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Unravelling animal exposure profiles of human Q fever cases in Queensland, Australia using natural language processing

Running title

Text mining to deduce Q fever exposure pathways

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Abstract

Q fever, caused by the zoonotic bacterium *Coxiella burnetii*, is a globally distributed emerging infectious disease. Livestock are the most important zoonotic transmission sources, yet infection in people without livestock exposure is common. Identifying potential exposure pathways is necessary to design effective interventions and aid outbreak prevention. We used natural language processing and graphical network methods to provide insights into how Q fever notifications are associated with variation in patient occupations or lifestyles. Using an 18-year time-series of Q fever notifications in Queensland, Australia, we used topic models to test whether compositions of patient answers to follow-up exposure questionnaires varied between demographic groups or across geographical areas. To determine heterogeneity in possible zoonotic exposures, we explored patterns of livestock and game animal co-exposures using Markov Random Fields models. Finally, to identify possible correlates of Q fever case severity, we modelled patient probabilities of being hospitalised as a function of particular exposures. Different demographic groups consistently reported distinct sets of exposure terms and were concentrated in different areas of the state, suggesting the presence of multiple transmission pathways. Macropod exposure was commonly reported among Q fever cases, even when exposure to cattle, sheep or goats was absent. Males, older patients and those that reported macropod exposure were more likely to be hospitalised due to Q fever infection. Our study indicates that follow-up surveillance combined with text modelling is useful for unravelling exposure pathways in the battle to reduce Q fever incidence and associated morbidity.

Keywords

Australia, *Coxiella burnetii*, Markov Random Fields, text mining, topic models, Q fever, zoonosis

Introduction

Q fever is a globally distributed emerging infectious disease caused by the bacterium *Coxiella burnetii* (Allan-Blitz, Sakona, Wallace, & Klausner, 2018; Bond, Franklin, Sutton, Stevenson, & Firestone, 2018; Gyuranecz et al., 2014; Van der Hoek et al., 2010). Acute infection with *C. burnetii* is commonly described as a flu-like illness with symptoms including high fevers, headaches or pneumonia, as well as atypical symptoms such as hepatitis or myocarditis (Didier Raoult & Marrie, 1995; Sellens et al., 2018). However, up to 60% of human cases are thought to be asymptomatic (Roest et al., 2011). Infection by *C. burnetii* rarely causes mortalities but can manifest as a wide spectrum of recurrent, focalized morbidities that result in debilitating conditions involving the cardiovascular system or lungs (Fenollar et al., 2001; Million & Raoult, 2017).

Infected livestock, particularly goats and sheep, are the most important sources of zoonotic Q fever outbreaks in humans (Arricau-Bouvery & Rodolakis, 2005; N. Clark & Soares Magalhães, 2018). Inhalation of robust and infective small cell variants (SCVs; sometimes referred to as 'spores') is the primary mode of animal-to-human transmission for *C. burnetii* (D Raoult, Marrie, & Mege, 2005). Large quantities of SCVs may occur in animal faeces, vaginal mucus, products of conception and unpasteurized dairy products (Guatteo et al., 2006). People whose occupations involve close livestock contact (e.g. abattoir workers, livestock transporters and veterinarians) are considered at highest risk of infection (Graves & Islam, 2016; Karagiannis et al., 2009; Mori & Roest, 2018; Van der Hoek et al., 2010).

In Australia, human Q fever infection has been a notifiable disease in all states and territories since 1977. Human notification rates of Q fever in Australia are amongst the highest in the world (Gidding, Wallace, Lawrence, & McIntyre, 2009; Lindsay, Rohailla, & Miyakis, 2018; Sloan-Gardner, Massey, Hutchinson, Knope, & Fearnley, 2017). Australia also has the world's only licensed human vaccine for Q fever (Q-Vax®, Seqirus Limited, VIC, Australia). Across the years 2001 – 2006 inclusive, the Australian Government funded a National Q fever Management Program, which involved screening and vaccination for specific at-risk populations including abattoir workers and livestock farmers (Gidding et al., 2009). This led to notable decreases in human Q fever notifications in subsequent years, particularly for the states of Queensland and New South Wales where the majority of Australian notifications occur (Karki, Gidding, Newall, McIntyre, & Liu, 2015; Sloan-Gardner et al., 2017).

Despite commendable vaccination and education efforts, Q fever persists as a public health concern in Australia (Lindsay et al., 2018; Sivabalan, Saboo, Yew, & Norton, 2017; S. Tozer, Lambert, Sloots, & Nissen, 2011). Moreover, recent notifications are now commonly attributed to people with no previous record of occupational exposure to risks associated with regular livestock contact, suggesting other transmission pathways may play roles in the epidemiology of the disease (N. Clark & Soares Magalhães, 2018; Reedijk, Van Leuken, & Van Der Hoek, 2013; Sloan-Gardner et al., 2017; S. Tozer et al., 2011). These underexplored transmission routes may differ substantially among people that live or work in different sectors (Clutterbuck, Eastwood, Massey, Hope, & Mor, 2018). *Coxiella burnetii* can persist in the environment, is resistant to harsh conditions and may be transported over long distances on prevalent winds (N. Clark & Soares Magalhães, 2018; Fitzpatrick, Kersh, & Massung, 2010; Reedijk et al., 2013). Coupled with the bacterium's long incubation period of up to 4 – 6 weeks (Didier Raoult & Marrie, 1995), these aspects of Q fever epidemiology make it difficult to investigate relevant exposure pathways. Nevertheless, a diversity of possible wildlife reservoirs has been identified through molecular and serological surveys, including wild and domestic mammals, birds and even ticks (Alanna Cooper, Barnes, Potter, Ketheesan, & Govan, 2012; A Cooper, Stephens, Ketheesan, & Govan, 2013; Flint et al., 2016; Webster, Lloyd, & Macdonald, 1995). Among these, macropods (including kangaroos, wallabies and wallaroos from the family Macropodidae) are of particular interest because (1) they are abundant and often share habitats with Australian livestock; (2) they are a common source of game meat for both humans and companion animals (Hoffman & Cawthorn, 2012); and (3) a range of macropod species have been documented as possible reservoir hosts of the bacterium using serological or molecular evidence (Banazis, Bestall, Reid, & Fenwick, 2010; Alanna Cooper et al., 2012).

Patients diagnosed with Q fever in the state of Queensland, Australia are interviewed with a series of questions designed to document and investigate possible transmission pathways. A questionnaire is completed over the telephone (within five days of positive Q fever confirmation) and contains fields including onset date, demographics (age, gender, indigenous status), occupation and several text-based fields aimed at describing the possible pathways of exposure to livestock / game animals (see **Appendix S1** for the full questionnaire template). In 2012, an extended surveillance form was introduced to allow patients to more directly list all possible animal exposures, adding an additional layer of rich enhanced surveillance data.

Identifying potential exposure pathways in people with confirmed Q fever infection is a key step to reduce disease incidence and severity. In this study, we applied natural language processing to an 18-year dataset of Q fever notifications in Queensland, Australia to investigate whether patients belonging to different demographic groups commonly report different potential exposure pathways. We then used multivariate graphical models to explore associations among reported animal-based exposures. Finally, we used infection-related hospitalisation records as a proxy for disease severity to test whether patients with reports of particular types of animal exposures suffer from more severe acute Q fever infections.

Methods

Ethics statement

This research used data on Q fever notifications collected by the Queensland Department of Health in accordance with Section 284 of the *Public Health Act 2005* and was completed under the ethical approval of The Children's Health Queensland Human Research Ethics Committee (HREC08/QRCH/66AM03 8/05/2017).

A state-wide dataset of Q fever notifications from Queensland, Australia

The primary data for this study encompassed all available human cases of Q fever infection notified to the Queensland Department of Health from 1 July 1984 to 31 December 2017 inclusive. According to national guidelines, human cases of Q fever must be confirmed using either laboratory definitive evidence or a combination of laboratory suggestive evidence and clinical evidence (Communicable Diseases Network Australia, 2018). Laboratory definitive evidence includes either (1) detection of *C. burnetii* by nucleic acid testing, (2) seroconversion or significant increase in antibody level to Phase II antigen in paired sera tested coupled with the absence of recent Q fever vaccination, or (3) detection of *C. burnetii* by culture. Laboratory suggestive evidence refers to detection of specific IgM in the absence of recent vaccination. The full dataset contained 7,495 Q fever notifications. We geocoded patient addresses to describe spatial variation in exposure reports. Based on available information, geocodes were taken from one of three hierarchical levels representing (from most to least precise) house number and street name of the patient's address (n = 4,217), centroid of the street (n = 784) or centroid of the Statistical Local Area (SLA; n = 2,494).

We filtered the data to only include cases from the years 2001 – 2017, as follow-up questionnaires became mandatory in 2001. This reduced dataset contained 4,068 individual Q fever notifications. Patients in this dataset had a median age of 39 years (interquartile range [IQR]: 27 – 52 years). Males accounted for 74% of notifications. Because reported animal exposures were more data-rich following the rollout of the improved surveillance form in 2012, we created a separate dataset containing only the 2012 – 2017 data (n = 979) for comparisons in co-exposure analyses (see "Identifying animal exposures and co-exposures using Markov Random Fields" below and see **Figure S1** in Supporting Information for a flowchart of observations used in each step of analysis).

Building an exposure dataset using text mining

We applied natural language processing to all open-ended (text-based) question fields to construct an exposure dataset whereby each patient's responses were represented as a distinct text unit. A series of quality control steps were used to correct spelling errors and filter out uninformative terms. Briefly, we first removed numerics and filtered out stop words (i.e.

words that are very common and are consequently considered unimportant for search queries, such as ‘the’, ‘about’ or ‘said’; Fox, 1989). Next, we singularized words (i.e. by changing ‘kangaroos’ to ‘kangaroo’) and applied a fuzzy pattern matching spell check algorithm that suggests replacements for misspelled words using a United States English language dictionary. Finally, we removed words containing fewer than three letters. Words reported by a total of 2,044 individual patients were included after these filtering steps (**Figure S1**). Text processing was carried out in R version 3.3.3 (R Core Team, 2018) and primarily used functions from the packages *tidytext* (Silge & Robinson, 2016), *hunspell* (Ooms, 2017) and *tidyverse* (Wickham, 2017).

Latent Dirichlet Allocation to identify discriminatory response ‘topics’

We applied a topic model algorithm, also known as Latent Dirichlet Allocation, to our exposure dataset to ask whether the composition of words in a patient’s responses could provide information about their demographic features. Topic models are a class of generative, unsupervised machine learning methods designed to identify latent ‘topics’ containing similar term compositions and frequencies within a given collection of texts (Blei, 2012; Hornik & Grün, 2011). This is accomplished with a mixture model whereby word frequencies in each latent topic are drawn from an unknown Dirichlet distribution (Blei, Ng, & Jordan, 2003). We pooled text from individual cases into eight demographic groups representing different sex and age classes (**Table 1**). Age categories were chosen to represent school-age children (ages 0 – 18), working age young adults (ages 19 – 34), working age older adults (ages 35 – 64) and retirees (ages 65 – 100), considering differing potential exposure risks. We did not have a sufficient sample size to analyse data from children under five years of age separately (only 16 pre-school age individuals were in the notification data). Words that were represented fewer than five times were removed to ensure we focused only on terms likely to be useful for discriminating between demographic groups.

We fit topic models to the resulting term matrix, which contained 14,338 observations for 397 unique terms. Because the number of word topics (k) must be specified prior to fitting the model, we used a data-driven approach to identify the optimal number. We tested six topic models (k = 2 – 7) and compared each model’s geometric mean per-word likelihood (also known as perplexity; Hornik & Grün, 2011). The model that minimized inverse perplexity while containing the fewest number of topics was considered the most parsimonious (see **Figure S2** in Supporting Information for perplexity scores from each tested model). From the best-fitting model, we calculated the relative contribution of each topic to each demographic group's response document to assess whether patients from different demographics provided different sets of responses. Topic models were fit using functions in the *topicmodels* R package (Hornik & Grün, 2011).

Identifying potential animal exposures and co-exposures using Markov Random Fields

We next determined whether free-text fields included information that might represent potential exposure to particular livestock species (cattle, sheep, goats or pigs) or macropods. This involved searching through patient answers for key terms associated with each of these target host species (e.g. 'cattle', 'heifer' or 'beef' for potential exposure to cattle; see **Table S1** in Supporting Information for a full list of search terms for each target host group). Mentions of these target species were recorded as binary indicator variables. A total of 1,380 cases mentioned exposure to at least one of the five target host species (**Figure S1**). Note that multiple binary fields exist for detecting sheep exposure, such as 'work with wool' or 'work in a shearing shed' (**Table S1**), and so detections of sheep exposure may have higher accuracy. Excluding these binary survey questions resulted in a total of 313 sheep exposures detected, compared to 384 with the binary fields included. We chose to use the full dataset for all analyses, though we recognise this slight potential for bias towards sheep exposure detection.

We fit a Markov Random Fields (MRF) model to our matrix of binary animal exposures (N. J. Clark, Wells, & Lindberg, 2018a). This framework, commonly used in multivariate classification problems (Fountain-Jones et al., 2019; Harris, 2016), is well-suited to our exploration of exposure pathways as it allows us to ask whether pairs of animal exposures were more or less likely to be jointly reported (co-exposure) after accounting for all other types of animal exposure (e.g. are pairs of exposures conditionally associated after accounting for all other exposures in the graph?). In our model, each type of animal exposure was included as a node in the undirected network, with edges between nodes representing the marginal relationships between pairs of reported exposures adjusting for all other relationships present (N. J. Clark, Wells, & Lindberg, 2018b). We also included an additional binary node representing whether or not the patient was hospitalised due to Q fever infection, allowing us to ask whether certain animal exposures were more or less likely to be statistically associated with hospitalisation. Conditional relationships were estimated using a regularized node-wise regression approach through functions in the *MRFcov* R package (N. J. Clark et al., 2018a). We fit a separate MRF using only the 2012 – 2017 data (n = 979) to investigate whether the extended surveillance questionnaire led to different estimates of co-exposure relationships.

Regression models to identify associations with hospitalisation probability

The above analyses explore patient exposure reports and how exposures may be related to one another. We supplemented these models by fitting a series of supervised machine learning regressions to identify important exposure correlates of a Q fever patient's probability of being hospitalised. Tested covariates were: sheep exposure, cattle exposure, macropod exposure, goat exposure, pig exposure, shooting / hunting participation, Indigenous status, age, sex, whether the patient was previously vaccinated and whether the patient reported that they previously assisted in animal births. All exposure / activity questions related to the month prior to the onset of illness. In addition, we constructed a binary variable to distinguish between pre-2012 and 2012-present observations to account for possible differences between the two time periods. We first fit two regularized spatial logistic regression models that applied a coordinated gradient descent LASSO regularization algorithm to select important predictor variables (Friedman, Hastie, & Tibshirani, 2010): the first included latitude and longitude as covariates; the second expanded these coordinates into Gaussian process spatial regression splines (Kammann & Wand, 2003) to account for non-linear spatial patterns. In addition, we accounted for possible non-linearity in predictor-outcome relationships by fitting a generalised additive logistic model that also included spatial regression splines (Wood, 2003). For each of these three competing models, we calculated their predictive performance using a cross-validation process that involved fitting models to a random subset of the data containing ~80% of observations (~1104 individuals) and calculating prediction accuracy (e.g. proportion of observations correctly predicted) for the remaining ~ 20% of observations. This cross-validation process was repeated 100 times to quantify uncertainty in predictive performances. Regressions were fit using functions in the *glmnet* and *mgcv* R packages (Friedman et al., 2010; Wood, 2003). Due to the sensitivity of the notification data, raw data is not publicly available. However, word strings for each demographic group and R scripts to replicate the topic model and posthoc analyses are available in the Supporting Information.

Results

Topic model analysis

Our text-mining dataset contained 14,337 words reported by 2,044 patients from eight demographic groups (**Table 1**). The richest sources of words came from working-age patients (19 – 34 and 35 – 64 years old), with both sexes well represented in the dataset (**Table 1**). The best-fitting topic model identified five word 'topics' that could successfully classify Q fever patients into categories based on their age group and sex (**Figure 1**). While a total of 397 words were included in the analysis, we identified some key influential terms that achieved high discriminatory power. In other words, the presence of these terms in a patient's answers likely represented important differences in the lifestyles and/or exposure pathways exhibited by demographic groups. Differences in answers between the two sexes were apparent, as two of the five identified topics were almost entirely associated with males. We describe each of the topic groups and some of their key discriminatory terms in detail below.

Topic 1: the most easily distinguishable demographic group, which belonged almost entirely to this topic, consisted of working age males (ages 19 – 34 years). This group consistently mentioned informative occupational terms associated with the livestock trade, such as 'export', 'abattoir', 'feedlot', 'beef', 'kill' and 'process', that were not commonly mentioned by other demographic groups (**Figure 1**).

Topic 2: children from both sexes (ages 0 – 18 years) belonged almost entirely to this topic, as did young females (ages 19 – 34 years). Discriminatory terms included words associated with education, including 'child', 'college', 'primary', 'school', and 'student', as well as the name 'Bollon' (a town in the inland shire of Balonne, which is a region that consistently has high rates of Q fever notifications in Queensland).

Topic 3: this topic was strongly associated with working age and retired females (35 years and older) as well as some males of retirement age (ages 65 – 100 years). Discriminatory terms included 'wife', 'housewife', 'husband', 'vet', 'nurse' and 'cook'.

Topic 4: this topic was entirely composed of working age and retired males (ages 35 years and older) and was distinguished by terms commonly associated with factory workers and tradesman, including 'drain', 'factory', 'weld', 'milk' and 'handyman'.

Topic 5: this group included working age males and females (ages 35 – 64) and some younger working females (ages 19 – 34). Discriminatory terms reflected possible indirect exposure routes, including 'manure', 'observe', 'post', and 'office', as well as some terms that may reflect direct exposure including 'bull' and 'meatworker'.

To assess spatial patterns in the distributions of topics, we predicted the most probable topic for each of the 2,044 patients using their individual responses. After adjusting for resident population sizes of the surrounding Local Government Area (LGA), we found that all topics were generally more common in central areas of the state where Q fever notifications have traditionally been high (**Figure 2**; S. J. Tozer, 2015). However, some key spatial differences across topics were evident. Topics associated with working age males (ages 19 – 34 years) and children (males and females ages 0 – 18 years) primarily occurred in the central and central-south areas of the state (Topics 1 and 2; **Figure 2**). In contrast, topics associated primarily with patients aged 35+ years (Topics 3 and 4) were both generally more common in central-north areas of the state (**Figure 2**). Topic 5, which contained a mix of words suggesting non-occupational exposure, was more evenly distributed across northern and southern areas in central Queensland (**Figure 2**).

Animal exposures reported by Q fever patients

From 2001 – 2017, a total of 1,380 individual Q fever cases reported potential exposure to at least one of the five target animal groups. Of these, 890 (64%) reported exposure to cattle, 638 (36%) to macropods, 384 (28%) to sheep, 347 (25%) to pigs and 237 (17%) to goats (note some individuals reported exposure to multiple animal groups; **Figure 3**). Notifications with reported exposures occurred across much of the state, though the majority were again concentrated in the central and central-south areas for each of the five target animal groups (**Figure 3**). This same pattern also held for those individuals that did not report exposure to any of the five target animal groups (**Figure S3**). Across years, cattle exposure was the most common animal exposure pathway, though reports of non-cattle exposure (particularly for macropods) were noticeably more common following the rollout of the expanded surveillance in 2012 (**Figure 4a**). Across all 1,380 individuals, a total of 187 cases (14%) were identified that reported exposure to macropods but did not report exposure to any livestock species. In contrast, 396 cases reported only cattle exposure (27%), 99 (7%) reported only sheep exposure and 30 (2%) reported only pig exposure.

Proportions of reported exposures attributed to each animal showed some noticeable variation across topic groups (**Figure 4b**). Most notably, patients belonging to Topic 3 (working age and retired females and some retired males, primarily located in the central-north areas of the state) and Topic 4 (working age and retired males associated with factories or trades, also commonly found in the central-north) more often reported macropod exposure than any other group, with 35.6% and 29.3% of exposures attributed to macropods, respectively (**Figure 4b**). Patients from these groups also tended to report fewer exposures to sheep and goats than patients from other groups. In contrast, groups more commonly found in south-central areas of the state, including patients from Topics 1 and 2 (working age males in the livestock trade and children / young females associated with the education industry), reported more even exposures across the five animal reservoir species (**Figure 4b**).

Animal co-exposures identified using Markov Random Fields

Our MRF model, built using the dataset of 1,380 patients from the years 2001 – 2017, identified a number of important conditional pairwise relationships between reported animal exposures (**Figure 5, top graph**). Patients that reported goat exposure were > 3 times more likely to also report sheep exposure after accounting for all other exposures (marginal Odds Ratio 95% credible interval [OR]: 2.88 – 3.71). A similarly strong positive relationship was found for macropod and pig exposures (OR: 2.81 – 3.59). In contrast, a strong negative relationship was identified between cattle and macropod exposures (OR: 0.29 – 0.36). In addition, we estimated that patients were approximately 50% more likely to be hospitalised if they reported macropod exposure than if they did not (OR: 1.32 – 1.65), while patients were 20% less likely to be hospitalised if they reported pig exposure (OR: 0.75 – 0.95).

Associations with probability of hospitalisation

A total of 672 of the 1,380 patients included in the analysis dataset were admitted to hospital as a result of Q fever infection. Of the three logistic regressions we tested, the LASSO algorithm without spatial regression splines was the best-fitting and most parsimonious model (prediction accuracy range: 0.53 – 0.66, compared to ranges of 0.51 – 0.64 for the gaussian process LASSO and 0.51 – 0.63 for the spatial GAM). This model retained five important predictors: exposure to macropods, exposure to animal births, sex (male = 1), age and year of notification. Effect sizes revealed that all of these variables increased risk of hospitalisation apart from exposure to animal births (**Figure S4**). Being male increased risk by 48% (effect size 95% CI [ES]: 1.16 – 1.90), exposure to macropods increased risk by 34% (ES: 1.07 – 1.66) and each additional 5 years of age increased risk by 16% (ES: 0.15 – 0.17). Hospitalisation risk also increased by 10% each year from 2001 – 2017 (ES: 0.10 – 0.12) (**Figure S3**). Exposure to animal births decreased risk by 67% (ES: 0.52 – 0.85). There was no difference in numbers of patients that reported animal birth exposure between the sexes (χ^2 test: $\chi^2 = 2.12$, $p = 0.15$), though there was a moderate difference in ages. Specifically, patients that reported animal birth exposure were 0.5 – 4.5 years younger than those that did not (t test: $t = -2.24$, $p = 0.03$).

Discussion

Our study provides new insights into the complexities of Q fever epidemiology and showcases the utility of incorporating enhanced surveillance data into disease monitoring and research programmes. The undifferentiated nature of clinical presentations associated with Q fever and the lack of awareness of this disease as a potential diagnosis across geographical regions means that adequate treatment will often be delayed or missed (Dahlgren, Haberling, & McQuiston, 2015; Lindsay et al., 2018; Million & Raoult, 2017; Didier Raoult & Marrie, 1995). A better understanding of exposure pathways is necessary to help design measures aimed at preventing exposure to *C. burnetii* (Angelakis & Raoult, 2011; Clutterbuck et al., 2018). The results of our text modelling approach demonstrate two clear patterns of reported exposures among Queensland's Q fever notifications: (1) responses to survey questions differed among demographic groups and (2) patients belonging to different exposure topics were often concentrated in different geographical areas. Moreover, we identify predictors of hospitalisation risk and show that the simplified exposure questionnaire performed similarly to the expanded questionnaire; these findings can help improve resource allocation to reduce the burden of Q fever infection. Collectively, our study indicates that follow-up surveillance combined with text modelling is useful for unravelling exposure pathways in the battle to reduce the incidence Q fever and other zoonotic diseases.

With one of the world's highest Q fever notification rates and a long history of livestock-based agriculture, Queensland is a focus area for research on Q fever epidemiology (Sivabalan et al., 2017; Sloan-Gardner et al., 2017; S. J. Tozer, 2015). Key among efforts to reduce Q fever incidence is Queensland Health's use of follow-up surveillance of notified cases. These crucial data, particularly following the 2012 rollout of an extended outbreak investigation form, are providing deeper insights into possible exposure pathways (Communicable Diseases Network Australia, 2018). However, making sense of text data that results from open-ended questions can be challenging and often requires model-based algorithms (Paul & Dredze, 2014; Roberts et al., 2014). By applying a topic model to an 18-year dataset of Queensland Q fever notifications, we show that patients from different demographic groups consistently reported distinct sets of exposure terms, suggesting demographic-specific transmission pathways. Moreover, our study expands on the well-known concentration of Q fever notification rates in rural Australia (Gidding et al., 2009) to demonstrate that patients associated with different exposure pathways showed different spatial patterns, with some concentrating more in the north and others in the south of the state. These findings provide an evidence-base for multifaceted and epidemiologically relevant health promotion campaigns that can act in tandem with ongoing Q fever occupational vaccination programmes to increase Q fever awareness and decrease burdens of disease.

Our models provide strong evidence that open-response answers from younger working males (ages 19 – 34 years; Topic 1) were compositionally different to those from older working males (35 – 64 years; Topic 3). In general, younger males reported terms associated with the livestock industry while older males reported indirect exposure terms or terms associated with trades. With known discrepancies between occupations considered 'high-risk' by Australian health bodies and those thought of as 'high-risk' by rural practitioners (Lindsay et al., 2018), this finding that males likely encounter different occupational exposures between age groups provides useful information for designing education and vaccination programmes. In contrast, children and young females commonly reported terms associated with education (Topic 2), perhaps indicating they were less likely to directly participate in traditional high-risk activities. However, this maternal-child word topic strongly overlapped in space with areas that harboured relatively high densities of working males from the traditional occupational group (Topic 1). Moreover, patients from these two groups (young working age males and children / young working age females) were also very similar in terms of their animal exposure profiles, with both groups reporting moderate cattle exposure but more commonly reporting pig exposure compared to other groups. These results have public health implications due to the fact that (1) the current advice for Q fever vaccination is that it should not be administered to patients younger than 15 years (Australian Technical Advisory Group on Immunisation (ATAGI), 2018) and (2) awareness programmes are not currently targeting family members, particularly children, of stockman (Armstrong et al., 2019; Gidding et al., 2009).

A prominent finding of our study is that older patients, particularly those residing in Queensland's northern regional areas, represent a key and epidemiologically distinct at-risk group for Q fever infection. Patients aged 65 years and older were (1) more concentrated in the central-north of the state, (2) more likely to report macropod exposure but less likely to report goat or sheep exposure and (3) more likely to be hospitalised due to infection. Interestingly, patients in this group also commonly reported occupational exposure terms associated with the veterinary industry, including 'vet' and 'nurse'. The recognition that older patients are exposed to *C. burnetti* through different pathways, and that risks of hospitalisation are higher, confirms previous findings from Australia (Karki et al., 2015) and elsewhere (Dupont et al., 1992). This has implications for the future distribution of public health resources. Population ageing resulting from accelerated expansion of older people is a major phenomenon affecting many of the world's developed countries, and Australia is no exception (Ofori-Asenso, Zomer, Curtis, Zoungas, & Gambhir, 2018). From the year 1996 to 2016, the proportion of Australia's population aged 65 years and over increased from 12.0 to 15.3%, and such increases are expected to continue (Australian Bureau of Statistics (ABS), 2016). By demonstrating a strong correlation between patient age and the probability of hospitalisation due to Q fever infection, our study contributes to growing evidence that aging populations are associated with increased demands for healthcare (Beard & Bloom, 2015). Understanding how much of this increasing demand is driven by changes in reporting, heightened awareness or the rollout of intervention programs (such as Q fever vaccination in Australia) should be a topic of future research. This is particularly true given our finding that probability of hospitalization increased with year of onset across our study's timeframe. It is unlikely that Q fever severity has increased over time. Rather, this pattern could reflect heightened awareness of the disease and its health impacts, or perhaps a shift from primarily acute cases in livestock workers to non-occupational cases that are more difficult to diagnose due to a lack of obvious exposure pathways. Indeed, the authors of a recent time-series analysis of Q fever notifications in Victoria, Australia found evidence for such a pattern and postulated that many mild cases likely remain undiagnosed, leading to a relatively high hospitalisation rate for those more severe cases that are confirmed as Q fever (Bond et al., 2018).

Many species of wildlife have long shown evidence of exposure to *C. burnetti*, and some authors have made the suggestions that these species can pose greater zoonotic risks than livestock in particular environments (Enright et al., 1971; González-Barrio & Ruiz-Fons, 2019; Koehler, Kloppert, Hamann, El-Sayed, & Zschöck, 2019). Multiple lines of evidence from our study confirm previous findings that macropods may be a primary reservoir host for *C. burnetii* (Banazis et al., 2010; Alanna Cooper et al., 2012; A Cooper et al., 2013). First, following the implementation in 2012 of the enhanced surveillance exposure questionnaire macropod exposure has become the second most common reported animal exposure among patients with confirmed Q fever infection. This pattern has been quite stable since 2012. Second, 14% of patients reported exposure to macropods without reporting exposure to any of the more frequently implicated livestock species such as cattle, sheep and goats. Finally, our study provides limited evidence that exposure to macropods may be an indicator of a Q fever patient's severity of disease. Reported macropod exposure correlated with an up to 66% increased risk of hospitalisation after accounting for other factors such as patient age, sex and the year of onset. We note however that increased rates of reported exposure to a particular animal species does not imply it represents a prominent source of *C. burnetii*. Many people in Australia observe and encounter macropods on a regular basis without contracting Q fever, and we are unaware of any empirical evidence that pigs are a source of *C. burnetii* in Australia. Our findings should be used to motivate further empirical studies to identify transmission pathways among cohorts of individuals reporting different exposure profiles. Useful future studies can also address whether there is any difference between domestic vs feral animal exposure rates and can investigate other possible animal exposures for their associations with patient cohorts

While risk of hospitalisation due to Q fever may not necessarily be a robust proxy for severity, associations with hospitalisation risk can still uncover important patterns in the burden of disease. In addition to the risk factor of macropod exposure and consistent with previous studies in Australia, we found that working-age and older males were at higher risk of hospitalisation (Garner, Longbottom, Cannon, & Plant, 1997; Sloan-Gardner et al., 2017). An interesting association was the negative influence of exposure to animal births on hospitalisation risk. Traditionally, assisting in livestock births is considered one of the riskiest occupational activities for acquiring Q fever, particularly if this occurs during a *Coxiella*-induced abortion wave (Berri, Rousset, Champion, Russo, & Rodolakis, 2007; Boden, Brasche, Straube, & Bischof, 2014). Without an in-depth understanding of who attends animal births on each property, it is difficult to ascertain whether this finding is being confounded by other factors that were not captured by our exposure dataset.

Several limitations of our study should be considered when interpreting our results. First, frequent patterns of reported co-exposures make it challenging to pinpoint the exact source of infection. For example, sheep and goat exposures were very commonly co-reported, as were macropod and pig exposures. This is not surprising. Mixed-species farms are common in Queensland and both macropods and feral pigs are widespread across the state (Bastin, Smith, Watson, & Fisher, 2009; Gentle, Speed, & Marshall, 2015; Woodall, 1983). Reports of 'exposure' may in many cases simply relate to observations of a nearby animal, rather than any meaningful interaction that could represent a transmission pathway. Household investigations to improve estimates of source attribution are needed to tease these patterns apart. Second, a lack of data to distinguish between pre-school and school-aged children meant that we could not assess whether these groups may have different exposure profiles. Variation in the stringency of follow-up investigation across different treatment centres may lead to inconsistencies in the detail of exposure reports. And finally, our reliance on notification data means that only a proportion of the total cases occurring in Queensland during the study period were included.

In conclusion, our study has demonstrated that Q fever epidemiology in Queensland is non-stationary in that exposure factors for Q fever notifications and risk of hospitalisation play different roles depending on location. Our findings suggest local investigations are necessary to uncover factors associated with exposure to infection in the high-risk areas and populations identified in this study.

Acknowledgements

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Conflict of interest statement

The authors declare that we have no conflict of interest

Data availability statement

Restrictions apply to the availability of these data, which were used under license for this study. Data are available upon justified request from Queensland Health’s Epidemiology & Research Unit.

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Table 1: Summary statistics for the eight demographic groups used in topic modelling analysis.

Demographic group	**# individuals**	**# total words (mean per individual)**	**# unique words (mean per individual)**
Females			
0 - 18 years	56	361 (6.45)	94 (1.68)
19 – 34 years	69	489 (7.09)	144 (2.09)
35 - 64 years	346	2,222 (6.42)	285 (0.82)
65 - 100 years	63	437 (6.94)	115 (1.83)
Males			
0 - 18 years	125	1,223 (9.78)	195 (1.56)
19 – 34 years	283	2,268 (8.01)	305 (1.08)
35 - 64 years	905	6,163 (6.81)	381 (0.42)
65 - 100 years	197	1,319 (6.70)	216 (1.10)

Individual patients were grouped by age and sex categories and their responses to open-ended exposure questions were pooled to form a document term matrix. Stop words, numerics and words recorded fewer than five times overall were removed prior to analysis.

FIGURE LEGENDS

Figure 1: Results from topic model analysis of Q fever patient responses to open-ended exposure questions. (Left) relative contributions of each of the five latent response word groups (i.e. topics) to each demographic group's total word composition; (Right) wordclouds depicting words that had the highest discriminatory power for each of the five latent response word topics. Colours of wordclouds correspond to colours of word topics. Sizes of words are proportional to their discriminatory power (larger size indicates a word is more strongly associated with that particular word topic). Bold text indicates key discriminatory words indicative of possible exposure pathways. Note that italic text refers to names of towns in rural Queensland: Chinchilla, Boonah, Winton, Isisford, Mitchell, Dirranbandi, Bollon, Charleville, Minnel, Morven, Emerald and Sarina.

Figure 2: Distributions of human Q fever notifications assigned to each word topic across Local Government Areas (LGAs) in Queensland, Australia from the years 2001 – 2017. Topics were identified by applying a topic model analysis of Q fever patient responses to open-ended exposure questions. Numbers of notifications are adjusted for the resident human population size in each LGA to present a notification rate. This figure was generated in R version 3.3.3 using a shapefile of Queensland LGAs, available from data.qld.gov.au.

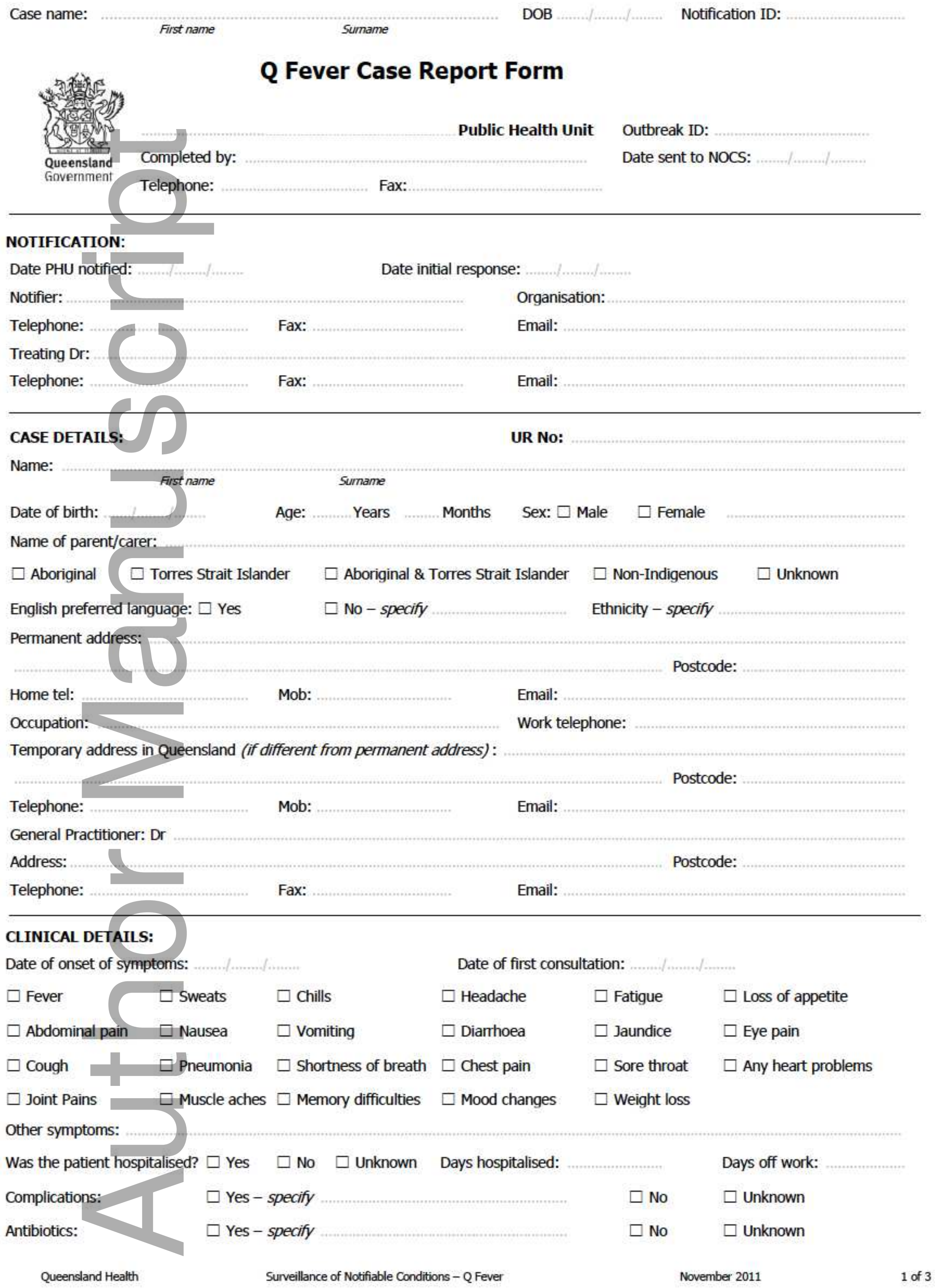
Figure 3: Locations of human Q fever notifications across Local Government Areas (LGAs) in Queensland, Australia with reported exposure to target animal groups from the years 2001 – 2017. Numbers of notifications are adjusted for the resident human population size in each LGA to present a notification rate. Note, the final dataset included 1,380 patients but some of these reported exposure to two or more animal groups. This figure was generated in R version 3.3.3 using a shapefile of Queensland LGAs, available from data.qld.gov.au.

Figure 4: Proportions of Q fever notifications in Queensland, Australia reporting potential exposure to target animal groups, by year (**a**) and word topic identified by Latent Dirichlet Allocation modelling (**b**). Colours of stacked bar charts represent the proportions of notifications with reported exposure for each of the five animal groups. Note that an expanded surveillance form was rolled out in Queensland from 2012 to specifically prompt patients to report animal exposures.

Figure 5: Conditional associations among exposure (recorded as 'reported exposure' or 'no reported exposure') and hospitalisation (recorded as 'hospitalised' or 'not hospitalised')

variables estimated from Markov Random Fields network models for the full dataset (from the years 2001 – 2017; n = 1,380; top graph) and a reduced dataset that followed the rollout of an extended surveillance form (years 2012 – 2017; n = 979; bottom graph). Numbers on the diagonals indicate the total number of Q fever notifications in Queensland, Australia in which a single exposure was recorded (i.e. the variable in the specified row was recorded as a '1' while all other variables were recorded as '0'). Numbers in the off-diagonals represent numbers of co-exposures. Darker reds indicate that a variable pair's exposure probabilities are positively associated after accounting for all other variables in the graph, while darker blues indicate negative associations among pairs of variables.

APPENDIX 1



Case name: .... DOB ..../......./....... Notification ID: ....
First name *Surname*

Q Fever Case Report Form

Queensland Government

.... **Public Health Unit** Outbreak ID: ....
Completed by: .... Date sent to NOCS: ..../......./.......
Telephone: .... Fax: ....

NOTIFICATION:

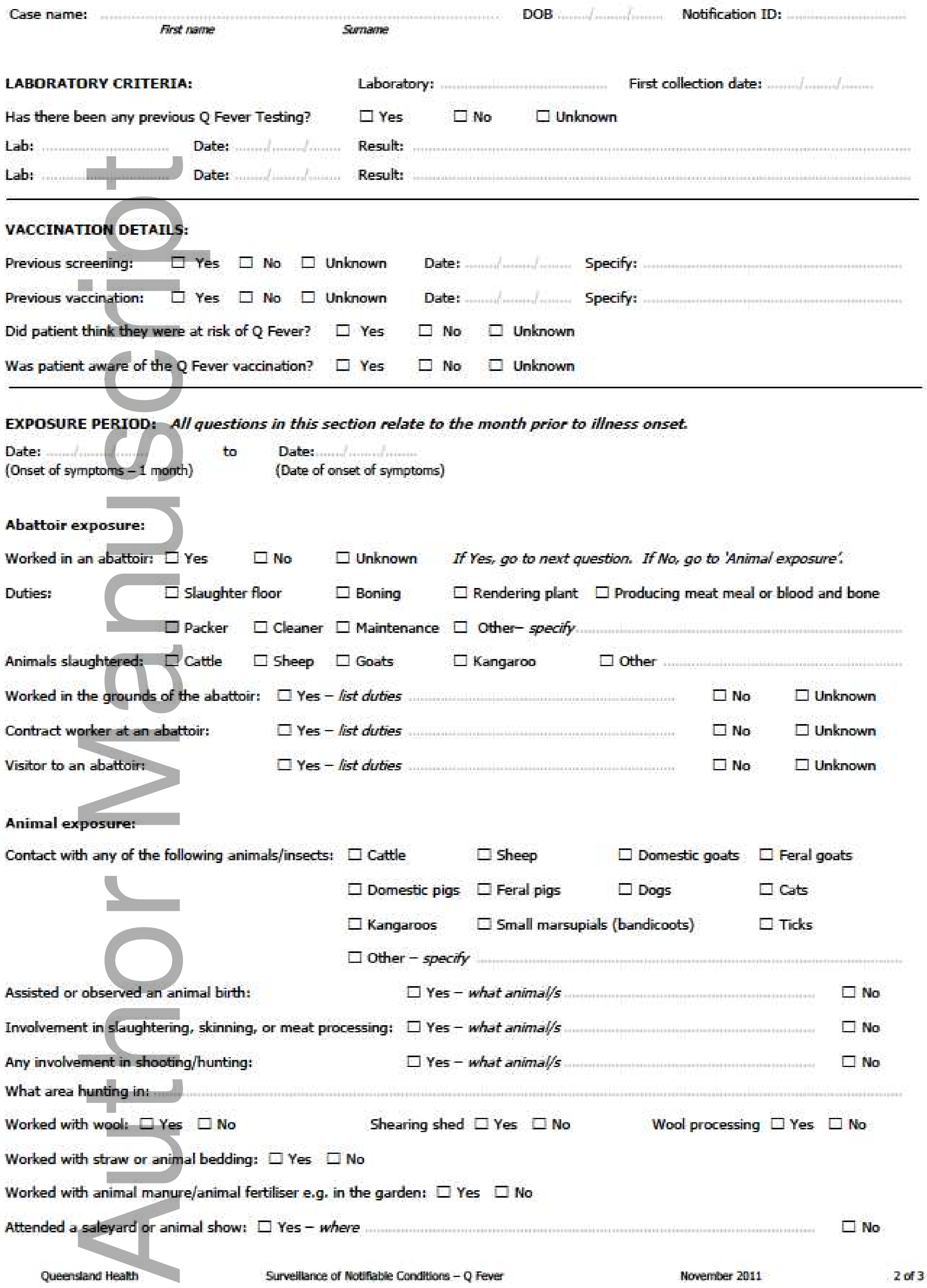
Date PHU notified: ..../......./....... Date initial response: ..../......./.......
Notifier: .... Organisation: ....
Telephone: .... Fax: .... Email: ....
Treating Dr: ....
Telephone: .... Fax: .... Email: ....

CASE DETAILS: **UR No:** ....
Name: ....
First name *Surname*
Date of birth: ..../......./....... Age: .... Years .... Months Sex: □ Male □ Female ....
Name of parent/carer: ....
□ Aboriginal □ Torres Strait Islander □ Aboriginal & Torres Strait Islander □ Non-Indigenous □ Unknown
English preferred language: □ Yes □ No – *specify* .... Ethnicity – *specify* ....
Permanent address: ....
.... Postcode: ....
Home tel: .... Mob: .... Email: ....
Occupation: .... Work telephone: ....
Temporary address in Queensland *(if different from permanent address)* : ....
.... Postcode: ....
Telephone: .... Mob: .... Email: ....
General Practitioner: Dr ....
Address: .... Postcode: ....
Telephone: .... Fax: .... Email: ....

CLINICAL DETAILS:

Date of onset of symptoms: ..../......./....... Date of first consultation: ..../......./.......
□ Fever □ Sweats □ Chills □ Headache □ Fatigue □ Loss of appetite
□ Abdominal pain □ Nausea □ Vomiting □ Diarrhoea □ Jaundice □ Eye pain
□ Cough □ Pneumonia □ Shortness of breath □ Chest pain □ Sore throat □ Any heart problems
□ Joint Pains □ Muscle aches □ Memory difficulties □ Mood changes □ Weight loss
Other symptoms: ....
Was the patient hospitalised? □ Yes □ No □ Unknown Days hospitalised: .... Days off work: ....
Complications: □ Yes – *specify* .... □ No □ Unknown
Antibiotics: □ Yes – *specify* .... □ No □ Unknown

Queensland Health Surveillance of Notifiable Conditions – Q Fever November 2011 1 of 3



Case name: ……………………………………………… DOB ……/……/…… Notification ID: ……………………
First name *Surname*

LABORATORY CRITERIA: Laboratory: …………………… First collection date: ……/……/……

Has there been any previous Q Fever Testing? □ Yes □ No □ Unknown

Lab: …………………… Date: ……/……/…… Result: ……………………………………………

Lab: …………………… Date: ……/……/…… Result: ……………………………………………

VACCINATION DETAILS:

Previous screening: □ Yes □ No □ Unknown Date: ……/……/…… Specify: ……………………

Previous vaccination: □ Yes □ No □ Unknown Date: ……/……/…… Specify: ……………………

Did patient think they were at risk of Q Fever? □ Yes □ No □ Unknown

Was patient aware of the Q Fever vaccination? □ Yes □ No □ Unknown

EXPOSURE PERIOD: ***All questions in this section relate to the month prior to illness onset.***

Date: ……/……/…… to Date: ……/……/……
(Onset of symptoms – 1 month) (Date of onset of symptoms)

Abattoir exposure:

Worked in an abattoir: □ Yes □ No □ Unknown *If Yes, go to next question. If No, go to 'Animal exposure'.*

Duties: □ Slaughter floor □ Boning □ Rendering plant □ Producing meat meal or blood and bone
□ Packer □ Cleaner □ Maintenance □ Other– *specify* ……………………

Animals slaughtered: □ Cattle □ Sheep □ Goats □ Kangaroo □ Other ……………………

Worked in the grounds of the abattoir: □ Yes – *list duties* …………………… □ No □ Unknown

Contract worker at an abattoir: □ Yes – *list duties* …………………… □ No □ Unknown

Visitor to an abattoir: □ Yes – *list duties* …………………… □ No □ Unknown

Animal exposure:

Contact with any of the following animals/insects: □ Cattle □ Sheep □ Domestic goats □ Feral goats
□ Domestic pigs □ Feral pigs □ Dogs □ Cats
□ Kangaroos □ Small marsupials (bandicoots) □ Ticks
□ Other – *specify* ……………………

Assisted or observed an animal birth: □ Yes – *what animal/s* …………………… □ No

Involvement in slaughtering, skinning, or meat processing: □ Yes – *what animal/s* …………………… □ No

Any involvement in shooting/hunting: □ Yes – *what animal/s* …………………… □ No

What area hunting in: ……………………………………………

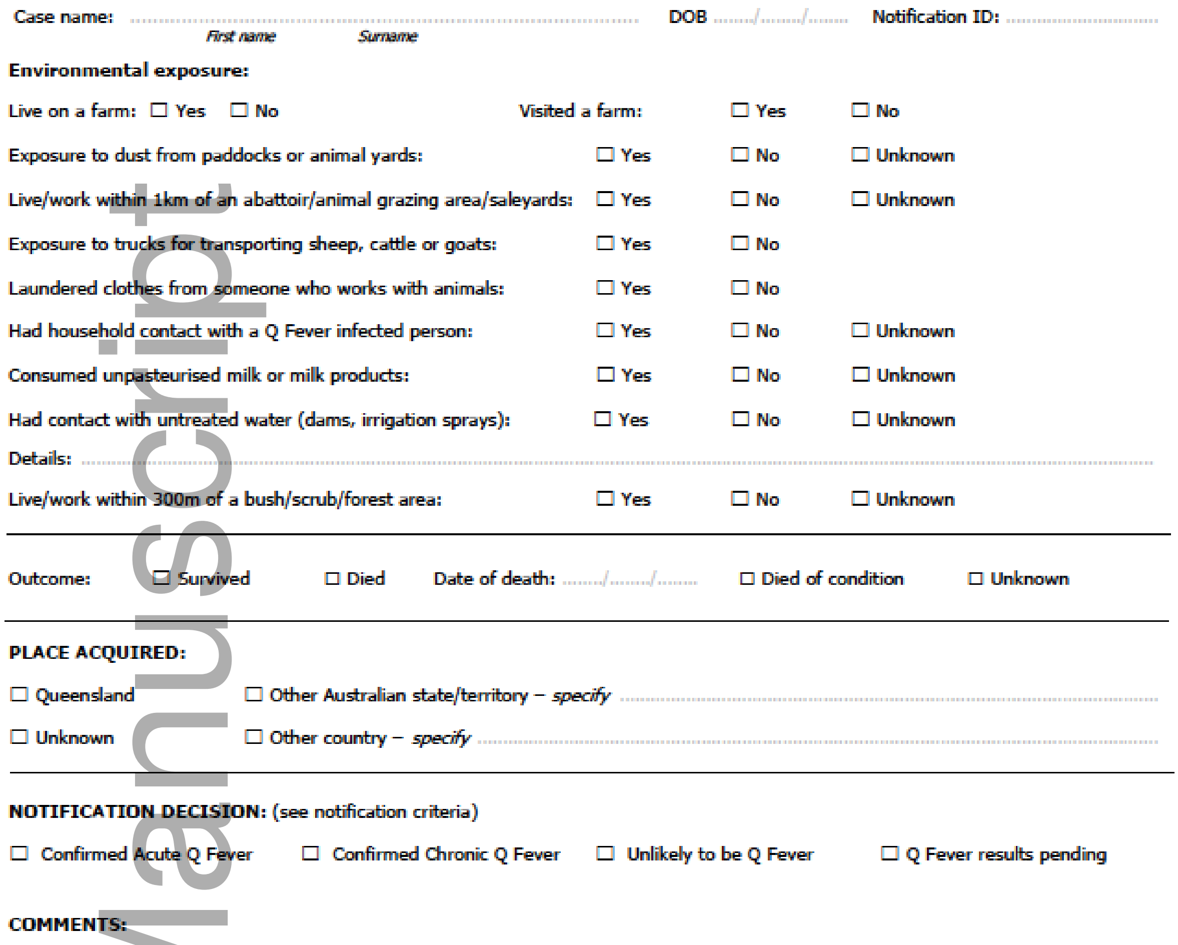
Worked with wool: □ Yes □ No Shearing shed □ Yes □ No Wool processing □ Yes □ No

Worked with straw or animal bedding: □ Yes □ No

Worked with animal manure/animal fertiliser e.g. in the garden: □ Yes □ No

Attended a saleyard or animal show: □ Yes – *where* …………………… □ No

Queensland Health Surveillance of Notifiable Conditions – Q Fever November 2011 2 of 3



Case name: .... DOB ..../......./....... Notification ID: ....

First name *Surname*

Environmental exposure:

Live on a farm: ☐ Yes ☐ No Visited a farm: ☐ Yes ☐ No

Exposure to dust from paddocks or animal yards: ☐ Yes ☐ No ☐ Unknown

Live/work within 1km of an abattoir/animal grazing area/saleyards: ☐ Yes ☐ No ☐ Unknown

Exposure to trucks for transporting sheep, cattle or goats: ☐ Yes ☐ No

Laundered clothes from someone who works with animals: ☐ Yes ☐ No

Had household contact with a Q Fever infected person: ☐ Yes ☐ No ☐ Unknown

Consumed unpasteurised milk or milk products: ☐ Yes ☐ No ☐ Unknown

Had contact with untreated water (dams, irrigation sprays): ☐ Yes ☐ No ☐ Unknown

Details: ....

Live/work within 300m of a bush/scrub/forest area: ☐ Yes ☐ No ☐ Unknown

Outcome: ☐ Survived ☐ Died Date of death: ..../......./....... ☐ Died of condition ☐ Unknown

PLACE ACQUIRED:

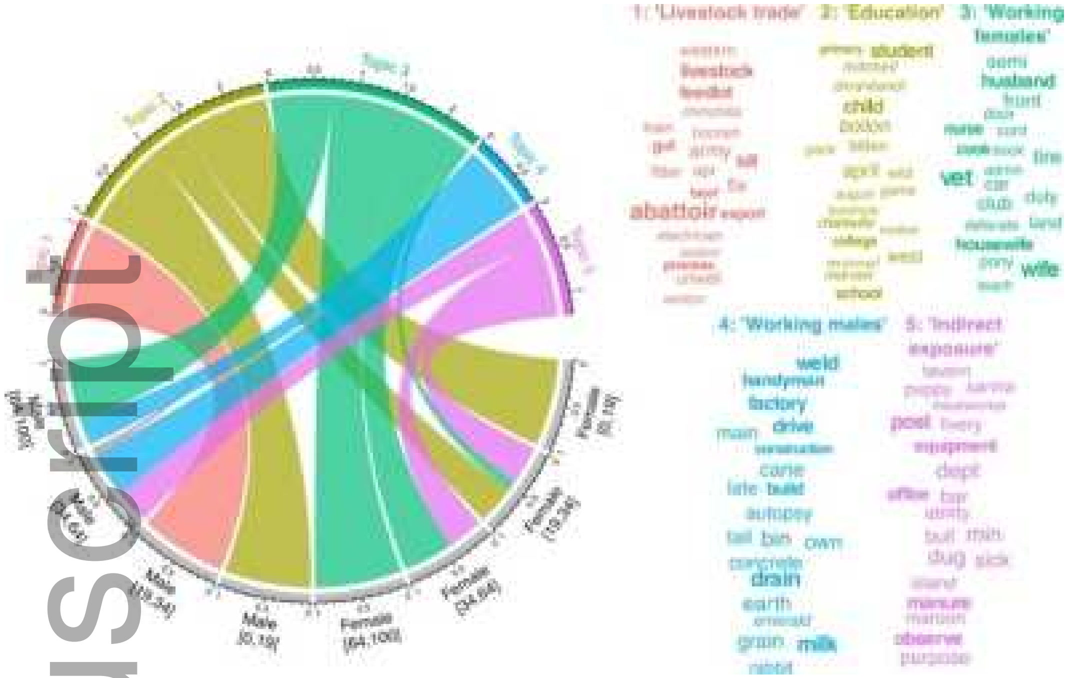
☐ Queensland ☐ Other Australian state/territory – *specify* ....

☐ Unknown ☐ Other country – *specify* ....

NOTIFICATION DECISION: (see notification criteria)

☐ Confirmed Acute Q Fever ☐ Confirmed Chronic Q Fever ☐ Unlikely to be Q Fever ☐ Q Fever results pending

COMMENTS:



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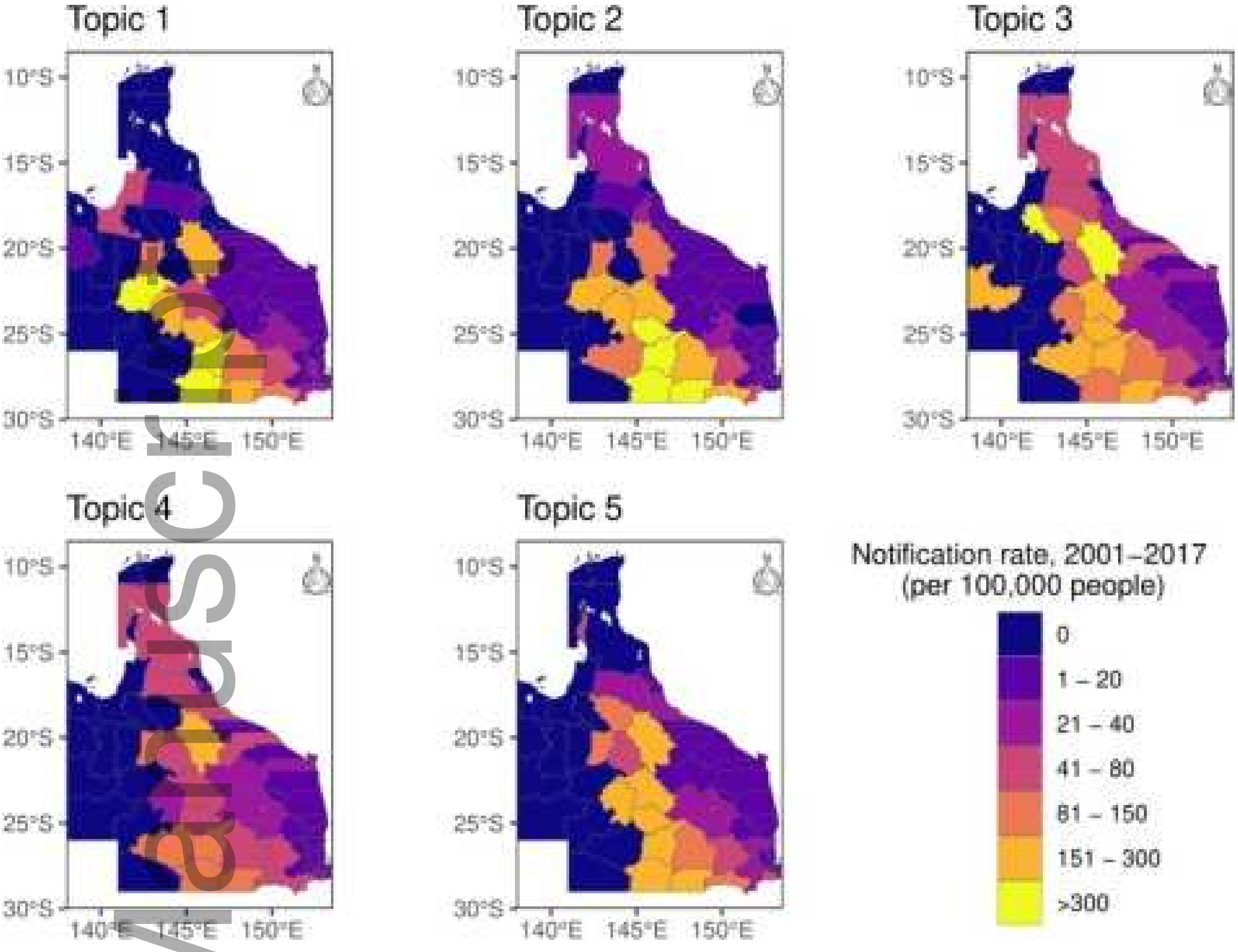

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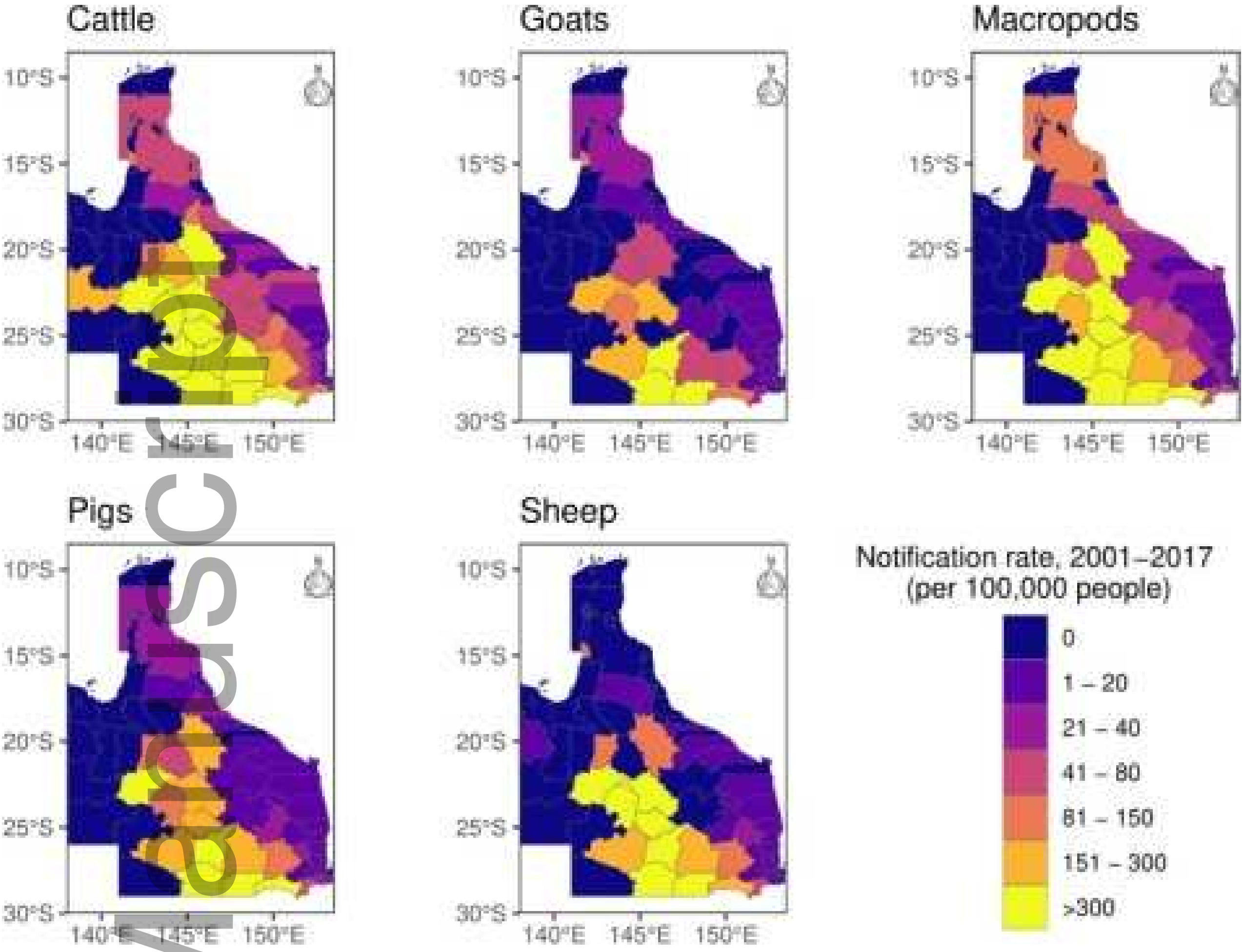

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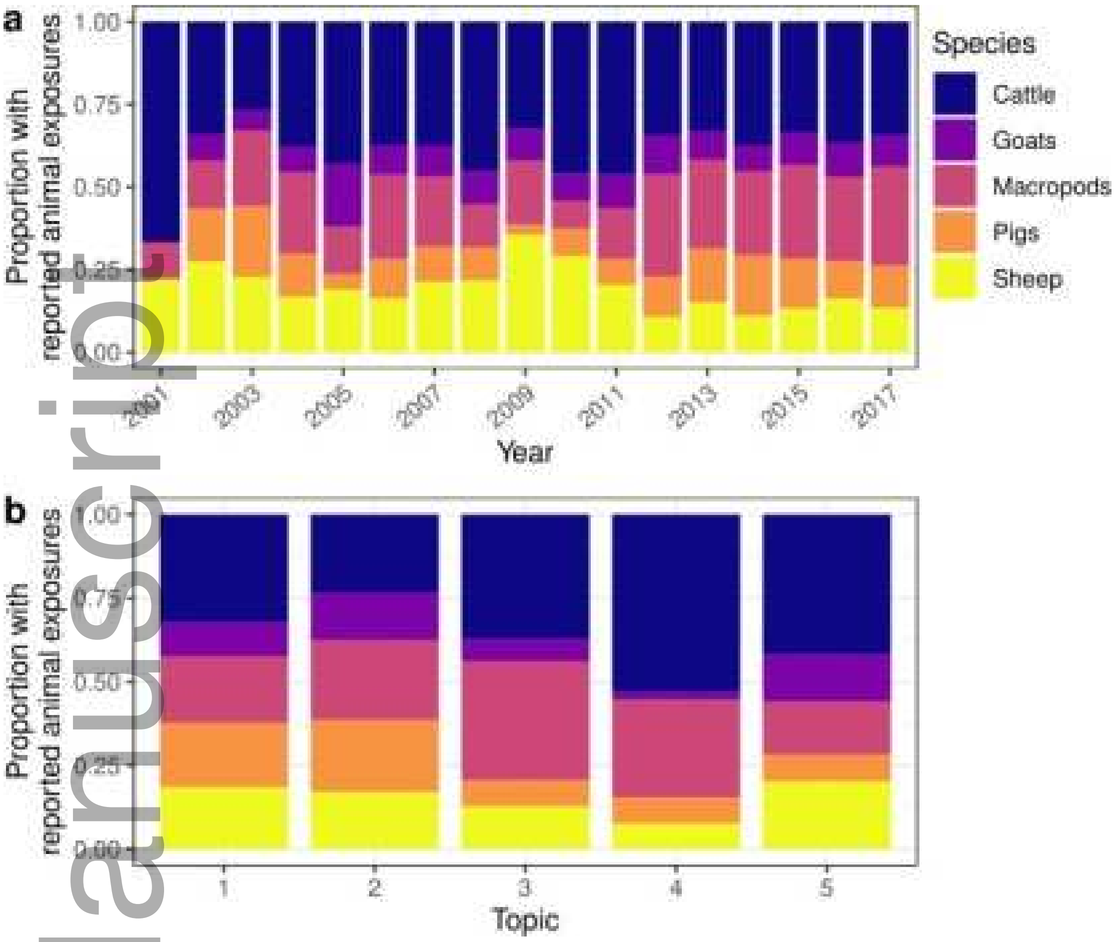

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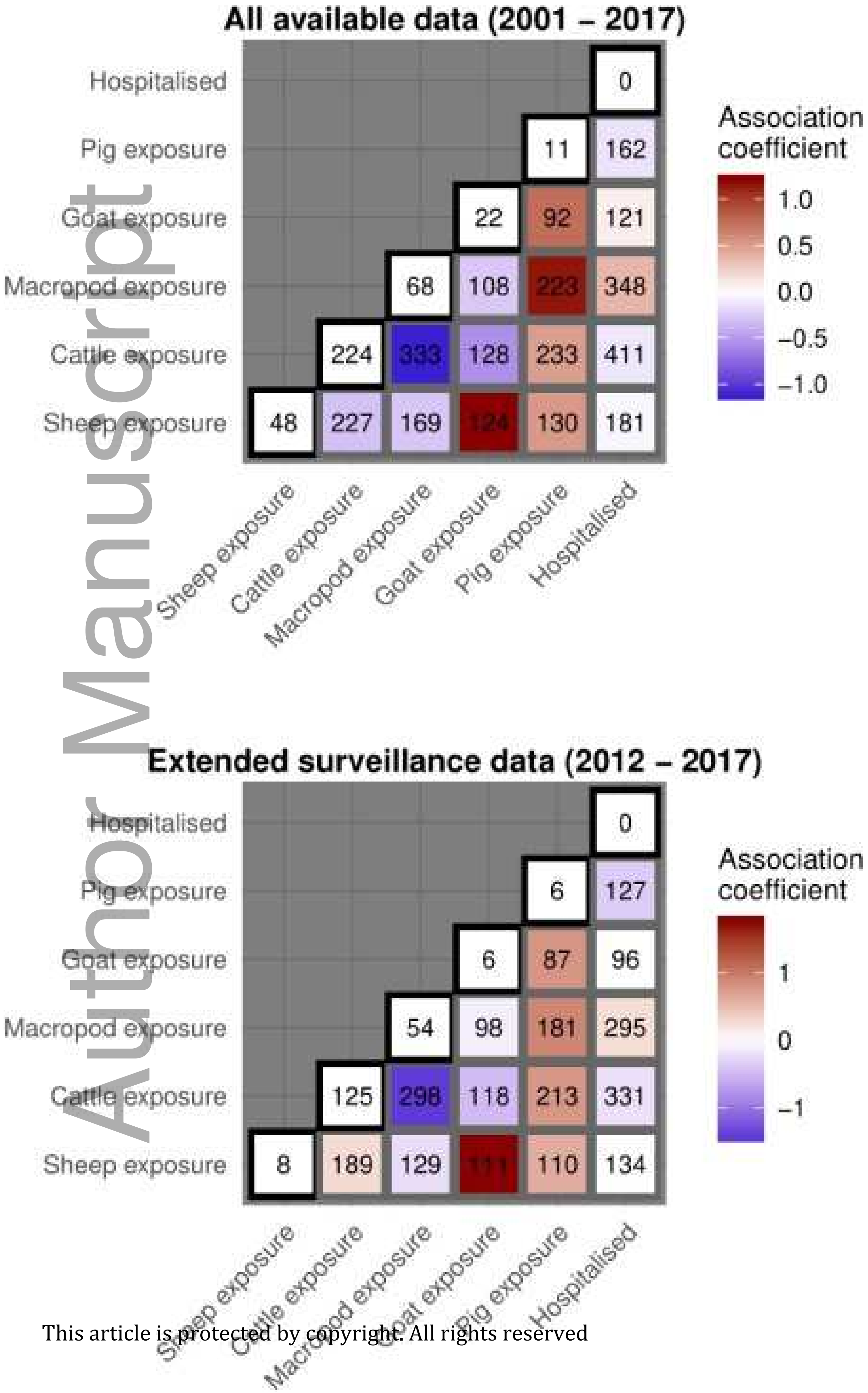
All available data (2001 – 2017)
Hospitalised
Pig exposure
Goat exposure
Macropod exposure
Cattle exposure
Sheep exposure
0
11
162
22
92
121
68
108
223
348
224
333
128
233
411
48
227
169
124
130
181
Sheep exposure
Cattle exposure
Macropod exposure
Goat exposure
Pig exposure
Hospitalised
Association coefficient
1.0
0.5
0.0
−0.5
−1.0
Extended surveillance data (2012 – 2017)
Hospitalised
Pig exposure
Goat exposure
Macropod exposure
Cattle exposure
Sheep exposure
0
6
127
6
87
96
54
98
181
295
125
298
118
213
331
8
189
129
111
110
134
Sheep exposure
Cattle exposure
Macropod exposure
Goat exposure
Pig exposure
Hospitalised
Association coefficient
1
0
−1

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Title:
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Date:
2020-04-20

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