Q fever: Are we protecting our vets, nurses and clients?

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Background
Q fever is a significant worldwide zoonosis caused by the bacterium *Coxiella burnetii*. It is the most common, non-food-borne, notifiable zoonosis in Australia with 400 – 600 medically diagnosed notifications in humans annually (http://www9.health.gov.au/cda/source/rpt_2.cfm). An estimated 40% of primary infections in humans are symptomatic, with serious acute (influenza-like) or persistently focal debilitating illnesses possible, including endocarditis, hepatitis, post-Q fever fatigue syndrome and recrudescent granulomatous lesions in bone or soft tissue. The very specific and sometimes complex nature of testing required to confirm a diagnosis in humans,[1] means that ongoing vigilance in promptly recognising clinical cases in humans and reappraisal of the potential risks created by animal exposure is required.

The bacterium itself has a duplicitous lifecycle: a metabolically active form that is obligated to replicate within macrophage cell lineage while an inactive form has extreme environmental resilience, providing a means to travel to new cells and new hosts. The bacterium has a potentially large, seemingly asymptomatic reservoir encompassing wild and domestic mammals, birds and arthropods.

The prevalence of *C. burnetii* in different species varies worldwide with geographical location and method of testing. Most *C. burnetii* prevalence studies measure serological or antibody evidence of previous exposure via Indirect immunofluorescence assay (IFA), Enzyme linked immunosorbent assay (ELISA) or the complement fixation test (CFT), however some studies utilise polymerase chain reaction (PCR) to look for actual bacterial DNA (e.g. measure/detect shedding of bacteria in milk). Bacterial culture is not routinely performed due to the requirement for physical containment level 3 (PC3) facilities due to the bacterium's zoonotic nature. One of the major problems with trying to compare, evaluate and assess risk from these studies is that there is variation in the method used, what the method actually measures and validation of the testing methodology utilised.[2] Methodologies such as CFT are now considered insensitive compared to newer technologies such as IFA, ELISA and PCR.

Recently, NSW Health developed a General Practitioner (GP) training module aimed at expanding GP knowledge of the broader host range and risk factors to ensure practitioners are cognisant of the potential for Q fever to be the cause of disease in a broad range of the human population and to appropriately pursue diagnostic testing. In the veterinary profession, this has traditionally focused on practitioners treating ruminants but with cases of Q fever seen in veterinary personnel treating non-traditional species this diagnostic algorithm needs broadening.

Livestock
Notifications of Q fever disease occur in people across all age groups with overrepresentation of males aged 40 to 69.[3] There is overrepresentation of those in occupations associated with the livestock (sheep, cattle, feral and farmed goats) or food and fibre production industries (including abattoir workers, meat inspectors, dairy farmers, shearers, and veterinarians).[4] A recent Australian report indicated that association with cattle was the most commonly reported risk factor.[5]
Published studies on prevalence of *C. burnetii* in ruminant species in Australia are few, and additionally, many are older studies.[6] A meta-analysis of 69 selected publications reporting prevalence of *C. burnetii* in ruminants worldwide came up with a seroprevalence of 20% in cattle and 15% in sheep and goats.[7] One of the largest outbreaks of Q fever associated with intensive dairy goat farming occurred in The Netherlands (2007 – 2010). During this outbreak, a total of 4,026 human cases were notified and it is likely that up to 44,000 individuals were infected. Deaths are still ongoing due to the chronic nature of the disease however, as of 2016, had reached 74 people. Infection is thought to have been associated with at least 10 separate genotypic clusters and therefore with multiple sources of exposure. In 2012-13, an outbreak of Q fever associated with a dairy goat farm occurred in Victoria, Australia in which 18 cases were reported over a 19 month period[8] and the follow on from this outbreak will be discussed further in another presentation at this conference. There have been few recent studies of prevalence of *C. burnetii* in goats specifically in Australia, however a study in feral goats at abattoir in South Australia published in 1981 described a prevalence of 51.5% (method not specified)[9] and another study published in 1979 found two out of 20 feral goats (10%) were serologically positive on CFT.[10]

As with goats, there are few studies of prevalence of *C. burnetii* in Australian sheep and cattle however one study of beef cattle in Northern and north west Queensland reported a seroprevalence of 16.8% by ELISA[11] and another study of sheep (n=50) and beef cattle (n=329) in Western Australia found antibodies against *C. burnetii* with a commercially available ELISA in 0.5% of animals tested and ~11% animals were positive on faecal PCR.[12] Less recent studies include one of beef cattle from northern South Australia that examined 617 head on 10 properties finding only a single positive on one property by CFT,[13] another study of Victorian dairy cattle (1,576 cattle from 49 herds) whereby 8/1576 cows (0.5%) in 6/49 herds were positive by CFT serum;[14] and finally a study of Victorian dairy cattle and NSW beef or dairy cattle which detected no positives by CFT.[15] The latter three studies all utilised CFT which is known for its low sensitivity as a means of detecting previous exposure to *C. burnetii*.[6]

**Companion animals**

Reports of feline or canine associated Q fever cases in humans are infrequent given the millions of cats and dogs worldwide, which may imply low carriage rates in these animal species. Supporting this notion is the finding that cat and dog ownership is not associated with increased seroprevalence of antibodies to *C. burnetii* in humans.[16] However the consequence of Q fever for those individuals at risk such as unvaccinated veterinary personnel or breeders of pets, both of which are more likely to be exposed to peri-parturient pets, may be severe.[17-19]

A survey of Australian cat breeders found a significant Q fever knowledge gap amongst cat breeders with potential associations between risky husbandry practices and Q fever transmission as well as a higher rate with medically diagnosed Q fever (6% compared with mean annual notification rate of general Australian population of 0.002%; even considering sample bias of the survey, this is alarming).[20] As veterinarians we are responsible for the health and welfare of our staff and clients whilst in the clinic environment or externally whilst under our professional guidance, so it is essential that we provide adequate education of Q fever risks and facilitate prevention measures such as vaccination.[21] Following outbreaks of Q fever within small animal veterinary practices in Australia resulting from peri-parturient cats and dogs and the subsequent research at the Sydney School of Veterinary Science, cat and dog breeders have been added to the Australian Immunisation Handbook as an ‘at risk’ group recommended for Q fever vaccination. A broad and coordinated approach is required for future research from medical and veterinary clinicians and researchers, to raise the profile of Q fever
as a diagnostic consideration and to investigate the rate at which dogs and cats may shed the bacterium.\[19\]

Determining *C. burnetii* infection in dogs and cats has been complicated by the lack of confirmed disease associations and until recently, the absence of standardised sensitive and specific diagnostic techniques.\[22, 23\] The standardisation of serological tests for determining *C. burnetii* exposure in cats and dogs has been hampered to some extent by the absence of clearly identified clinical disease associations (coxiellosis) in these animal species (limiting the ability to define true positives and negatives) and the dangers of laboratory culture of this bacterium, which requires high security PC3 facilities. The tendency of many researchers looking at the broader question of the prevalence of infection in dog and cat populations therefore has been to extrapolate diagnostic testing methods and cut off points used for human serum or to use positive and negative controls from non-canine or non-feline species which raises questions over the reliability of results. Shapiro and colleagues\[22, 23\] used the serum from cats/dogs at the centre of a Q fever cluster in small animal veterinary practices in NSW, to validate the use of IFA for serological testing in these species.

Reported isolated outbreaks of community acquired Q fever related to dog or cat contact has stimulated opportunistic seroprevalence studies searching for answers as to how widespread infection of cats and dogs may be. In maritime Canada, exposure to parturient cats and newborn kittens has been identified as a significant risk factor for Q fever,\[24\] with seroprevalence of *C. burnetii* infection in cats in these regions varying from 6.2 to 32%. In other countries (such as South Africa, Japan and USA), seroprevalence has ranged from 1.9 to 42%. However the serological testing methods varied between studies with explanation of positive and negative controls insufficient to determine the choice of cut off value. In contrast, some studies have cross checked results from other methods and used serum samples from cats at the centre of a Q fever outbreak in humans to determine positive controls.\[25\] Thus, comparison of results of differing studies should not be performed without knowledge and critique of the methods used. In Australia, seroprevalence was highest in cattery-confined breeding cats (9.3%) while virtually absent from pet (1%), shelter (0%) or feral cats (0%) although the recent outbreak associated with an animal shelter in SE QLD indicates that shelter animals should not be ruled out as a source of infection.\[19\] Dogs from Aboriginal communities had the highest seroprevalence (6.5%) while breeding (2.3%), pet (3%) or shelter dogs (1.9%) had much lower rates of exposure to *C. burnetii*.\[22, 23\]

Other seroprevalence studies in dogs have produced variable results (0%-35%) using ELISA or IFA from dogs sampled in Canada, Italy, Egypt, France and French colonies, Australia and post-Iraq military deployment dogs from USA. Again, the variation in methods used, explanation (or absence) of positive and negative controls, description of sample population and determination of cut off values makes comparison between studies difficult and determination of real prevalence in dog populations complex from these data.

Recently, molecular methods used to determine the presence of *C. burnetii* DNA on vaginal or uterine tissues of healthy cats pre or post-desexing in USA found 4/47 pet cats (8.5%) had evidence of *C. burnetii* DNA.\[26\] In a more recent study by the same research group,\[27\] uterine tissues of 26 normal cats and 11 cats with histopathological evidence of uterine disease or other reproductive abnormalities were evaluated for the presence of *C. burnetii* DNA using a PCR amplifying the *IS1111* insertion sequence of *C. burnetii* identified three positive samples, two of which were from cats with normal reproductive systems. In the Netherlands following the 2007-2010 Q fever outbreak, *C. burnetii* DNA was not detected in placentas from cats (n=15) but was found in four of
54 (7%) dog placentas derived from veterinary clinical practices focused on breeding pets.\(^{[28]}\) A molecular study in Italy examining over 100 cases of feline and canine abortion and neonatal mortality for evidence of a range of aetiologic agents did not find \textit{C. burnetii} or \textit{Leptospira}. A study from Japan published nearly 30 years ago examined deep vaginal swabs from healthy and sick cats from three clinics in Shizuoka city and using an inoculation model (into mice; so not a molecular method but a validated one) found 31% of 29 cats carrying the bacterium (mixture of sick and healthy).

Future research into the potential role that our closest companions may play in Q fever needs to take a broader population perspective, comparing the incidence of Q fever and prevalence of prior infection in subpopulations of potentially at-risk people such as veterinary personnel, and dog and cat breeders, with the broader Australian population. From a canine and feline perspective, further refinement and standardisation of serological assays and molecular methods is required to determine the true prevalence of asymptomatic infection, persistence of infection, and to explore potentially unrecognised disease associations and risk factors within subpopulations of the stray, feral, pet and breeding cat and dog subpopulations.

**Wildlife**

In the natural lifecycle of \textit{C. burnetii}, transmission occurs between wildlife and birds and their ticks enabling spread to livestock and companion animals which are then a source of infection for humans\(^{[29]}\). However, recently, a rise in notifications in people reporting direct contact with wildlife (especially macropods) and no contact with other sources such as livestock has been identified\(^{[5, 30]}\). In the small number of seroprevalence studies in macropods in Australia, rates of prior exposure to \textit{C. burnetii} of 20-25% have been reported\(^{[31, 32]}\) and \textit{C. burnetii} DNA has been detected in faeces of kangaroos co-grazing with livestock\(^{[12]}\). However it was not known whether this represented infection or passage of environmental bacteria through the gut. In a pilot study of raw meat sold for pet consumption by our research group, \textit{C. burnetii} DNA was identified in samples containing kangaroo. While all these studies suggest a potential role for macropods, particularly kangaroos, as a source of \textit{C. burnetii} infection for humans, there have been no studies that have investigated the cycle of infection of \textit{C. burnetii} in kangaroos. The role of other native Australian mammals or wildlife is currently uncertain.

**Prevention**

Given the known possibility of Q fever in a broad range of veterinary personnel there is a need to ensure all staff are adequately protected against Q fever. Two resources providing excellent guidelines for prevention of Q fever in veterinary practice include the AVA Biosecurity Guidelines 2017 (http://www.ava.com.au/sites/default/files/Guidelines-for-veterinary-personal-biosecurity-2017-FINAL.pdf ) and the NSW Health Q fever and veterinarians factsheet http://www.health.nsw.gov.au/infectious/factsheets/pages/q-fever.aspx. Their recommendations include vaccination as the primary prevention method but also training in infection control, precautions specific to birthing and caesareans including disinfectants and waste disposal, and the recommendation that snout-to-mouth resuscitation never be performed.

Recommendations for personal protective equipment (PPE) include the wearing of gloves and outerwear such as overalls, as well as the wearing of a P2 surgical mask by all staff in the vicinity of a caesarean. One feature of the outbreak associated with a cat caesarean in a small animal hospital in outer Sydney\(^{[17]}\) was that staff that were absent from the premises on the day of the caesarean, still seroconverted or contracted Q fever through exposure to aerosolised viable bacteria on their subsequent return to the practice the following day. This indicates that PPE would have to be worn beyond the
immediate period of exposure due to the ability of the organism to be aerosolised and its long (two week) survival period as an aerosol. Thus, vaccination and strict infection control practices are central to protection against acquiring this disease. Staff who are not immune to Q fever (from vaccination or previous infection) may be refused entry to the workplace under work health and safety legislation (federal legislation which all states and territories follow; https://www.legislation.gov.au/Details/C2017C00305).

Australia is the only country where vaccination is routinely offered with an effective vaccine (Q-VAX® vaccine produced by CSL Biotherapies) having been available since 1989. This vaccine is composed of a purified, formalin-inactivated suspension of C. burnetii (Henzerling strain).[^6] Vaccination involves skin and serological testing for previous exposure prior to administration. Those with evidence of previous exposure are not vaccinated due to the likelihood of severe adverse reactions. Efficacy is reported to be between 83 and 100%.

Due to their higher occupational risk, most veterinarians (~74%)[^33] across Australia are routinely vaccinated due to compulsory vaccination during veterinary training. Conversely less than 30% of veterinary nurses are vaccinated[^33], despite being similarly at risk. Barriers to vaccination among those not vaccinated did not differ between cohorts, and included a lack of perceived risk, financial expense, time constraints, and difficulty in finding a vaccine provider. Poor knowledge and awareness of Q fever disease and vaccination were additional and notable barriers for the veterinary nursing cohort, suggesting veterinary clinics and veterinarians may not be meeting their legal responsibility to educate staff about risks and risk prevention.

Further analysis[^34] of the data revealed the factors significantly associated with a willingness to recommend Q fever vaccination, expressed by 35% of veterinarians, were (a) being very concerned for their colleagues regarding C. burnetii, (b) disagreeing that the vaccine is harmful, (c) high Q fever knowledge, (d) working within small animal practice, (e) disagreeing that Q fever vaccination is expensive, and (f) age, with veterinarians under 39 years of age most likely to recommend vaccination. Of the veterinary nursing cohort seeking vaccination was significantly associated with (a) being convinced of the importance of the Q fever vaccine, (b) moderate to high Q fever knowledge, (c) working in Queensland, (d) working within livestock/mixed animal practice, (e) disagreeing that the vaccine is expensive, (f) strong reliance on work culture for biosecurity information, (g) perceiving personal level of exposure to C. burnetii to be at least low/moderate, and (h) agreeing the vaccine is safe while working within a corporate practice structure. These factors clearly identify the influence and responsibility that veterinarians have on and for workplace health and safety promotion.

Concerns about the safety of the Q fever vaccine (Q-VAX®) have been addressed in a survey of adverse events following immunisation (AEFI)[^35] with data collected from veterinary and animal science students at Australian universities. This study revealed that of the 60% (499/830) that responded, local injection site reactions (ISRs) occurred in 98%, of which 30% were severe. Systemic AEFI occurred in 60%. Medical attention was sought by 19/499 (3.8%) vaccinees, however no serious AEFI were reported. No significant difference was found for AEFI in 17–20 year olds versus those aged 21 years and over. These safety data are important for future Q fever vaccine programmes and suggest that although Q-VAX® is reactogenic, it is safe for use in young adults.

**Obligation to clients**
Under WH&S legislation veterinarians are similarly obligated to protect clients against Q fever as they would their staff (and families). This may include restricting unvaccinated clients from participating in parturition or caesarean sections within the
veterinary practice. While the recently-developed NSW Health GP Q fever training module is a step towards expanding GP knowledge of the broader host range and risk factors associated with Q fever, veterinarians are in a unique position to advise clients and owners of the risks of acquiring Q fever from their animals (particularly livestock and breeding clientele) and recommend seeking medical advice about vaccination to those identified as being at risk.

Clearly there is a role for all veterinarians in the prevention of Q fever no matter what stream of practice they are involved in. Our training and the growing number of readily available resources help prepare us for this role.

References


34. Sellens, E., et al., Willingness of veterinarians in Australia to recommend the Q fever vaccine to veterinary personnel: Implications for workplace health and safety compliance. PLoS ONE. Accepted for publication 22nd May 2018.