decline by 50% from 2002 to 2006.[14] Since 2006, the vaccine, supplied by Seqirus, is only available via private prescription,[16,17] and there has been an increase in notifications of Q fever. In 2009, notifications in Queensland were 3.0 per 100 000 and in New South Wales 2.0 per 100 000. The corresponding figures in 2015 were 5.3 and 3.4, respectively.[15]

Pre-vaccination screening is required to exclude persons who are already sensitised to Q fever antigens and who may experience hypersensitivity reactions if vaccinated.[18] Individuals with no history of Q fever undergo a serological test and a skin test with intradermal injection of diluted Q fever vaccine.[19]

Despite increasing recognition of Q fever exposure and disease in children, preventative strategies in this age group have been limited. Vaccination is not yet licenced in children younger than 15 years of age due to limited data on safety and efficacy in this group. However, off-label administration of the Q fever vaccination to children younger than 15 years has been utilised by clinicians in selected cases, where significant concern exists for acquisition. A retrospective review was conducted of paediatric patients (aged younger than 15 years), who received Q fever vaccination, to determine practice, feasibility and safety of Q fever vaccination.

Methods

Cases were sought from all states and territories in Australia and were identified by communication with clinicians with a special interest in Q fever. Further enquiry was made to local public health units, a travel medicine clinic and available Q fever registries. An appeal was made on a professional online tropical medicine forum. Following identification of children who received the Q fever vaccine, informed consent was obtained from their guardians, as well as the patient's clinical practitioner who undertook the administration of the vaccination. A standardised data extraction form was utilised to obtain retrospective data. Data included parental occupation, potential Q fever exposure of parent or child, family history of vaccination against Q fever or Q fever infection, the indication for vaccination and vaccination procedures, results of skin testing and serology performed prior to vaccination and dose of vaccine administered. Adverse events were recorded in addition to follow-up details including serology testing where available.

Ethics approval for the study was obtained from the Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (reference: HREC/16/QRCH/383).

Results

Twelve children were identified as having received the Q fever vaccine between 2006 and 2017, with seven families in total. Five families had two vaccinated siblings in each family, while two families had one vaccinated child each. The median age at vaccination was 12 years (range 1–14 years). Children had been vaccinated in the Northern Territory (2), Queensland (2), Victoria (2), New South Wales (4) and South Australia (2).

Five children were male. Potential exposure to Q fever was described for all the vaccinated children (Table 1). Of the 12 patients, 10 (all children from six families) described close contact with cattle. The source of contact was from their own or from a neighbouring property. The remaining two patients had potential exposure through their parents' laboratory work with Q fever. Four participants (two each from two different families) were recommended vaccination by an infection specialist who was managing their sibling with chronic recurrent Q fever osteomyelitis. Four children had vaccination recommended by medical doctors with an interest in Q fever on the basis of significant animal contact. Of 14 parents from seven families, 7 had received Q

Table 1 Demographic and clinical details of patients

Patient number	Year of vaccination	Gender	Age	Risk factor	Dose of vaccine, mL
1	2006	Male	6	Parental laboratory exposure	0.2
2	2006	Male	7	Parental laboratory exposure	0.3
3	2007	Female	12	Cattle exposure	0.5
4	2007	Female	14	Cattle exposure	0.5
5	2009	Female	12	Cattle exposure	0.5
6	2012	Female	14	Cattle exposure	0.5
7	2014	Female	1	Cattle exposure and sibling with Q fever OM	0.07 (0.0083 mL/kg)†
8	2014	Male	2	Cattle exposure and sibling with Q fever OM	0.125 (0.0078 mL/kg)
9	2014	Female	9	Cattle/Other animal exposure and sibling with Q fever OM	0.5
10	2014	Male	12	Cattle/Other animal exposure and sibling with Q fever OM	0.5
11	2017	Female	12	Cattle exposure	0.5 (0.013 mL/kg)
12	2017	Male	14	Cattle exposure	0.5 (0.0079 mL/kg)

†Dose of vaccine mL/kg if available. OM, osteomyelitis.

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fever vaccination. Two had positive Q fever serology and hence did not proceed to vaccination. Neither of these parents could identify a prior consistent clinical illness. Another two parents had a diagnosis of Q fever, with consistent symptoms of acute disease. One father had had a positive skin reaction to screening and therefore did not proceed to vaccination.

All patients had documented negative Q fever serology prior to vaccination. All patients underwent skin screening on the forearm with a dose of 0.1 ml (diluted Q-Vax® Skin Test),[19] with no reaction recorded when reviewed 7 days after administration. Dose of vaccination varied (Table 1). Eight patients received the recommended adult dose of 0.5 mL. During the study period, general practitioners had been advised by medical practitioners with experience in Q fever management to adjust the volume of vaccination if children weighed less than 70 kg. Ten patients had vaccine administered via the subcutaneous route and two via intramuscular route. All vaccines were administered to the deltoid region.

Adverse effects from vaccination were mild. Three patients described transient self-limiting pain at the injection site. Two patients described slight erythema at the injection site, with one of these patients also describing localised pruritus. No serious adverse effects were noted.

Discussion

This brief report suggests that Q fever vaccination of children could be safe and feasible. The lack of observed significant side effects is encouraging. Minor side effects of headache and delayed skin reaction, which occur commonly in adults,[14] were not observed. If correctly administered in adults, vaccine efficacy has been estimated to be between 83 and 100%.[12] Q fever vaccination of paediatric patients could limit transmission of this potentially serious disease to children. While no children have developed a clinical illness consistent with Q fever post-vaccination, the study did not specifically look at vaccine efficacy, and follow-up was limited. This highlights the need for ongoing data in this age group.

A national database of Q fever infection in children, such as the Australian Paediatric Surveillance Unit, would inform the need for Q fever vaccination in children. Extensive epidemiological and clinical data of Q fever in children will help to identify children who are at risk of acquiring the disease and, as such, guide vaccination strategy.[20] Currently limited paediatric-specific data are a concern, with much of our current knowledge extrapolated from studies that focus on adults or are based on case reports.[3] Likely acquisition risks in children include place of residence (close to a property with cattle or living near an abattoir); parents in high-risk groups such as cattle farmers, abattoir workers, Q fever researchers or veterinarians; and a family history of Q fever in parents or siblings.[21] Q fever vaccination is likely to be beneficial for these children.

Vaccination dose varied in this series of patients, in part due to weight-based dosing recommendations. The dose in some patients was very small. A minimum dose recommendation should be clarified prior to more widespread adaptation of vaccination in children. Evidence-based fractional dosing recommendation cannot be made based on this study. Further prospective studies are needed to facilitate standardised dosing and administration practice, including skin testing. Ongoing data regarding safety and efficacy in vaccinated children will be essential to inform practice.

Conclusions

Q fever vaccination in children may be feasible and safe. The vaccine should be considered for children at high risk of Q fever infection. A prospective study of the safety and efficacy of Q fever vaccination in children is recommended. This could be facilitated by the development of a Q fever register in vaccinated children.

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