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ARTICLE

Q fever seroprevalence in metropolitan samples is similar to rural/remote samples in Queensland, Australia

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Abstract Q fever is a vaccine preventable disease; however, despite this, high notification numbers are still recorded annually in Australia. We investigated the seroprevalence of *Coxiella burnetii*, the Q fever agent, in a Queensland sample population. Notification data (N=6425) from 1984–2008 were collated, identifying high risk areas of Q fever exposure. Of these 177 were recorded in children. Serum samples were collected from Queensland and screened using both an immunoflourescence assay at 1:10 dilution and a commercially available ELISA kit. Results were collated based on age, geographical location and sex. From 1988 Queensland samples screened, 103 were identified as Q fever IgG-positive, giving a seroprevalence of 5.2% (95% CI 4.3–6.2%). Seroprevalence in the rural/remote population was 5.3% (95% CI 4.6–6.6%), and the metropolitan Brisbane population, which is considered not at risk, was 5.0% (95% CI 3.7–6.7%). Sixty-three seropositive males and 40 females were identified, along with an increase in seropositivity with increasing age. The seropositivity of children was 1.3% (95% CI 0.7–2.3%) from 844 samples. We have shown that both metropolitan and paediatric populations which are considered low risk of Coxiella exposure have surprisingly high seropositivity. These emerging groups require further investigation and consideration for the introduction of preventive measures.

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Introduction

Q fever is a zoonosis caused by the inhalation of aerosols contaminated with the gram negative, intracellular bacteria, *Coxiella burnetii* [1–3]. Q fever has been reported worldwide except for New Zealand and Antarctica [4, 5]. The organism resides within host macrophages and replicates in the placenta and reproductive tissues of infected animals, most prolifically in sheep, goats and cattle. Bacteria are widely disseminated into the environment from infected animals and their products where the organism is able to withstand harsh conditions for long periods of time [1–3].

Q fever infections in humans present as a variety of clinical syndromes and are classified as either acute or chronic [6]. Acute Q fever infections may be asymptomatic and present as a self-limiting febrile illness such as pneumonia or hepatitis [7–9]. Chronic Q fever disease follows an acute episode resulting most commonly in endocarditis, particularly in patients with previous valvulopathy and those that are immunocompromised or pregnant. It may also manifest as a chronic hepatitis or osteomyelitis; the later common in paediatric chronic infections [6].

Q fever is a vaccine preventable disease in humans. Australia is the only country that has a licensed vaccine, with approximately 12,000 adults vaccinated each year [10]. Since 1989, the vaccine Q-Vax (CSL Ltd, Parkville, Victoria, Australia) has been available to prevent acute Q fever infections in personnel working in high risk occupations [11–15]. A Commonwealth Government funded

program, the National Q Fever Management Program (NQFMP), was implemented in 2000 to provide vaccine free of charge to abattoir workers and shearers, in an effort to reduce the numbers of acute Q fever infections associated with occupational outbreaks. Following the implementation of NQFMP, notifications of Q fever infection peaked in 2001 and 2002, but declined rapidly to the lowest annual counts on record in 2005 and 2006 [16]. A review of Queensland notification data indicates there are an increasing number of acute Q fever infections being identified in children each year, particularly from rural and remote regions [17]. Q-Vax, however, is not recommended for use in children aged <15 years as safety, tolerability, and effectiveness of the vaccine has not been determined in this age group [18].

In Australia, Q fever became a nationally notifiable disease in 1977, and the surveillance of Q fever infections via notification data shows that notifications are highest in Queensland and New South Wales [16, 19]. Notification data alone however, are not a true indication of the prevalence of the disease within the population, because these represent confirmed clinical cases only [7]. Q fever is underestimated in Australia, particularly in Queensland where the highest rate of laboratory confirmed infections occur [7]. The underestimate can be mainly attributed to a large number of asymptomatic cases, or symptomatic cases where the diagnosis was not considered or testing not performed, and poor sensitivity of currently used diagnostics. In Australia, Q fever diagnostic testing is largely performed using serological methods, with some laboratories introducing molecular assays. The current gold standard method for Q fever is the immunoflourescence assay (IFA) [6], which is used in pre-vaccination screening and diagnosis because of its high sensitivity [6, 20, 21].

Although Q fever cases and epidemics have been reported from many countries around the world, there have been few large population-based studies examining the seroepidemiology of this infection in humans [6, 7, 22–24]. We sought to investigate the seroprevalence and disease notification of Q fever in the Queensland population and evaluate the need for extending vaccination into currently non-targeted groups.

Materials and methods

Q fever notification data

Since 1977, all laboratory confirmed cases of Q fever in Queensland, Australia have been recorded in a database collated by public health units [25]. Q fever notification data from the office of the Director General of Queensland was obtained and reviewed to identify areas of high notification. From this data series we analysed Q fever notification data from 1984 to 2008 for Queensland by geographical residential location (using Australian Bureau of Statistics Statistical Subdivisions [SSDs]), age-group, sex, and time period of infection. Employment history was not available for each notified case, meaning occupational risk could not be assessed.

Serum bank

We assembled a serum bank to assess Q fever seroprevalence. Similar to previous studies, Queensland Q fever notification data suggest a predominantly rural disease. With this in mind, we deliberately over-sampled sera from rural/remote areas. We sought to better define exposure in paediatric age-groups—children younger than 15 years of age and too young for vaccine—by over-sampling this age-group also.

The serum bank contained a total of 2,122 de-identified serum samples which were screened for phase II Q fever IgG antibodies. The sera were collected from patients with non Q fever related pathology requests, and data obtained on each sample included date of collection, date of birth, age, sex and postcode. Samples collected from October 2008 to June 2009 (n=18,16) were obtained from Pathology Queensland at both the Herston and Toowoomba hospital sites. Additional sera (n=306) collected from January to May of 2007 and from January to April of 2008 as part of an investigation into allergies in children, were obtained from a private pathology laboratory in Brisbane.

The age distribution amongst the serum bank was 0–98 years of age, with an average age of 33.0 years and a median age of 19.6 years. We defined paediatric samples as those from children younger than 15 years of age.

Laboratory testing

Serum samples were initially screened for Q fever IgG antibodies using two screening assays: a modified, in-house IFA method from the Institute of Medical and Veterinary Science (IMVS, Adelaide) [26] and a commercially available ELISA method (Pan Bio Ltd, Brisbane, Queensland, Australia).

The published IMVS IFA method measures all serological markers IgA, IgG, and IgM for both phase I and II of the *C. burnetii*; we used the method to measure only the IgG. Briefly, slides were prepared using Menzel-Glaser 24 dot wells and Virion\Serion CFT *C. burnetii* antigen diluted 1:20 with 0.5% chicken yolk sac (CYS). Slides were spotted with the antigen, allowed to air dry, and then immersed in methanol for five minutes to fix organisms. Serum samples were diluted using 3% CYS to a 1:10 dilution for IgG screening. Diluted sera were loaded to the

slide and incubated at 37°C for 30 minutes. Slides were then washed two times for 5 minutes in fresh phosphate buffered saline (PBS) and air dried. Goat anti-human IgG Fluorescein isothiocyanate (FITC) (Chemicon, North Ryde, New South Wales, Australia) conjugated was diluted (1:50) with a counter stain and incubated at 37°C for 30 minutes. Slides were again washed and dried and mounted for examination using a Nikon Eclipse E600 (Japan) immunofluorescent microscope. Presence of fluorescent, apple green-stained bacteria was indicative of a positive result. Results were either recorded as detected or not detected.

The commercially available ELISA kit (Pan Bio Ltd, Brisbane, Queensland, Australia) was used for the detection of IgG antibodies against phase II *C. burnetii* organisms only. Results were recorded as positive, negative, and equivocal according to manufacturer's instructions. For the purpose of this study an equivocal result was repeated and if still equivocal it was deemed to be negative by the ELISA assay.

A third assay was used for discrepant analysis of discordant results that occurred between the two screening assays. This was a commercially available IFA kit assay (Focus Diagnostics, California, USA) and specimens were recorded as detected or not detected. The assay was performed according to the manufacturer's instructions with a documented sensitivity of 100% and specificity of 99% when compared to another IFA and a complement fixation assay.

A specimen that was determined to be positive by the two screening assays was considered a true positive, and the commercial IFA was not performed. Where a positive result was recorded by only one of the screening methods, the commercial IFA was performed and the result in this assay was considered the final result.

Data analysis

Data were analysed on date of collection, date of birth/age, sex and postcode. Two distinct geographical populations were defined based on patients' postcode sorted into the 39 statistical subdivisions (SSD) within Queensland [27]. On this collation there were 1,988 serum samples with postcodes from Queensland SSDs. When samples were collated based on postcodes, it was shown that there was at least one sample from each of the 39 SSDs within Queensland. We divided samples by whether they were received from Metropolitan Brisbane—traditionally with low rates of Q fever notification—or the rest of the state—containing rural and remote areas with the highest rates of Q fever notification. SSDs beginning with the code 305 were considered metropolitan Brisbane, and the remaining SSDs considered rural/remote. Data were analysed and 95% confidence intervals were calculated using Stata 10 (Stata Corp, College Station, Texas, USA).

Ethics approvals

We obtained approval to conduct this study from the Queensland Children's Health Services Ethics Committee.

Results

Q fever notification data

Q fever related data from the office of the Director General of Queensland was obtained and reviewed to identify areas of high notification rates. There were a total of 6,425 notifications within the 25 year period (1984–2008) investigated. Of these, 5,157 notifications were from males and 1,268 notification from females. There was a clear difference in the notification numbers between the defined rural/remote and metropolitan Brisbane populations (Fig. 1), with a total of 5,436 notifications from the rural communities compared to 989 from the metropolitan population.

A total of 177 clinically confirmed cases of Q fever were recorded in children over the 25-year period, with the average age being 9 years old and an age range spanning newly born to 14 years old. Notifications in children increased over time, with only 62 notifications recorded in the 17 years up to and including the year 2000, the year the NQFMP commenced, at an average number of annual notifications of 3.7 paediatric notifications per year. Following the introduction of the NQFMP there was a marked increase in notifications of paediatric confirmed cases from 2001 to 2008, with 115 notifications recorded, giving an average annual number of notifications of 14.4. Of the 177 notifications, ten were from metropolitan

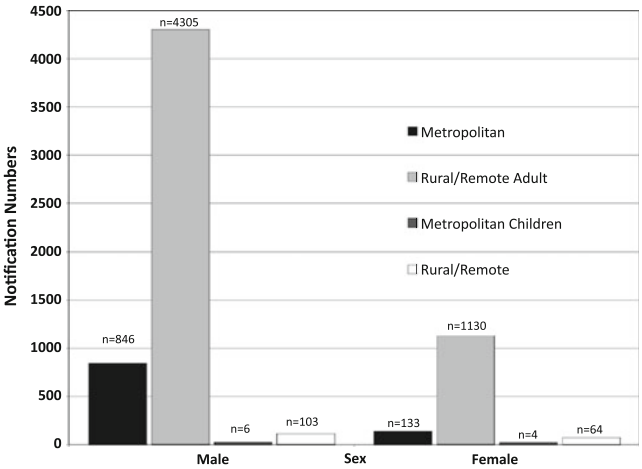

Fig. 1 Q fever notification data from 1984–2008. Q fever notifications by sex, location, and age-group in Queensland over a 24-year period

Queensland and 167 were from rural/remote Queensland (Fig. 1).

Laboratory analysis

Of the 2,122 specimens, 98 were positive by both screening methods (IMVS IFA and Pan Bio ELISA), and 1,997 samples were negative by both methods, leaving 27 discrepant results—21 positive by the IFA assay only and six positive by ELISA only. Further testing of these discrepant samples with the commercially available IFA (Focus Diagnostics) confirmed 11 of 21 IMVS IFA positive specimens and none of the ELISA positive results. This resulted in a total of 109 positive specimens for further analysis.

Seroprevalence of Q fever in Queensland

Sample demographics were collated and only sera from patients with a current Queensland residential postcode were included in the seroprevalence analysis. There were a total of 1,988 serum samples from Queensland in the serum bank. Of these, 103 were Q fever IgG-positive, giving a seroprevalence in the total sample population of 5.2% (95% CI 4.3–6.2%). The seroprevalence among the 1,182 serum samples tested from a rural/remote population was 5.3% (95% CI 4.6–6.6%), compared to a seroprevalence of 5.0% (95% CI 3.7–6.7%) in 806 serum samples from the metropolitan Brisbane population. Of the 63 seropositive males identified, 36 (57%) were from rural/remote Queensland, and from the 40 female seropositives detected 27 (68%) were from rural/remote communities (Table 1). A total of 1,144 serum samples were collected from adults, with 92 (8.0%) of these positive for Q fever IgG. The rural/remote population of 649 samples had a seropositivity of 8.8% (57) and similarly the metropolitan adult population showed a seropositivity of 7.1% (35) from 495 samples. There was an increase in seropositivity with an increase in age shown in this sample population (Table 1).

Also, 844 samples were from children under the age of 15. Of these 11 showed previous exposure to Q fever; five boys and six girls, giving a seroprevalence in the Queensland paediatric population of 1.3% (95% CI 0.7–2.3%). The split between rural/remote and metropolitan Brisbane populations were six seropositive from rural Queensland with four of these from females and two from males. The metropolitan population had five seropositives with two female detections and three male.

Table 1 Q fever seropositives by sex, location, and age group

Characteristic	Number in sample	Seropositive (*n*, %, 95% CI)
Sex		
Female	1,020	40, 3.9% (95%CI 2.9–5.3)
Male	968	63, 6.5% (95%CI 5.1–8.2)
Location		
Metropolitan	806	40, 5.0% (95%CI 3.7–6.7)
Rural/remote	1,182	63, 5.3% (95% CI 4.2–6.8)
Age group		
0–14	844	11, 1.3% (95% CI 0.7- 2.3)
15–39	371	17, 4.6% (95% CI 2.9- 7.2)
40–64	385	38, 9.9% (95% CI 7.3–13.3)
65+	388	37, 9.5% (95%CI 7.0–12.9)
Total sera	1,988	103, 5.2% (95% CI 4.3–6.2)

CI confidence interval

Discussion

It is known that human Q fever infections are acquired through the inhalation of contaminated particles released by infected animals, and hence the disease is more frequently recorded in rural/remote settings where close contact with ruminant animals is common. In 2006, Queensland reported a rate of 107 Q fever infections per 100,000 people, where the majority of these occurred in Southwest Queensland, a rural area with a large agricultural base [16].

This fact was supported by notification data for the Queensland population in this study, which showed that the highest numbers of confirmed Q fever cases occurred in the rural communities, with a ratio of 5.5:1.0 of rural/remote to metropolitan confirmed cases. However, this difference was not observed in the seroprevalence results for these two populations in our study. The seroprevalence of Q fever in rural/remote samples tested was 5.3% compared to 5.0% for the metropolitan population. Our results are also at odds with other studies [1, 7, 23, 28–30], and reflect a significant level of exposure in the metropolitan Brisbane Queensland population without clinical manifestation, compared to more overt disease seen in the rural population. The general awareness of the disease may be higher in the rural/remote communities resulting in more Q fever testing being performed. The encroachment of urban housing at the outskirts of cities on land previously used for rural purposes, in particular cattle grazing and abattoir sites, and the fact that Queensland cities are intermittently enveloped by dust storms originating in rural areas and containing Q fever particles, may have resulted in further unrecognised metropolitan cases [1]. Finally, there may also be a potential for spread of the disease from domesticated animals such as parturient cats [31, 32].

The notification data support observations made by others, that males are more often diagnosed with Q fever than females [19, 33, 34]. This presumably is due to the fact that occupational exposure is the primary cause of infection and occurs predominantly in the male workforce. Although

the seroprevalence data supported this finding, the ratio of male to female exposure to Q fever was less pronounced. This may be explained by an increasing need and interest from women to be involved in animal handling jobs that may have previously been performed by men and hence increasing their risk of disease; or perhaps women are exposed via their male partners with a lower dose and go on to develop an asymptomatic infection.

The seroprevalence of 8.0% in the Queensland adult population was low compared to other seroprevalence studies performed in Australia and overseas (Table 2), which show values ranging from 3% to 66%. However most of these studies are performed on "at risk" populations such as rural workers or a general population of adult age. This studied however investigated samples taken from the general Queensland population which included subjects with a varied age range.

There are a limited number of seroprevalence studies that have investigated Q fever in a paediatric population. Previous studies have been limited by either small numbers of samples, and being drawn from a high risk population. The seroprevalence of 1.3% in our paediatric sample set reflects results reported by others in a recent study of children <15 years of age from South West Queensland, which showed a seroprevalence rate of 2.5% from 237 samples examined [35]. However theses children are known to reside in a high risk area according to the notification data and previous reports [16].

Overall, our results support the hypothesis that currently the greatest risk of Q fever infection in Queensland is for males living or working in a rural environment. Although the seroprevalence in children is significantly lower than adults, of concern is the observation that the average annual notification rate of Q fever in Queensland children has increased nearly four-fold over the last 7 years. The reasons for this are unclear but the introduction of the NQFMP may have increased awareness of the disease and the use of diagnostic testing. This highlights the need to closely examine public health measures which may prevent or limit the acquisition of Q fever in the paediatric population, and vaccination for children and adolescents in high-risk settings should be considered.

Conclusion

Q fever is a vaccine preventable disease in Australia. We have shown an unexpectedly high seropositivity in our metropolitan Brisbane population, who have previously been thought of as low risk of Q fever exposure. Similarly, children are an emerging group at risk. Further work is needed to improve Q fever awareness in unexpected and

Table 2 Q fever seroprevalence studies

Publication year	Origin	Seropositive	Sample, *n*	Positives, *n*	Population	Ages	Author
1980	Brisbane Queensland	16%	139	22	Meat workers	Adults	McKelvie [37]
1984	Adelaide South Australia	45%	1922	875	Abattoir	Adults	Mamion et al. [13]
1986	Switzerland	7-32%	5446	381-1743	General	Adults	Dupuis et al. [38]
1987	Netherlands	37% 70%	30 65	21 19	General dairy farming	0–14 years	Richardus et al. [39]
1995	England	19%	730	143	Farming	10–70 years	Thomas et al. [40]
1995	Nova Scotia	15%	492	72	General	18–70 years	Marrie and Pollak [30]
1999	New South Wales	11%	829	89	Abattoir	Adults	Casolin [36]
2000	New South Wales	27%	1417	394	Cattle handlers	Adults	Hutson et al. [41]
2001	Germany	22%	1651	51	General	Adults	Hellenbrand et al. [42]
2001	Central Queensland	19%	272	49	Rural/farming	12–79 years	Taylor et al. [43]
2003	Kimberly Western Australia	66%	59	39	Rural/farming	16–65 years	Mak et al. [44]
2006	Barcelona	15.3%	216	33	General	0–91 years	Cardenosa et al. [45]
2006	Eastern Turkey	19.5%	92	18	Cattle farmers	Adults	Seyitoglu et al. [46]
2008	Ankara Turkey	32%	601	194	General	18–61 years	Kilic et al. [47]
2008	Ireland	13%	2394	306	General	12–64 years	McCaughey et al. [48]
2009	USA	3%	4437	133	General	>20 years	Anderson et al. [49]
2010	South West Queensland	7%	447	29	Rural	<25 years	Parker et al. [35]
2010	Northern Turkey	12.3%	407	50	General	>5 years	Gozalan et al. [50]

emerging subgroups, and it may be, in high risk areas, preventive programs could be considered.

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