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Coxiella burnetii seroprevalence in unvaccinated veterinary workers in Australia: Evidence to support Q fever vaccination

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Abstract

Q fever (caused by *Coxiella burnetii*) is a serious zoonotic disease that occurs almost worldwide. Occupational contact with animals increases the risk of exposure, and Q fever vaccination is recommended for veterinary workers in Australia. This study aimed to investigate *C. burnetii* seroprevalence among unvaccinated veterinary workers in Australia and determine factors associated with a positive serological result. During 2014 and 2015, convenience sampling at veterinary conferences and workplace vaccination clinics was undertaken. Participants completed a questionnaire and provided a blood sample for *C. burnetii* serology. Participants were predominantly veterinarians (77%), but veterinary support staff, animal scientists, and administration workers also participated. Blood samples (n = 192) were analysed by an immunofluorescence assay and considered positive where the phase I or phase II IgG titre was ≥1/50. Seroprevalence was 19% (36/192; 95% CI 14%–25%). A positive serological result was significantly associated with (a) working in outer regional/remote areas (odds ratio [OR] 6.2; 95% CI 1.9–20.8; reference = major cities; p = .009) and (b) having spent more than 50% of total career working with ruminants (OR 4.8; 95% CI 1.7–13.5; reference = <15% of career; p = .025). These findings confirm an increased risk of exposure to *C. burnetii* compared to the general population, providing new evidence to support Q fever vaccination of veterinary workers in Australia.

KEYWORDS
Coxiella burnetii, Q fever, seroprevalence, veterinary workers

1 | BACKGROUND

Q fever is a disease of people caused by the zoonotic pathogen *Coxiella burnetii*, a small obligate intracellular Gram-negative bacterium (Angelakis & Raoult, 2010). Except for New Zealand and French Polynesia, *C. burnetii* has been described worldwide; occurring as sporadic cases, small clusters or large outbreaks such as occurred in the Netherlands in 2007–2010 (Million & Raoult, 2015; Roest et al., 2011). A range of non-specific symptoms may occur following exposure to *C. burnetii*, which vary according to the route of transmission, inoculum dose, geographical region and patient factors (Angelakis & Raoult, 2010). Infection may be asymptomatic, or present as a

self-limiting flu-like illness which often remains undiagnosed (Million & Raoult, 2015). However, some Q fever patients experience severe symptoms including but not limited to pneumonia, hepatitis, obstetric complications including foetal death, and persistent endocardial, vascular and osteoarticular infections (Angelakis & Raoult, 2010; Carcopino, Raoult, Bretelle, Boubli, & Stein, 2007; Million & Raoult, 2015, 2017). Post-Q fever fatigue syndrome (QFS) is experienced by up to 20% of Q fever patients and may persist for years with debilitating consequences (Morroy et al., 2016).

Many production, companion and wild animal species harbour *C. burnetii*, shedding bacteria into the environment in placental tissues, faeces, urine and milk (Angelakis & Raoult, 2011; Tozer et al., 2014). Large numbers of bacteria are also shed in the faeces of ticks, an important reservoir for the pathogen (Angelakis & Raoult, 2010). Cattle, sheep and goats have been implicated as the source of *C. burnetii* in most human Q fever outbreaks globally; however, other species including cats and dogs have been associated with disease in people (Angelakis & Raoult, 2010; Komiya et al., 2003; Kopecny, Bosward, Shapiro, & Norris, 2013; Marrie, Durant, Williams, Mintz, & Waag, 1988). Environments may remain contaminated with viable *C. burnetii* for many months, with bacterial spread occurring via wind and animal transport (Kersh et al., 2013; Nusinovici, Frossling, Widgren, Beaudeau, & Lindberg, 2015; Tissot-Dupont, Amadei, Nezri, & Raoult, 2004; Tozer et al., 2014; Wallensten et al., 2010). Inhalation is the primary route of infection for people, while transmission via ingestion, transcutaneous, transfusion and sex have also been reported (Angelakis & Raoult, 2010).

Since 1989, a Q fever vaccine for people (Q-VAX®, Seqiris Pty. Ltd.) has been licensed for use in Australia, where it is recommended for those with an occupational risk of exposure to *C. burnetii*, including abattoir workers, farmers and veterinary personnel (Australian Immunisation Handbook, 2018). Veterinary students at all Australian veterinary schools are routinely vaccinated prior to, or on commencement of their veterinary studies. As a result, approximately 74% of all veterinarians in Australia have sought vaccination for Q fever, with 61% receiving the vaccination and 12% unable to be vaccinated due to evidence of prior exposure to *C. burnetii* (Sellens et al., 2016). However, veterinary nurses in Australia report lower vaccine uptake, with only 29% having sought vaccination of which 24% are vaccinated. This is attributed to a variety of reasons a variety of reasons, including a perception that they are not at risk of exposure to *C. burnetii* (Sellens et al., 2016). Additionally, medical practitioners in Australia have reportedly advised veterinary workers against Q fever vaccination on occasion, due to a perception that the workers were not at risk of Q fever (Sellens et al., 2016). This is contrary to the recommendations of the Australian Immunisation Handbook, and evidence of Q fever disease primarily affecting support staff in outbreaks of Q fever in Australian veterinary clinics (Australian Immunisation Handbook, 2018; Gibbons & White, 2014; Malo et al., 2018; Maywood & Boyd, 2011).

Seroprevalence studies can be utilized to estimate exposure as antibodies against phase II *C. burnetii* are usually highly persistent following natural infection, with immunoglobulin (Ig) G persisting longer than other antibody classes (Teunis et al., 2013).

Impacts

- This research confirms that veterinary workers have an increased risk of exposure to *Coxiella burnetii* compared to the general population, providing evidence that supports recommending Q fever vaccination of veterinary workers in Australia.
- This research highlights that four out of five veterinarians in Australia who have not been previously vaccinated for Q fever may be eligible to receive the vaccine.
- This research will assist veterinary workers and medical practitioners in making informed decisions regarding Q fever prevention and vaccination.

Seroprevalence for *C. burnetii* has been reported for veterinary populations in other countries but not yet in Australia. Most commonly, immunofluorescence assays (IFA) for phase I and phase II IgG and IgM have been utilized, with these studies reporting a *C. burnetii* seroprevalence of 65.1% in Dutch livestock veterinarians (n = 189) (Van den Brom et al., 2013), 59.4% in small ruminant veterinarians and veterinary students in Ontario, Canada (Meadows et al., 2016), 58.3% in livestock veterinarians in Belgium (n = 82) (Pozzo et al., 2017), 18.7% in veterinary students in the Netherlands (n = 674) (de Rooij et al., 2012) and 13.5% in veterinarians in Japan (n = 267) (Abe et al., 2001). Enzyme-linked immunosorbent assays (ELISA) for phase I and II IgG were utilized in studies reporting a *C. burnetii* seroprevalence of 22.2% and 38.2% in veterinarians in the United States (n = 508) and Germany (n = 424), respectively (Bernard et al., 2012; Whitney et al., 2009). Complement fixation for phase II IgG was utilized to study veterinary students in Spain where *C. burnetii* seroprevalence was reportedly 11.0% (Valencia, Rodriguez, Puñet, & Blas Giral, 2000). Risk factors for seropositivity were similar between these studies, with recurrent factors including increasing age or years of veterinary work or study, increasing contact with livestock and rural location.

This study aimed to investigate the *C. burnetii* seroprevalence among unvaccinated veterinary workers in Australia. These data are essential for gaining an understanding of the risk of exposure to *C. burnetii* associated with veterinary work in Australia, including support and administration roles. The findings will assist veterinary workers and medical practitioners in making informed decisions regarding the prevention of Q fever, particularly with regard to Q fever vaccination.

2 | METHODS

2.1 | Study design and recruitment

This study utilized convenience sampling to survey the veterinary workforce in Australia. Participation required the provision of a blood sample and completion of a paper questionnaire.

Box 1 *Coxiella burnetii* serology classification criteria applied to veterinary workers participating in a seroprevalence study in Australia, 2014–2015. Criteria were adapted from Healy et al. (2011).

	Criteria
Serological result	
Positive	Phase II or phase I IgG titre ≥1/50
Equivocal	Phase II IgG and/or phase I IgG = 1/25
Negative	Phase II IgG and phase I IgG <1/25
Serological classification of seropositive workers	
Relatively recent exposure	Phase I and/or phase II IgG ≥1/50 and phase II IgM ≥1/50
Past exposure	Phase I and/or phase II IgG ≥1/50 and phase II IgM <1/50

Participation was voluntary, and individuals could elect to receive a copy of their Q fever serology results. Veterinary workers from Australia who were over the age of 18 years were eligible to participate. Both vaccinated and unvaccinated workers were recruited, but only unvaccinated workers were included in this seroprevalence study.

Veterinary workers were opportunistically recruited during the Australian Veterinary Association (AVA) national conference in Perth in 2014, the AVA New South Wales (NSW) divisional conference in Goulburn in 2014, and the AVA Pan Pacific Veterinary Conference in Brisbane in 2015. Attendees at these conferences, who were mostly veterinarians, were free to approach the study booth during conference hours. Additional participants, including research, clinical and administrative staff, were recruited via Q fever vaccination clinics for staff within the veterinary departments at the University of Sydney Camperdown and Camden campuses in 2015. Participants from the vaccination clinics were enrolled by research staff and sampled at the time of pre-vaccination screening appointments.

2.2 | Questionnaire

Participants were required to complete a paper-based questionnaire at the time of blood sampling that contained 15 questions regarding demographics, history of workplace animal exposures, Q fever disease, and Q fever vaccination (Appendix S1). This survey was completed by the participants independently, but in the presence of research staff, surveys were labelled with the participant's unique lab identification number only.

2.3 | Laboratory methods

2.3.1 | Blood samples

Approximately 10 ml of venous blood was taken from participants, refrigerated and couriered as soon as practically possible to the Australian Rickettsial Reference Laboratory (ARRL), Victoria, Australia, for *C. burnetii* serology. Where it was not possible to courier samples in a timely manner, they were stored frozen at −20°C until transport. Each sample was labelled using a unique lab identification number, and no patient details were made available to the ARRL. Survey responses were manually entered into a Microsoft® Access® database (Microsoft Corporation).

2.3.2 | Serology

The IFA was conducted using a National Association of Testing Authorities accredited in-house indirect immunofluorescence assay (IFA) (accreditation No. 14342). The IFA utilized fluorescein-labelled goat anti-human IgM, IgG, IgA and a mixture of all three anti-isotypes combined, separately for phase I and phase II bacterial antigens (a total of eight tests per serum dilution). Phase I (cat # 1227) and phase II (cat # 1123) *Coxiella burnetii* antigens from Serion-Virion were obtained from DKSH Australia. These semi-purified bacterial antigens were fixed onto micro-wells on glass slides. The slides were then treated with patient sera; then, the four different fluorescein-labelled goat anti-human immunoglobulins; one to each well to detect antibodies against *C. burnetii*. Positive and negative control sera were run on every slide.

Patient samples were initially screened at a 1/25 dilution and a 1/400 dilution; the latter to detect any prozone phenomenon. When positive on screening immunofluorescence, samples were titrated out further to a 1/3,200 dilution or to a definitive end point where appropriate. The highest dilution of patient serum showing immunofluorescence equivalent to the positive control was designated as the end point of the titration and recorded as the patient's antibody titre.

2.3.3 | Interpretation

Participants returning an anti-phase II or anti-phase I IgG titre ≥1/50 were considered positive. Serological profiles of participants returning a positive result were further classified as past or relatively recent exposure, as per the criteria outlined in Box 1, adapted from Healy et al. (2011). A category for "chronic infection" was not included in the interpretation, due to the complexities of diagnosing persistent infection. Instead, the serological profiles were additionally assigned as "possible increased risk for persistent infection (endocarditis/ vascular infection)" where phase I IgG was ≥1/800 and phase I IgA was ≥1/50. These serological criteria were derived from criteria proposed by Raoult (2012), based on the modified "Duke" criteria, and modified by Graves at the Australian Rickettsial Reference Laboratory. Importantly,

these criteria do not imply a diagnosis of chronic (or focal, persistent) Q fever, but may prompt further investigation for a focus of persistent infection in a clinical scenario, particularly where other risk factors for persistent infection exist (Million & Raoult, 2015; Raoult, 2012).

2.4 | Statistical analysis

2.4.1 | Variables

The primary outcome of interest was whether the worker was *C. burnetii* seropositive or seronegative, with equivocal (1/25) serological results considered negative for this outcome. The secondary outcome of interest was whether the serological profile of the worker reflected relatively recent exposure to *C. burnetii* (Box 1). These outcomes were dichotomous.

Explanatory variables were drawn from the questionnaire. Categorical responses were grouped according to biologically or demographically sensible categories. Continuous explanatory variables were categorized if the association between the variable and the outcome was not linear on the log odds scale. A category for missing data was included for variables with any incomplete responses. This category was only included in statistical analysis where it represented five per cent or more of the total responses.

Explanatory variables included gender, age, job description, total years working with animals, total hours per week currently working with animals, percentage of career working with small animals (dogs, cats, pocket pets), percentage of career working with ruminants (cattle, sheep, goats), percentage of career working with horses, percentage of career working with other species, percentage of career not working directly with animals, currently working in a private practice, currently working in a laboratory, currently working in government/ industry (excluding abattoirs), currently working in an "other" type of organization.

Workplace postcode (four-digit mail delivery number) was utilized to generate two additional variables: (a) Australian geographical state and (b) Australian Statistical Geography Standard (ASGS) Remoteness Area. The ASGS was developed by the Australian Bureau of Statistics (ABS) and divides Australia into broad geographical regions that share common characteristics of remoteness for statistical purposes (http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/1270.0.55.005Main+Features1July%202016?OpenDocument). Study postcodes were matched to remoteness areas utilizing the ABS July 2016 remoteness structure. Where a postcode spanned more than one remoteness category, the category allocated was the one for which the majority of that postcode was assigned.

2.4.2 | Modelling

Univariable logistic regression analyses were undertaken to identify the unadjusted association between explanatory variables and each of the two outcome variables. Variables with a *p*-value of <.25 in the univariate analyses were considered in the multivariable logistic regression modelling procedures, which were undertaken manually via forward and backward stepwise selection. Where a strong correlation (Spearman rank correlation coefficient >0.7; $p < .05$) was identified between variables, the variable with the least significant association with the outcome was excluded from multivariable modelling. Gender and age were included in multivariable modelling as confounders a priori due to previous Australian studies reporting increased seroprevalence with male gender and increasing age (Gidding et al., 2019; Islam, Ferguson, Givney, & Graves, 2011; Tozer, Lambert, Sloots, & Nissen, 2011). These were also included to account for bias in the cohort due to the exclusion of previously vaccinated workers that were proportionately likelier to be female and young. Biologically plausible interactions identified a priori exhibiting some ($p < .25$) univariable association with the outcome were tested and retained if they caused more than a 20% change in the beta values of significant variables in the model. The significance of the full model was determined with the likelihood-ratio test, and a Hosmer–Lemeshow goodness-of-fit test was performed on the final model to determine whether the model was a good fit for the data.

2.5 | Ethics approval

Primary ethics approval was granted through the University of Sydney Human Research Ethics Committee (#2014/245), and secondary approval through the Charles Sturt University Human Research Ethics Committee (#2015/289). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

3 | RESULTS

3.1 | Responses

The serological results of 192 veterinary workers who had not been previously vaccinated for Q fever were included in this study. The response rate for the vaccination clinics at the University of Sydney was 92%, reflecting participation from 19/22 and 37/39 clinic attendees at the Camden and Camperdown campuses, respectively. At the AVA national conference in Perth (2014), 189/730 delegates were sampled of whom 74 were not-vaccinated for Q fever. At the AVA NSW divisional conference in Goulburn (2014) 48/81 delegates were sampled, of whom 14 were not-vaccinated for Q fever. The AVA Pan Pacific Conference in Brisbane (2015) was attended by 1,110 delegates of whom 124 were from New Zealand and ineligible. Of the remaining 986 delegates, 95 were sampled of whom 48 were not-vaccinated for Q fever. An overall response rate could not be determined for this study due to sampling at conferences, where considerable overlap of attendees is expected, and the exact number of eligible workers is not known.

3.2 | Demographics

Of the 192 unvaccinated veterinary workers, 77% were veterinarians (Table S1). The median age of participants was 50 years (range 18–75; IQR 20), and females constituted 53% of the study cohort. All Australian geographical states and territories were represented. However, the state category of New South Wales (NSW)/ Australian Capital Territory (ACT) was overrepresented at 57% (NSW 53%; ACT 4%), compared to available national veterinary workforce data for 2014 (NSW 28%; ACT 2%; combined 30%) (Australian Veterinary Workforce Survey, 2014). Participants mostly worked in major cities (64%), followed by inner regional areas (22%) and outer regional/remote areas (9%), which was similar to the distribution of the general Australian population for these remoteness categories (70%, 28% and 11%, respectively) according to census data (http://ruralhealth.org.au/book/demography). Further information on the demographic and work characteristics of the studied cohort is reported as supplementary data (Table S1).

3.3 | Serology

Thirty-six (19%; 95% confidence interval [CI] 14%–25%) of the 192 veterinary workers were *C. burnetii* seropositive. Of the positive serological profiles, 53% (19/36) were classed as past exposure and 47% (17/36) were classed as relatively recent (Table 1). Three (8%) of the seropositive workers returned a serological profile consistent with a possible increased risk for persistent infection.

3.4 | Previous Q fever diagnosis

Four participants reported having been medically diagnosed with Q fever, confirmed with laboratory testing (Table 2). Three of these patients were veterinarians with varied animal exposures, all having worked in the veterinary industry for 35 years or more. The fourth was an administration worker within a small animal veterinary clinic in a major city, who had worked in the industry for only 6 years and reported no direct occupational animal handling in that time. All four Q fever patients returned a positive serological profile, including two who were diagnosed over 30 years ago (Table 2). The administration worker, who was most recently diagnosed, exhibited a serological profile of possible increased risk of persistent infection (Table 2).

3.5 | Variables associated with a positive *C. burnetii* serology result

The univariable association between each variable and a positive serological result is shown in the supplementary data (Table S1). Two variables were identified as having a significant univariable association with a positive *C. burnetii* serology result: (a) workplace remoteness classification (p = .004) and (b) percent of career spent working with ruminants (sheep, cattle, goats) (p = .002) (Table S1). Seroprevalence among veterinary workers currently working in outer regional/ remote areas was 53% (9/17; 95% CI 31%–74%), compared to 13% (16/123; 95% CI 8%–20%) among metropolitan workers and 21% (9/43; 95% CI 11%–35%) among inner regional workers. Seroprevalence among workers who had spent more than 50% of their total career working with ruminants was 38% (12/32; 95% CI 21%–54%), while seroprevalence among workers who had spent 15% or less of their total career working with ruminants was 11% (13/118; 95% CI 7%–18%) (Table S1).

Five variables exhibited some association (p < .25) with a positive serological result (Table S1). Number of years working in the veterinary industry was excluded from multivariable modelling due to a strong correlation (spearman rank coefficient 0.81; p < .001) with age. No significant interactions were identified and no confounders, with the exception of age and gender, were retained in the final model.

In the final model, there were two significant variables: (a) workplace remoteness area classification (p = .025) and (b) percent of total career spent working with ruminants (sheep, cattle, goats) (p = .009) (Table 3). Veterinary workers who returned a positive *C. burnetii* serological result were most likely to be currently working within outer regional/ remote areas of Australia (odds ratio [OR] 6.2; 95% CI 1.9–20.8; reference category = major cities), and most likely to have spent more than 50% of their total career working with ruminants (OR 4.8;

TABLE 1 Summary of serology results and serological profiles of veterinary workers participating in a *Coxiella burnetii* seroprevalence study, Australia, 2014–2015

	n	%	95% lower confidence limit	95% upper confidence limit
Serology result[a]				
Positive	36	18.8	13.9	24.9
Negative	151	78.6	72.3	83.9
Equivocal	5	2.6	1.1	6.0
Column total	192	100.0	–	–
Serological profile of seropositive workers				
Relatively recent exposure	17	47.2	32.0	63.0
Past exposure	19	52.8	37.0	68.0
Column total	36	100.0	–	–

[a]Refer to Box 1 for criteria used to classify serological profile.

TABLE 2 Characteristics and serological results of veterinary workers participating in a *Coxiella burnetii* seroprevalence study, Australia, 2014–2015, who reported being medically diagnosed with Q fever during their career

Role	Years working	Career animal exposure	Workplace remoteness[a]	Year of diagnosis	P1 IgA titre	P1 IgM titre	P1 IgG titre	P2 IgA titre	P2 IgM titre	P2 IgG titre
Admin	6	No animal handling (100%);	Major City	2014	1/100	1/50	1/1600	1/200	1/100	1/1600
Vet	40	Small animals (89.5%); ruminants (7.5%); horses (1%); Other (2%)	Inner Regional	1980	1/25	<1/25	1/400	<1/25	1/100	<1/25
Vet	43	Small animals (16%); ruminants (65%); horses (16%); Other (3%)	Major City	1982	<1/25	<1/25	1/100	<1/25	<1/25	<1/25
Vet	35	Small animals (25%); ruminants (45%); horses (30%); Other (0%)	Outer Regional	2002	<1/25	<1/25	1/800	<1/25	<1/25	1/1600

Abbreviations: P1, Phase I *C. burnetii*; P2, Phase II *C. burnetii*; Vet, veterinarian.
[a]According to the Australian Statistical Geography Standard (http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/1270.0.55.005Main+Features1July%202016?OpenDocument) Admin; administration worker.

95% CI 1.7–13.5; reference category = 15% or less) (Table 3). The final model was significant (p = .003) and the Hosmer and Lemeshow goodness-of-fit test was not significant (p = .439), suggesting the model was a good representation of the data.

3.6 | Variables associated with relatively recent exposure

Seventeen workers were classified as having a serological profile suggestive of a relatively recent exposure. Univariable analysis revealed one variable with a significant association with this outcome: job description (p = .025). Veterinary support workers (nurses, kennel hands, farm hands) were more likely to have been recently exposed than veterinarians and animal scientists (OR 5.1; 95% CI 1.4–16.4), comprising 29% (5/17) of the recently exposed cohort compared to only 9% of the total cohort. However, all these support workers were sampled within workplace vaccination clinics across two veterinary sites, and this clustering may have biased the result. Other workers who were positive for this outcome were unrelated by workplace.

Age category was not significant for relatively recent exposure (p = .283). However, the median age of the recently exposed group (40 years; IQR 16 years) was significantly younger (p = .0106) than the median age of the remainder of the cohort (51 years; IQR 21 years), as assessed using the Wilcoxon rank-sum scores method and Kruskal–Wallis test for significance. Again, this result may be influenced by the clustering of veterinary support staff previously reported, as the cohort of support staff studied were younger (median 35 years; IQR 18) than the general cohort.

Although geographical state was not found to be significant (p = .393), some states exhibited high odds ratios for recent exposure. Recently exposed workers were more likely to work in WA/ NT (OR 5.8; 95% CI 0.7–122.7) or NSW/ACT (OR 4.1; 95% CI 0.8–75.8) compared to the reference category of South Australia/ Tasmania/ Victoria. These odds remained high (WA/NT OR 5.9, 95% CI 0.6–131.8; NSW/ACT OR 3.2, 95% CI 0.5–62.2) after adjusting for job description, to account for overrepresentation of nurses from NSW/ACT, and for age, sex and rurality. Recently exposed workers were also more likely to be working within outer regional/ remote areas (OR 2.4; 95% CI 0.5–9.1) but again this was not significant (p = .605). None of the workers currently working in government (n = 15), laboratories (n = 10), or "other" organizations (n = 30) returned a profile suggestive of recent exposure, indicating these workplaces may be lower risk for *C. burnetii* exposure. A larger sample size of workers is required to investigate these associations further.

4 | DISCUSSION

This is the first study to assess *C. burnetii* seroprevalence among veterinary workers in Australia who have not been vaccinated for Q fever. Overall seroprevalence for the cohort studied was 19%. A positive serological result was associated with increasing exposure to ruminants and working in regional or remote areas. These associations are consistent with similar studies in veterinary populations around the globe (Abe et al., 2001; Bernard et al., 2012; Chang et al., 2010; Pozzo et al., 2017; de Rooij et al., 2012; Valencia et al.., 2000; Van den Brom et al., 2013; Whitney et al., 2009), and the overall seroprevalence was similar to that of veterinarians in the United States (22.2%) (Whitney et al., 2009) and veterinary students in the Netherlands (18.7%) (de Rooij et al., 2012). These findings confirm that veterinary workers in Australia have an increased risk of exposure to *C. burnetii* compared to general populations, with previous studies reporting an overall seroprevalence of two to seven per cent for general populations in Queensland and New South Wales (Gidding et al., 2019; Islam et al., 2011; Tozer et al., 2011). The results additionally suggest that there may be a considerable proportion of unvaccinated veterinary workers that may be eligible for, and could benefit from, Q fever vaccination.

Due to antibody decline over time and heterogeneity of individual antibody responses, the 19% seroprevalence reported represents the minimum level of *C. burnetii* exposure in this study cohort. Additional analysis of cell-mediated immune response, via intradermal skin test or interferon-gamma production by T lymphocytes following in vitro stimulation with *C. burnetii* antigen, would likely identify additional workers as positive for previous *C. burnetii* exposure (Schoffelen et al., 2013). Unfortunately, such testing was

TABLE 3 Final multivariable model for factors significantly associated with a positive *Coxiella burnetii* serology result among Australian veterinary workers sampled from 2014–2015

Parameters	Seroprevalence % (*n*)	Odds ratio	95% LCL	95% UCL	*p*-Value[†]
% of career working with ruminants (cattle, sheep, goats)					
15% or less	11% (13/118)	ref	–	–	.009
>15% up to 50%	26% (11/42)	2.5	1.0	6.6	
More than 50%	38% (12/32)	4.8	1.7	13.5	
Workplace remoteness[a]					
Major cities of Australia	13% (16/123)	ref	–	–	.025
Inner regional Australia	21% (9/43)	1.7	0.6	4.5	
Outer regional/ remote Australia	53% (9/17)	6.2	1.9	20.8	
Missing/not classified	22% (2/9)	2.3	0.3	11.4	

Note: n = 192; model adjusted for age and sex.
Abbreviations: LCL, lower confidence limit; UCL, upper confidence limit.
[a]Remoteness determined from postcode according to the Australian Statistical Geography Standard (http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/1270.0.55.005Main+Features1July%202016?OpenDocument).
[†]Wald chi-square *p*-value.

beyond the scope of this study. This does not impact the validity of comparisons with other studies, as this limitation is universal to seroprevalence studies.

Increasing career exposure to ruminants (cattle, sheep and goats) was significantly associated with a positive *C. burnetii* serological result, confirming that ruminants pose a high risk of exposure to *C. burnetii* among veterinary workers in Australia. Similarly, veterinarians in the United States who worked with cattle were found to have an increased risk for *C. burnetii* exposure (OR 2.8) (Whitney et al., 2009), as did veterinarians working with cattle (OR 2.8) or sheep (OR 2.1) in Bavaria (Bernard et al., 2012). In southern Belgium, seroprevalence among veterinarians having contact with livestock was 58.5% compared to 6.3% among veterinarians working only with companion animals (Pozzo et al., 2017). Practicing small ruminant veterinarians in Ontario, Canada, exhibited a very high seroprevalence of 76.2%, although this finding could not be conclusively attributed to ruminant exposure (Meadows et al., 2016).

Veterinary workers within remote or outer regional locations were significantly more likely to be seropositive for *C. burnetii*. This association remained significant after adjusting for ruminant contact in multivariable modelling. Rural location was found to be a significant factor for *C. burnetii* exposure in veterinarians in the Netherlands (OR 6.6) (Van den Brom et al., 2013), while studies in Taiwan and Belgium identified rurality to be significant during univariable, but not multivariable, analysis (Chang et al., 2010; Pozzo et al., 2017). Globally, the association of rurality with *C. burnetii* seroprevalence appears to vary and is influenced by land use, geography and seasonal conditions (Angelakis & Raoult, 2011; Cikman et al., 2017; Clark & Soares Magalhaes, 2018; Hackert et al., 2012; Tozer et al., 2011). In Australia, rural populations of New South Wales and Queensland report increased *C. burnetii* seroprevalence and Q fever disease notifications (Gidding et al., 2019; Islam et al., 2011; Lowbridge, Tobin, Seale, & Ferson, 2012; Tozer et al., 2011). Rural location may increase exposure to *C. burnetii* due to the proximity of farms, livestock facilities, and animal transport routes (Clark & Soares Magalhaes, 2018; O'connor, Tribe, & Givney, 2015). Geographical dispersal of *C. burnetii* may also be more pronounced where there are higher densities of wild and domesticated animal species and greater inter-species interaction, a concept that remains largely understudied (Clark & Soares Magalhaes, 2018).

This study also confirms that veterinary workers who were predominantly exposed to non-ruminant species and those in metropolitan areas remain at higher risk of *C. burnetii*, reporting 11% and 13% seroprevalence respectively. In comparison, general populations in Australia report a seroprevalence of two to five per cent in metropolitan areas (Gidding et al., 2019; Tozer et al., 2011). This is supported by reports of Q fever outbreaks associated with cat and dog births (Gibbons & White, 2014; Kopecny et al., 2013; Malo et al., 2018), Q fever disease among cat breeders (Shapiro, Norris, Bosward, & Heller, 2016), and the detection of *C. burnetii* in a large variety of domestic and wild animal species in Australia (Cooper, Barnes, Potter, Ketheesan, & Govana, 2012; Shapiro, Bosward, Heller, & Norris, 2015; Shapiro, Norris, Heller, & Bosward, 2016; Tozer et al., 2014). While reports of disease associated with non-ruminant species and within metropolitan areas are low, the consequence of clinical Q fever disease for those affected may be severe.

Although the risk of clinical disease and burden of chronic Q fever is not well studied in veterinary workers, the clinical history of Q fever is well defined in the literature. The incidence of symptomatic Q fever varies with demographics, geographical region, exposure setting (endemic vs. outbreak), and with bacterial dose and strain

(Brooke, Kretzschmar, Mutters, & Teunis, 2013; Hackert et al., 2015, 2012; Million & Raoult, 2015). Generally, symptomatic disease is estimated to occur in 20%–80% of individuals exposed to *C. burnetii* (Million & Raoult, 2015) and the increased risk of exposure identified in this study likely translates to significant Q fever related morbidity in these veterinary workers. Four (11%) of the 36 seropositive workers reported having been medically diagnosed with Q fever, which may reflect under diagnosis of clinical Q fever disease in the studied cohort. Two workers remained seropositive more than 30 years after Q fever diagnosis, suggesting recurrent exposure or the long-term persistence of antibodies following infection. Antibody profiles suggestive of possible persistent (chronic) infection were identified in five (14%) of the workers, which was similar to that reported for veterinarians in Belgium (12%) (Pozzo et al., 2017). These serological profiles appear to be more common in veterinarians following Q fever diagnosis compared to patients with no occupational risk of exposure, and may be due to persistent exposure rather than pathological disease (Wielders et al., 2015).

Few individuals in this study exhibited a serological profile suggestive of relatively recent exposure. Among those that did, veterinary support staff were overrepresented. However, these support staff were clustered within two related but geographically separated workplaces, possibly reflecting a workplace outbreak. Additionally, an administration worker from an urban small animal clinic, who reported no direct occupational animal exposure, had been recently diagnosed with Q fever. These findings highlight the risk of exposure of support and administration staff, who remain largely unvaccinated for Q fever in Australia. Efforts should be made by all veterinary employers and veterinary workers in Australia to ensure that Q fever vaccination is recommended and available to veterinary support staff (Sellens et al., 2016, 2018).

Current employment within government, laboratories or "other" organizations (excluding abattoirs) was possibly protective against relatively recent *C. burnetii* exposure. Compared to private practice, these roles may require less contact with animals, explaining the possible reduced risk for recent *C. burnetii* exposure. However, working in these organizations was not protective for a positive serology result generally. This may be because employment within such organization is either highly competitive or more attractive to experienced workers looking for a change from clinical work, resulting in these workers having usually spent many years working intensively with animals prior to securing such positions.

Increasing Q fever vaccine uptake in veterinary workers may be a cost-effective public health strategy. Indeed, an economic evaluation of increased vaccine uptake in abattoir and agricultural workers in Australia identified vaccination was a cost-effective public health strategy in those workers (Kermode, Yong, Jurley, & Marmion, 2003). The analysis used seroprevalence estimates of between 17% and 28% for modelling, and the burden of acute and persistent (chronic) Q fever disease and post-Q fever fatigue were considered (Kermode et al., 2003). The seroprevalence identified in this study was similar to that used in the Kermode et al. (2003) study, indicating that vaccination of veterinary workers is likely to be similarly cost-effective. Additionally, as the vaccine is not currently government funded for veterinary workers, the question of cost–benefit is left to the consumer. For some, the risk of short-term or chronic disease, or adverse pregnancy outcomes in this female-dominated industry, may far outweigh the cost of the vaccine.

The participants in this study were not aware of their *C. burnetii* serostatus at the time of sampling, and there were no incentives offered for participation. Subsequently, these results are likely to be valid for the sample. However, they may not be generalizable to all veterinary workers, particularly veterinary support staff who were under-represented and mostly clustered within two related workplaces. Additional seroprevalence studies in Australia should aim to gather further data from veterinary support workers, who report a low level of knowledge regarding Q fever and remain largely unvaccinated (Sellens et al., 2016).

5 | CONCLUSION

This study contributes valuable information for employers and employees within the veterinary industry. The findings confirm that veterinary workers have an increased risk of exposure to *C. burnetii*, supporting the Australian Government recommendation for Q fever vaccination of all veterinarians, veterinary students, and veterinary nurses. This recommendation should be extended to cover broader veterinary support staff, such as kennel hands, farm hands and administration workers, particularly in regional and remote areas and clinics working with ruminants. This study also highlights that four out of five unvaccinated veterinary workers are potentially eligible for Q fever vaccination despite many years working with animals. These findings will assist medical practitioners and veterinary workers in making informed decisions regarding the prevention of Q fever, particularly with regard to Q fever vaccination.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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