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# Assessing the probability of acquisition of meticillin-resistant *Staphylococcus aureus* (MRSA) in a dog using a nested stochastic simulation model and logistic regression sensitivity analysis☆

J. Heller[a,*], G.T. Innocent[b], M. Denwood[a], S.W.J. Reid[a], L. Kelly[c,d], D.J. Mellor[a]

[a] *Boyd Orr Centre for Population and Ecosystem Health, Institute of Comparative Medicine, Faculty of Veterinary Medicine, University of Glasgow, Bearsden G61 1QH, UK*
[b] *Biomathematics and Statistics Scotland, JCMB, The King's Buildings, Edinburgh EH9 3JZ, UK*
[c] *Department of Statistics and Modelling Science, University of Strathclyde, Livingstone Tower, Richmond Street, Glasgow G1 1XH, UK*
[d] *Centre for Epidemiology and Risk Analysis, Veterinary Laboratories Agency, New Haw, Addlestone, Surrey KT15 3NB, UK*

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ABSTRACT

Meticillin-resistant *Staphylococcus aureus* (MRSA) is an important nosocomial and community-acquired pathogen with zoonotic potential. The relationship between MRSA in humans and companion animals is poorly understood. This study presents a quantitative exposure assessment, based on expert opinion and published data, in the form of a second order stochastic simulation model with accompanying logistic regression sensitivity analysis that aims to define the most important factors for MRSA acquisition in dogs.

The simulation model was parameterised using expert opinion estimates, along with published and unpublished data. The outcome of the model was biologically plausible and found to be dominated by uncertainty over variability. The sensitivity analysis, in the form of four separate logistic regression models, found that both veterinary and non-veterinary routes of acquisition of MRSA are likely to be relevant for dogs.

The effects of exposure to, and probability of, transmission of MRSA from the home environment were ranked as the most influential predictors in all sensitivity analyses, although it is unlikely that this environmental source of MRSA is independent of alternative sources of MRSA (human and/or animal). Exposure to and transmission from MRSA positive family members were also found to be influential for acquisition of MRSA in pet dogs, along with veterinary clinic attendance and, while exposure to and transmission from the veterinary clinic environment was also found to be influential, it was difficult to differentiate between the importance of independent sources of MRSA within the veterinary clinic.

The implementation of logistic regression analyses directly to the input/output relationship within the simulation model presented in this paper represents the application of a variance based sensitivity analysis technique in the area of veterinary medicine and is a useful means of ranking the relative importance of input variables.



## 1. Introduction

Meticillin-resistant *Staphylococcus aureus* (MRSA) is a well described, clinically important nosocomial pathogen in human hospitals. Exposure of at-risk humans to MRSA may result in infectious disease ranging from skin and soft tissue infection to fulminant pneumonia and refractory

☆ In this document, 'meticillin' has been used in place of 'methicillin' in accordance with the International Pharmacopoeia guidelines.

* Corresponding author. Present address: School of Animal and Veterinary Sciences, Charles Sturt University, Locked Bag 588, Wagga Wagga, NSW 2678, Australia. Tel.: +61 (0) 2 69332839; fax: +61 (0) 2 69332991.
*E-mail address:* jheller@csu.edu.au (J. Heller).

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sepsis. Infection with MRSA is associated with a poorer outcome and increased mortality, when compared with meticillin-susceptible *S. aureus* infection (Whitby et al., 2001). However, the description of the epidemiology of MRSA is not constrained to the hospital environment. As with many other opportunistic pathogens, MRSA may be found as a commensal, most commonly located in the anterior nares, but also in the pharynx, perineum and other skin sites (Wertheim et al., 2005). MRSA is also recognised as an emerging pathogen within the community, with enhanced virulence factors in this sub-population of community-associated MRSA and an increased likelihood of infection of non-compromised individuals (Elston, 2007). Recent identification of a distinct MRSA clone, termed ST-398, amongst pigs, pig farmers and veterinarians in The Netherlands (Voss et al., 2005) highlights the potential contribution of animals to the spread of this pathogen within the community setting (van Loo et al., 2007).

In contrast to the MRSA strains most commonly found in pigs, MRSA found in dogs are indistinguishable from the most common hospital acquired strains found in humans; predominantly EMRSA-15 in the UK (Baptiste et al., 2005; Loeffler et al., 2005; Moodley et al., 2006). While the number of reports of MRSA in dogs has increased over the past decade and considerable interest exists in this area from a canine health and welfare perspective, the relationship between MRSA in humans and dogs is poorly defined. It is known that dogs may act as reservoirs, defined as having the potential for direct or indirect transmission, of MRSA for humans and that the same strain is often found in dogs and humans inhabiting the same household, or veterinary workers in contact with infected dogs (Cefai et al., 1994; Manian, 2003; Leonard et al., 2006). However, to date it has not been possible to describe definitively the primary direction of transfer between humans and dogs (Baptiste et al., 2005; Leonard and Markey, 2007). Consequently, while it is assumed that humans are the most important source of MRSA for dogs, it is not clear where the greatest risk for acquisition in dogs originates. Similarly, the potential contribution of dogs that carry or are infected with MRSA to the burden of disease in humans and, conversely, the potential contribution of colonised and infected humans to canine disease, has not been directly quantified.

Risk assessment is widely accepted and prescribed as a set of technical approaches that can be used to explore the combined effects of multiple factors implicated in a risk pathway. Critically, it is claimed that one of the first purposes and greatest strengths of risk assessment is its ability to rank the effect of multiple inputs on a single output and thus identify high priority data gaps, or priority candidate mitigation targets (Saltelli, 2000; Vose, 2000). In order to begin to quantify the contributions of dogs and humans to zoonotic transfer of MRSA, an initial assessment of the risk of acquisition of MRSA in dogs was undertaken to allow the identification of important sources of the pathogen and the overall risk of acquisition of MRSA. Given the data-sparse nature of this field an additional important aim was to assess the ability of a risk assessment approach to identify priority data gaps for future research.

This paper describes a quantitative stochastic model with resultant exposure assessment and accompanying sensitivity analysis, constructed to define the most influential sources for the acquisition of MRSA in dogs, enabling the first step in quantification of the relationship between MRSA in dogs and humans.

## 2. Materials and methods

### 2.1. Data sources

Data were sourced from published reports and where experimental or observational studies were unavailable, from expert opinion obtained using a structured expert opinion elicitation technique. Briefly, useable opinions were obtained from 14 experts using a written questionnaire[1] that followed previously defined techniques (Dillman, 1983; Vose, 2000) and the results for each parameter under consideration were combined with equal weightings. Validity was assessed using estimates of agreement between experts, along with self-assessed confidence, 'expertness' and the use of 'seed' variables (Cooke and Goossens, 2000). Experts were selected with varied backgrounds and experiences, spanning areas of medical and veterinary microbiology, antimicrobial resistance and epidemiology. All sources of data are presented briefly in Tables 1 and 2.

### 2.2. Simulation model

A stochastic model was developed to simulate the proportion of dogs that would acquire MRSA, as colonisation, carriage or infection, over a 24 h period. Colonisation and carriage are defined by the presence or absence of attachment of the bacteria to target areas (cells or extracellular matrices) respectively, whereas infection refers to disease resulting from MRSA (Projan and Novick, 1997). The model structure was based on a pre-defined conceptual model that outlined the likely pathways of acquisition of MRSA for a single dog over a 24 h time period identifying seven pathways for acquisition and stratified to represent human family member, non-family member or veterinary worker; animal, limited to dogs in the community or at veterinary clinics; and environmental sources of MRSA that could be accessed through community and veterinary hospital routes. The seven separate pathways for acquisition were considered to be non-sequential and were not mutually exclusive. All of the identified potential routes of acquisition of MRSA were accessible if a veterinary clinic was attended in the 24 h under consideration, but pathways were restricted to the community routes only if a veterinary clinic had not been attended during this period.

Two sub-steps were considered within each pathway: first, the probability of exposure to a positive source of MRSA (human, animal or environmental) and, second, the probability of transmission of MRSA from that source, given that exposure has occurred. Simplified scenario pathway models showing different factors considered in the probability of MRSA acquisition at each sub-stage of the conceptual model are presented in Fig. 1.

[1] Elicitation material available from the author on request.