Risk factors and burden of acute Q fever in older adults in New South Wales: a prospective cohort study

Abstract

Objectives: To measure the acute burden of and to identify risk factors associated with notified Q fever in older adults in New South Wales.

Design, settings and participants: A prospective cohort of adults aged 45 years and over (the 45 and Up Study) recruited during 2006–2009 and followed using linked Q fever notifications, hospital records and death records during 2006–2012.

Main outcome measures: Incident cases of Q fever, based on a linked Q fever notification; proportion of cases with a Q fever-coded hospitalisation.

Results: A total of 266 906 participants were followed up for 1254 650 person-years (mean, 4.7 ± 1.0 years per person). In our study population, the incidence of notified Q fever during follow-up was 3.6 (95% CI, 2.7–4.8) per 100 000 person-years. After adjustments, age (≥ 65 years v 45–54 years: hazard ratio [HR], 0.39; 95% CI, 0.16–0.96), sex (women v men: HR, 0.48; 95% CI, 0.26–0.88), and area and type of residence ($P < 0.001$ for trend) remained significantly associated with Q fever. Compared with those living in an inner regional area but not on a farm, the risk of notified Q fever was highest for those living on a farm in outer regional or remote areas (HR, 11.98; 95% CI, 5.47–26.21), followed by those living on a farm in inner regional areas (HR, 4.95; 95% CI, 1.79–13.65). Of notified Q fever cases, 15 of 39 (38%) had been hospitalised with a diagnosis consistent with Q fever.

Conclusions: Adults living on a farm in outer regional and remote areas are at a substantially greater risk of contracting Q fever. This suggests that, as well as targeting specific occupational groups for vaccination, there would be benefits in increasing public awareness of Q fever and vaccination among those living on and near farms in outer regional and remote areas of Australia.

Q fever is a highly infectious zoonotic disease caused by the bacterium *Coxiella burnetii*.[1-3] The main reservoirs for this bacterium are domestic and wild animals, and it can be excreted in their urine, faeces, milk and products of conception, and can survive in harsh environmental conditions.[1] Transmission to humans occurs mainly through direct contact with infected animal products or by inhalation of contaminated dust or aerosols.[4] In humans, Q fever manifests as an acute flu-like illness or, less frequently, with pneumonia or hepatitis; infection is often asymptomatic.[1] Chronic Q fever, most frequently presenting as endocarditis, occurs in about 5% of symptomatic cases.[1] Q fever fatigue syndrome is the most frequently reported sequela of acute infection (10%–20% of cases).[5]

A Q fever vaccine is available in Australia and is recommended for those at high occupational risk of infection.[6,7] During 2001–2006, the federal government funded the National Q Fever Management Program (NQFMP) in various states, including New South Wales; under this program, people at high risk were screened and vaccinated, including abattoir workers, sheep shearers, and sheep, dairy and beef cattle farmers and their farm workers. Uptake of the vaccine was almost 100% among abattoir workers and about 43% among farmers; the program significantly reduced the number of notified cases of Q fever in abattoir workers.[7] National notification rates suggest there was some decline in the incidence of Q fever during 2006–2009 — from 2.0 to 1.4 notified cases per 100 000 population — but this was followed by a gradual return to 2.0 cases per 100 000 population by 2014; the highest reported rates were among adults aged 45–69 years.[8]

Most epidemiological studies have been retrospective and focused on specific occupational groups,[9,10] and there are only limited data on factors associated with Q fever risk outside these populations. We therefore examined the risk and acute burden of Q fever in a population-based prospective study of Australian adults aged 45 years and over living in NSW.

Methods

Participants

We used data for participants recruited in NSW during 2006–2009 for a prospective study of adults aged 45 years and over (the Sax Institute's 45 and Up Study); the recruitment procedures have been published elsewhere.[11] In brief, NSW residents aged 45 years or over were randomly selected from the Australian Medicare database and invited to participate. The 45 and Up Study oversampled residents in rural and remote areas, and those aged 80 years and over. At recruitment, participants completed a baseline questionnaire that provided information on their sociodemographic factors, behaviour and health.[12]

Participants consented to long-term follow-up and linkage of their data.[11] For the study described in this article, participants were linked to the NSW Notifiable Conditions Information Management System (NCIMS), the NSW Admitted Patient Data Collection (APDC) and the NSW Registry of Births, Deaths and Marriages (RBDM). The NSW Centre for Health Record Linkage (CHeReL) performed the linkage independently of the study investigators, using probabilistic matching.

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The NCIMS database records all notifications of Q fever in NSW residents; it includes information on the date of onset and details of laboratory confirmation, including the type of specimen used. Notifications of Q fever require laboratory definitive evidence or laboratory suggestive evidence together with clinically compatible disease (Box 1).[13] The APDC records information about all admissions to hospitals in NSW, including the date of admission and discharge, the primary diagnosis, and up to 49 secondary diagnoses affecting treatment or length of stay, coded according to the International Classification of Diseases, 10th revision, Australian modification (ICD-10-AM). The RBDM records the date of death of NSW residents.[14] For this study, the data from the NCIMS and RBDM were complete to 31 December 2012, and the APDC data were complete to 30 June 2012.

All participants provided written informed consent. This study was approved by the NSW Population Health Research Ethics Committee (approval number, 2010/12/292) and the University of New South Wales Human Research Ethics Committee.

1 Australian national notifiable diseases case definitions — Q fever[13]

Confirmed case

A confirmed case requires either:

1. Laboratory definitive evidence

OR

2. Laboratory suggestive evidence AND clinical evidence.

Laboratory definitive evidence

1. Detection of *Coxiella burnetii* by nucleic acid testing

OR

2. Seroconversion or significant increase in antibody level to Phase II antigen in paired sera tested in parallel in absence of recent Q fever vaccination

OR

3. Detection of *C. burnetii* by culture (note this practice should be strongly discouraged except where appropriate facilities and training exist.)

Laboratory suggestive evidence

Detection of specific IgM in the absence of recent Q fever vaccination.

Clinical evidence

A clinically compatible disease ◆

Outcome definitions

The study outcomes were incident Q fever diagnoses (cases) and the proportion of these patients who were admitted to hospital. We defined participants as having an incident Q fever diagnosis if they had a linked record of notified Q fever in the NCIMS database after recruitment. Cases of Q fever with linked hospital records between 6 weeks before and after the Q fever notification date were examined, and classified as follows:

- primary Q fever: at least one hospitalisation for which the ICD-10-AM code A78 was recorded as the primary diagnosis
- secondary Q fever: at least one record including A78 as a secondary diagnosis
- Q fever-related: no A78 codes but one of the following primary diagnoses recorded: A49.9 (bacterial infection, unspecified), B17.9 (acute viral hepatitis, unspecified), B34.9 (viral infection, unspecified), J18.9 (pneumonia, unspecified organism), or R50.9 (fever, unspecified);[15,16] and
- presumed unrelated: none of the above recorded.

The 6-week window was chosen because most cases of acute illness resolve within 6 weeks of onset.[17] The number of deaths among notified Q fever patients within 6 weeks of the recorded onset of disease were determined.

Statistical analyses

Analyses excluded those with a record of Q fever notification before study recruitment. Person-years at risk were calculated from the date of study recruitment to the date of Q fever onset or death, or 31 December 2012, whichever occurred first. Hospitalisation analyses were restricted to cases with a diagnosis date on or before 20 May 2012; ie, 6 weeks before the last date for which we had complete hospital records. This restriction was imposed to ensure that all hospitalisation events within 6 weeks of the onset of Q fever were captured.

The incidence of notified Q fever cases was estimated according to age (stratified as 45–54 years, 55–64 years and 65 years or older); sex; area and type of residence (a composite variable that includes both area of residence — major city, inner regional or outer regional/remote/very remote, according to the Accessibility/Remoteness Index of Australia [ARIA+] — and accommodation type — living on a farm or not); smoking history (never or ever smoked); and number of hours spent outdoors each day (less than 4, 4 to less than 8, 8 hours or more).

We used Cox proportional hazard models to estimate unadjusted (univariate) hazard ratios (HR) for Q fever according to these characteristics. Variables associated with Q fever ($P < 0.1$) were included in a multivariable model, with the final model determined using a backward elimination method. Variables for which $P < 0.05$ were retained in the final model. Missing categories were only included in the multivariable model and reported if the proportion of missing cases was greater than 5%.

We also examined the proportion of notified patients who were hospitalised, their concurrent diagnoses on admission, and, for those with a Q fever-coded hospitalisation, the median length of stay. Kruskal–Wallis

tests were used to compare the median number of hours spent outdoors each day according to area and type of residence. $P < 0.05$ was defined as statistically significant. All analyses were performed with Stata 12 (StataCorp).

Results

After excluding 202 participants with notified Q fever before recruitment, our analysis included 266 906 participants who were followed up for 1 254 650 person-years (mean follow-up time, 4.7 ± 1.0 years per person). The mean recruitment age was 62.7 ± 11.2 years, and 53.6% were women. There were 45 participants with a linked Q fever notification during follow-up (for 44 there was positive serological evidence; for one, the diagnosis method was unknown).

In our study population, the incidence of notified Q fever was 3.6 (95% CI, 2.7–4.8) per 100 000 person-years. The relationship of incidence with various sociodemographic characteristics is shown in Box 2. In unadjusted models, age ($P = 0.01$), sex ($P = 0.03$), area and type of residence ($P < 0.001$ for trend), and time spent outdoors each day ($P < 0.001$ for trend) were significantly associated with Q fever notification, while smoking was not ($P = 0.8$). Only age ($P = 0.03$), sex ($P = 0.02$), and area and type of residence ($P < 0.001$ for trend) remained significant in the multivariable model. There was a gradient of increasing risk according to geographic area and residence on a farm. Those living on a farm in outer regional/remote areas were at greatest risk, followed by those living on a farm in inner regional areas, with those not living on farms least at risk (Box 2). The relative risk of Q fever for those aged 65 years or over was significantly lower than for younger participants, and was also lower for women than men (Box 2). The amount of time spent outdoors each day was related to the area and type of residence, ranging from 2.6 hours for living in a major city to 4.6 hours for those living on a farm in outer regional/remote areas (Kruskal–Wallis test, $P < 0.001$). However, differences in time outdoors did not remain significant ($P = 0.4$ for

2 Incidence of and hazard ratios for notified Q fever in NSW according to various sociodemographic characteristics, 2006–2012

	Cases	Population	Person-years	Incidence per 100 000 person-years (95% CI)	HR* (95% CI)	Adjusted HR† (95% CI)
All participants	45	266 906	1 254 650	3.6 (2.7–4.8)		
Age group						
45–54 years	16	78 756	377 770	4.2 (2.6–6.9)	1.00	1.00
55–64 years	22	85 654	408 515	5.4 (3.5–8.2)	1.27 (0.67–2.42)	1.20 (0.63–2.29)
≥ 65 years	7	102 496	468 365	1.5 (0.7–3.1)	0.35 (0.14–0.85)	0.39 (0.16–0.96)
Sex						
Men	28	123 766	579 608	4.8 (3.3–7.0)	1.00	1.00
Women	17	143 140	675 042	2.5 (1.6–4.0)	0.52 (0.28–0.95)	0.48 (0.26–0.88)
Smoking						
Never	27	152 427	718 838	3.7 (2.6–5.5)	1.00	na
Ever	18	113 052	529 243	3.4 (2.1–5.4)	0.90 (0.50–1.64)	na
Area and type of residence						
Major city	‡	120 267	562 377	0.2 (0.1–1.3)	0.07 (0.01–0.55)	0.07 (0.01–0.54)
Inner region; not on farm	10	84 699	398 756	2.5 (1.3–4.7)	1.00	1.00
Outer region/remote; not on farm	11	42 006	198 012	5.5 (3.1–10.0)	2.21 (0.94–5.21)	2.21 (0.94–5.21)
Inner region; on farm	6	9 082	43 511	13.8 (6.2–30.6)	5.51 (2.00–15.15)	4.95 (1.79–13.65)
Outer region/remote; on farm	17	10 657	51 090	33.3 (20.7–53.5)	13.28 (6.08–29.01)	11.98 (5.47–26.21)
Time spent outdoors§						
< 4 hours/day	19	172 874	814 719	2.3 (1.5–3.6)	1.00	1.00
4–7 hours/day	14	57 363	269 247	5.2 (3.1–8.8)	2.23 (1.12–4.45)	1.21 (0.58–2.51)
≥ 8 hours/day	6	16 432	76 995	7.8 (3.5–17.3)	3.35 (1.34–8.38)	1.20 (0.45–3.19)
Missing data	6	20 237	93 689	6.40 (2.9–14.2)	2.74 (1.09–6.86)	1.93 (0.75–4.93)

HR = hazard ratio; na = not applicable. * Unadjusted results. † Variables in final model: age group, sex, area and type of residence. ‡ Number of cases not displayed due to small numbers. § Adjusted for age group, sex, and area and type of residence. ◆

trend) after adjustment for area and type of residence in the multivariable model.

Of 45 incident notifications, we had complete follow-up of hospital records for 39 patients. Of these, 17 (44%) were hospitalised at least once (for any cause) within 6 weeks of the recorded disease onset date (before or after onset). The hospitalisation was coded as being for Q fever in 15 cases (seven patients with primary Q fever or secondary Q fever, eight as Q fever-related). The median length of stay for patients with these diagnoses was 4 days (interquartile range, 3–9 days). There were no deaths or intensive care unit stays recorded for the notified cases.

According to the APDC database, 11 participants had been hospitalised with primary Q fever or secondary Q fever, but four of these were not recorded as Q fever cases in the NCIMS database.

Discussion

This is the first population-based prospective study of the risk and burden of acute Q fever in a general adult population in Australia. We found that a clear increase in the risk of notified Q fever in adults was associated with living on a farm and with geographic remoteness. Those living on farms in outer regional and remote areas were at highest risk, and the hazard was lowest for those living in major cities. Risks were also greater for those under 65 years of age and for men, but risk was not increased for smokers or associated with greater time spent outdoors. Fifteen of 39 notified Q fever cases (38%) were hospitalised with a diagnosis consistent with Q fever.

In this study, we observed an incidence of notified Q fever of 3.6 per 100 000 person-years, with the highest rate among those aged 55–64 years (5.4 per 100 000 person-years). This is broadly consistent with Q fever notification rates for the total NSW population aged 45 years or over reported during 2009–2012 (2.9 per 100 000 persons, with the highest average annual rates for those aged 55–64 years: 4.1 per 100 000 persons).[7,8,18] The slightly higher disease burden in our study is not surprising, as the 45 and Up Study oversampled the residents of rural and remote NSW, where Q fever notification rates are much higher than in urban centres.

We estimated that the notified Q fever risk was about five times higher for adults living on a farm in inner regional areas and about 12 times higher for those living on a farm in outer regional and remote areas than for those in inner regional areas not living on a farm. This finding is consistent with other reports that found farmers to be at greater risk of Q fever,[18,19] and suggests that immunisation coverage in this group is inadequate. Even though the NQFMP provided free vaccination to farmers, uptake was estimated to be only about 43%, and in NSW the vaccination program ended in 2004.[7] After allowing for workforce turnover, it is likely that an even lower proportion of current farmers have been vaccinated. An alternative explanation would be that vaccine-induced immunity has waned, but there is good evidence that the vaccine is highly effective, with immunity lasting for at least 5 years and probably for life.[20]

Massey and colleagues[19] have suggested that demographic factors other than occupation should be identified to better define risk groups, as a fifth of notified Q fever cases from rural areas did not report occupational exposure to Q fever. Similarly, the recent major Q fever outbreak in the Netherlands found that people living near farms, but not specifically working on one, were also at increased risk of disease.[21-23] We did not have information on the occupations of participants in our study, but our finding of increased Q fever risk for those living in more remote areas but not living on a farm are consistent with the results of these other studies. Taken together, they support calls for medical practitioners in regional and remote Australia to routinely consider Q fever in their differential diagnosis of acute flu-like illnesses, even for patients not living on farms.[24]

We also examined other factors potentially relevant to Q fever risk. Time spent outdoors was not significant in our multivariable model, as any effect was almost completely explained by the area and type of residence variable. There was no indication of an increased risk for smokers. A significant fraction (44%) of notified Q fever cases had been hospitalised. This is within the higher range of hospitalisation estimates reported by an extensive review.[1] Studies suggest that up to 20% of those with Q fever will develop chronic conditions, such as endocarditis or chronic fatigue syndrome, that also require health care outside of hospitals, and which also entail losses of productivity and quality of life.[14,25-27] This lends further weight to calls for improving disease prevention efforts.

We identified 15 cases of Q fever for which a hospitalisation code consistent with Q fever was recorded, but only seven were specifically coded as Q fever (ICD-10-AM, A78). This suggests that limiting analysis to hospital admissions specifically coded as primary or secondary Q fever diagnoses is likely to substantially underestimate the true burden of Q fever-related morbidity. We also identified four participants linked to hospitalisations coded as Q fever, but for which there was no record of Q fever in the NCIMS database. It is possible that these were clinically compatible cases that did not meet the case definition of confirmed Q fever because of negative diagnostic test results, and were therefore not notified, or it may indicate under-reporting of genuine cases.

To our knowledge, our study is the first using prospectively ascertained events to examine the risk and burden of Q fever in older adults in a general population of Australian residents. Our study encompassed a time period during which no major Q fever outbreaks were reported, and thus more accurately assesses the risk and burden of endemic Q fever. Potential limitations include the fact that we used notification data to identify Q fever cases, and such data usually underestimate the number of

infections; they may also depend on the propensity of physicians to consider the diagnosis, which may differ according to the characteristics of their patients. In addition, we had no data on the occupations or the vaccination status of participants. The numbers of Q fever cases were relatively small, leading to wide confidence intervals for the risk estimates. Similarly, the small numbers meant that we could not stratify the "ever smoked" category into current and past smokers. Finally, the study cohort was probably healthier than the overall NSW population of the same age range, as indicated by a lower rate of smoking.[11]

In conclusion, our results support current recommendations for Q fever vaccination of farmers and add to the existing body of evidence that suggests targeting a broader, geographically based population in regional and remote regions is required to reduce the burden of Q fever in Australia.

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