A Cross-Sectional Study of Antimicrobials used for Surgical Prophylaxis by Bovine Veterinary Practitioners in Australia

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Abstract

Introduction: Antimicrobials are widely used in veterinary practices, but there has been no investigation of antimicrobial classes used or the appropriateness of their use in bovine practice. This study investigated antimicrobial use for surgical prophylaxis in bovine practice in Australia.

Methods: A cross-sectional study of veterinarian antimicrobial usage patterns was conducted using an online questionnaire. Information solicited included respondent’s details, the frequency with which antimicrobials were used for specific surgical conditions (including the dose, timing and duration of therapy) and details of practice antimicrobial use policies and sources of information about antimicrobials.

Results: In total, 212 members of the Australian veterinary profession working in bovine practice completed the survey. Antimicrobials were always or frequently used by more than 75% of respondents in all scenarios. Generally, antimicrobial drug choice was appropriate for the reported surgical conditions. Procaine penicillin and oxytetracycline accounted for 93% of use. However, there was a wide range of doses used, with under-dosing and inappropriate timing of administration being common reasons for inappropriate prophylactic treatment. There was very low use of critically important antimicrobials (3.3% of antimicrobials reported).

Conclusions: Antimicrobial use guidelines need to be developed and promoted to improve the responsible use of antimicrobials in bovine practice.

Keywords
Antibiotic; stewardship; resistance; cattle
Introduction

Antimicrobial use in humans and animals generates selective pressure that increases the prevalence of antimicrobial resistance in bacterial populations (Jiang and others 2006; Leite-Martins and others 2014; Rentala and others 2004). With the growing threat of antimicrobial resistant bacteria in medical hospitals, the community, and in animals, there is an increasing focus on veterinary antimicrobial usage (The Review on Antimicrobial Resistance 2014) and many global antimicrobial resistance strategies emphasise antimicrobial stewardship in both human and veterinary medicine (Commonwealth of Australia 2016; United Nations General Assembly 2011; World Health Organisation 2015). In addition, veterinarians, farm workers, and their families, have been shown to have a risk of acquiring multidrug resistant bacteria from livestock (Bosch and others 2015; Dohmen and others 2015; Liu and others 2015).

Data on quantities of veterinary antimicrobials in Australia is limited to periodic reports by the Australian Pesticides and Veterinary Medicines Authority, which records total volumes of antimicrobials imported for use in the veterinary and agricultural sectors (Australian Pesticides and Veterinary Medicines Authority 2014). However, the distribution of use of these antimicrobials cannot be tracked further except for specific formulations, such as intramammary therapies, where use is largely limited to the treatment of clinical and subclinical mastitis in dairy cows. Recent publications from Europe have investigated the common reasons for antimicrobial use in cattle (De Briyne and others 2014) and factors that influence prescribing habits among veterinarians (De Briyne and others 2013; Gibbons and others 2013). However, there has been no investigation of antimicrobials used for surgical prophylaxis in cattle. In addition, the classes of antimicrobial used, the appropriateness of the doses administered and the duration of therapy in cattle have not been evaluated.
The Australian Strategic and Technical Advisory Group on Antimicrobial Resistance (ASTAG) issued an importance rating and summary of antibacterials used in human health in Australia in 2015 (Australian Strategic and Technical Advisory Group on Antimicrobial Resistance 2015). Those given a high importance rating include piperacillin-tazobactam, ticarcillin-clavulanate, the 3rd and 4th generation cephalosporins, aztreonam, tigecycline, vancomycin, teicoplanin, amikacin, the streptogramins, fluoroquinolones and rifampicin. The Australian Strategic and Technical Advisory Group on Antimicrobial Resistance have recommended that these antimicrobials should be used as third line therapies - that is, they should only be used when culture and susceptibility testing or other compelling clinical evidence justifies their use. The 3rd generation cephalosporins are the only critically important antimicrobials that are registered for use in cattle in Australia.

There are no guidelines for antimicrobial use in cattle in Australia. Despite this, appropriateness of drug doses and timing of administration can be deduced from the pharmacokinetics of antimicrobials in cattle. Guidelines provide a necessary first step towards the implementation of veterinary antimicrobial stewardship, but audit and feedback are necessary to improve prescribing practices. Antimicrobial use for surgical prophylaxis has been an area in human medicine where application of guidelines and monitoring has led to more appropriate antimicrobial therapy (Nelson and others 2009).

The aim of this study was to investigate self-reported antimicrobial use in a range of surgical conditions in bovine practice in Australia and to assess appropriateness of drug doses and timing of administration to prevent surgical site infection.

Materials and Methods
The survey study population and distribution is described elsewhere (Hardefeldt and others 2017a). The study population comprised those veterinarians who completed surgery on cattle as part of their weekly practice (estimated to be 2400 (THINC 2015) in 2015). Sample size calculations were carried out to determine the number of respondents required to make appropriate inferences from the survey. To be 95% certain that our estimate of the population prevalence of veterinarians using a given class of antimicrobials was within 7.5% of the true population prevalence of 50%, a total of 160 completed surveys were required. Sample size calculations were carried out assuming a 50% population prevalence because this provided the largest sample size estimate for a constant margin of error.

Survey details are described elsewhere (Hardefeldt and others 2017a). The bovine surgical scenarios included in the survey were correction of a left displaced abomasum, caesarean section, eye ablation, exploratory laparotomy, and repair of an umbilical hernia.

Data were downloaded from the survey software to spreadsheets (Microsoft Office Excel, 2016). The entire bovine section of the survey had to be completed by the respondent to be included in the analysis. Descriptive statistics were computed with percentages being reported as the proportion of the total respondents answering a given question. Where respondents reported that they did not perform a specific surgery, these individuals were excluded from the analyses of that question. Comparison of proportions was performed using chi-squared tests using functions within Stata v13.

This research was approved by the University of Melbourne Faculty of Veterinary and Agricultural Sciences Human Ethics Advisory Group under Approval No. 1646102.
Results

A total of 212 members of the Australian veterinary profession completed the section of the survey addressing bovine practice. All states and territories were represented, as were recent and older graduates (Table 1). Livestock-only practitioners represented only 8% (95% CI, 4-12%) of respondents, while the remaining 92% (95% CI, 88-96%) treated a mixture of species (4.2% bovine and equine, 6.6% bovine and companion animals, 81% bovine, equine and companion animals), and 23% of the respondents treated only dairy cattle, 45% treated only beef cattle, and 32% treated both dairy and beef cattle. A relatively small proportion of practices had an antimicrobial use policy (22%, 95% CI, 16-28%). A wide range of sources of information on antimicrobials for surgical prophylaxis were used, with no single source of information predominating. Practitioners reported using experience (56%), textbooks (52%) and undergraduate course notes (51%) most frequently, with continuing education (50%), colleagues (48%) and the product label (43%) also frequently cited. Having an antimicrobial use policy did influence the sources of information used by some veterinarians, but only 38% of practitioners who reported having an antimicrobial use policy in place cited this practice policy as a source of information. The amount of contamination during surgery (82%) and surgical conditions (60%) were the most frequently reported influences on the decision to prescribe antimicrobials in the surgical scenarios.

The five categories indicating the frequency of antimicrobial use for each surgical condition were combined into three groups (always/frequently, sometimes/rarely and never). The majority of respondents indicated that they administered antimicrobials always or frequently in all scenarios. Eye ablation and repair of an umbilical hernia were the only scenarios in which fewer than 80% of respondents indicated that they administered antimicrobials always or frequently. Eye ablation had the least antimicrobial use; antimicrobials were used always
or frequently by 76% of respondents, sometimes or rarely by 13% of respondents and never
by 11% of respondents. The pattern of response was similar for surgery to repair an umbilical
hernia - antimicrobials were used always or frequently by 77% of respondents, sometimes or
rarely by 13% of respondents and never by 10% of respondents (Figure 1).

Overall, the most frequently prescribed antimicrobial classes in this survey were penicillins
(47%) and tetracyclines (specifically oxytetracycline, 46%). All other classes represented less
than 7% of all reported antimicrobials in the survey (3rd generation cephalosporins 3.3%,
trimethoprim sulphonamides 1.9%, erythromycin 1.1%, and tulathromycin 0.2%) (Figure 2).
There were no significant differences in the classes of antimicrobials used in the different
surgical scenarios (Figure 3). There was a very low prevalence of use of critically important
antimicrobials (3.3%), with 3rd generation cephalosporins the only drugs with this rating
reported, and use not exceeding 6% of antimicrobials used in any one scenario (Figure 3).

There was wide variation in duration of therapy across scenarios. Eye ablation and repair of
an umbilical hernia were the only scenarios in which antimicrobial therapy was halted within
24 h by more than 40% of respondents (45% and 42%, respectively). Antimicrobial therapy
was longest for correction of a left displaced abomasum, with 49% of respondents indicating
therapy was typically continued for 4-7 days (Figure 4).

The dose of procaine penicillin and oxytetracycline administered for surgical prophylaxis
varied widely. The dose of procaine penicillin administered ranged from 7.5 - 24 mg/kg, with
the most frequent dose rates being 12.5 mg/kg (37% of respondents) and 15 mg/kg (43% of
respondents). Procaine penicillin was administered once daily by 96% of respondents using a
short acting formulation, with less than 5% of respondents reporting 12 hourly
administration. Similarly, for oxytetracycline the dose range was wide (2.5 - 13.5 mg/kg),
with the most frequent dose rates being 4-5 mg/kg (52% of respondents) and 10 mg/kg (38% of respondents). Most respondents reported administering oxytetracycline once daily when using a short acting formulation (97%), with the remainder reporting that they administered it every 12 hours (2.8%). Half of the respondents reported that they administered antimicrobials for surgical prophylaxis before surgery and 50% indicated that they administered them after surgery. In addition, 20% of respondents indicated using intraperitoneal or incisional antimicrobials during surgery. There was no significant difference in the proportions of recent graduates (graduated after 2010) and older graduates using appropriate doses (70% and 67%, respectively, P = 0.97) nor in the proportion of these groups appropriately timed antimicrobial administration (48% and 44%, respectively, P=0.96). Similarly, there was no significant difference in proportions of male and female respondents using appropriate doses (32% and 33% respectively, P = 0.99) nor in the proportions of these groups using appropriately timed antimicrobial administration (47% and 45%, respectively, P=0.98). There was also no significant difference between respondents from small practices (1 or 2 veterinarians) and respondents from larger practices (more than 2 veterinarians) in either the proportions using appropriate doses (17% and 16%, respectively, P=0.99) nor in the proportions using appropriately timed antimicrobial administration (31% and 48%, respectively, P=0.89).

**Discussion**

To the best of our knowledge this is the first survey to investigate antimicrobial use by bovine veterinarians in Australia. We found that antimicrobials are used by most veterinarians for all surgical scenarios presented and that β lactams (predominately procaine penicillin) and oxytetracycline were the antimicrobials that were most commonly administered. The frequent use of prophylactic antimicrobials for routine elective surgeries,
such as hernia repairs, might be expected in ambulatory practice due to the necessity to perform surgery in exposed (outdoor) conditions. Consistent with this, 60% of respondents indicated that surgical conditions influenced their decision making about antimicrobial therapy for surgical prophylaxis. In addition, the amount of contamination was the most cited factor influencing antimicrobial use (82% of respondents). The duration of therapy was longest for correction of a left displaced abomasum, which is not an emergency procedure and does not require enterotomy, so should be able to be performed as a clean procedure. This suggests that use of antimicrobials for surgical prophylaxis is routine in bovine practice in Australia, even for clean surgeries, and that there is little consideration of the need for antimicrobial therapy in these scenarios. There is evidence that, in some situations, clean surgical procedures performed without antimicrobial prophylaxis have similar complication rates to those with antimicrobial therapy (Borg and Carmalt 2013), which should prompt a re-evaluation of the need for antimicrobial therapy in every surgical case.

A minority of respondents reported having an antimicrobial use policy in the clinic at which they practiced (22%). However, as more than 90% of the veterinarians who completed the survey were working in mixed species veterinary clinics, it is not clear whether these policies were only for companion animal species, or for all species treated by the practice. Consistent with studies on European veterinarians, experience, published literature and course notes were the most cited sources for information about antimicrobial use (De Briyne and others 2013). Experience was also the most important basis for decision making about antimicrobial use by cattle veterinarians in Ireland (Gibbons and others 2013). In contrast to equine veterinarians in Australia (Hardefeldt and others 2017b), but similar to companion animal veterinarians (Hardefeldt and others 2017a), the presence of an antimicrobial use policy in the practice did change the sources of information used for decisions about use of
antimicrobials for surgical prophylaxis, with 38% of veterinarians working in a practice with a policy citing this as an important source of information compared to 13% of those working in a practice without such a policy. However, more than 40% of practitioners with an antimicrobial use policy in their practice did not identify this as an important source of information. The failure of guidelines to influence antimicrobial prescribing behaviour in human medicine is multifactorial, with a lack of appreciation of an individual’s role in addressing the wider issue of antimicrobial resistance (Giblin and others 2004), the failure to get senior practitioners to support the use of guidelines (Cortoos and others 2008; De Souza and others 2006), the perceived inconvenience of appropriate timing of administration of drugs (Tan and others 2006), and interference of guidelines in clinical autonomy (Cribb and Barber 1997) having all been found to play a role in different scenarios. Some, or all, of these factors may also influence the successful implementation of guidelines into bovine veterinary practice.

Antimicrobials are used for surgical prophylaxis to reduce the risk of surgical site infections (Burdon 1982; Ronald 1983; Stone 1984). For this to be effective there must be adequate serum levels of antimicrobials present at the time of surgery (Classen and others 1992), which is reliant upon administration of an effective dose of antimicrobial at the appropriate time. Appropriate timing of administration can be estimated from pharmacokinetic properties of antimicrobials (time to maximal antimicrobial concentration) as can the repeat dosing intervals (twice the elimination half-life). For procaine penicillin and oxytetracycline administered intramuscularly appropriate timing would require administration two (Dubreuil and others 2001) and eight (Mevius and others 1986) hours, respectively, prior to surgical incision. If oxytetracycline is administered intravenously, administration 30 minutes prior to surgery should allow for adequate tissue concentrations at the surgical site. In this survey,
around half of the veterinarians reported administering antimicrobials after surgery was performed, and thus clearly not achieving this critical goal. In addition, the doses of procaine penicillin used varied, and were predominately lower than those recommended, and the frequency of administration was generally once daily. This dose and frequency of administration for procaine penicillin is unlikely to generate serum levels effective against common bovine pathogens (Papich and others 1993). Administration of sub-therapeutic doses may promote the development of antimicrobial resistance. Research is needed to establish minimum inhibitory concentrations for common bovine pathogens to allow for evidence based recommendations on treatment regimes. This is especially relevant in bovine practice, as off-label administration, at a higher dose or more frequent administration, has implications for with-holding periods for meat and milk. The lack of data for with-holding periods for meat and milk for appropriate doses of antimicrobials is probably a significant barrier to antimicrobial stewardship in cattle practice.

The use of intraperitoneal and intra-incisional antimicrobials by 20% of the respondents to this survey is lower than in a similar survey of Canadian veterinarians, in which more than half of the respondents reported using intraoperative antimicrobials (Chicoine and others 2008). The intraperitoneal route is used in human abdominal surgery, but the recommended formulations are those suitable for intravenous use and these are diluted in lavage solutions (Yelon and others 1996). The intraperitoneal use of some intramuscular formulations has led to severe intra-abdominal inflammation in cattle in some instances (Klein and others 1989), but safety has not been established in most cases. Research supporting efficacy is lacking in both veterinary and human medicine. Similarly, for intra-incisional antimicrobials, in human surgery some efficacy has been reported with infiltration of aqueous solutions prior to surgical incision (Pollock and others 1989; Taylor and others 1982), but there are no reports
of studies in veterinary medicine. Formulations used by respondents to this survey were predominately intramammary preparations (for intra-incisional applications) and procaine penicillin (for intra-peritoneal applications), for which there is no evidence for safety nor efficacy (data not shown).

As with procaine penicillin, reported doses of oxytetracycline varied widely. Serum concentrations of oxytetracycline can be maintained above 1 µg/mL for 24 hours after intramuscular injection at a dose of 5 mg/kg (Nouws and others 1985), which may be appropriate for some bovine pathogens (Pitkala and others 2004), but not for others (Harada and others 2005; Yoshimura and others 2001). Administration of oxytetracycline at 10 mg/kg is much more likely to maintain serum levels above minimum inhibitory concentrations for bovine pathogens over a 24 h period (Mevius and others 1986). Importantly, no current minimum inhibitory concentration data on Australian bovine pathogens are readily available to enable development of evidence based dosage recommendations, nor are data describing the organisms commonly responsible for surgical site infections in cattle. Skin pathogens such as *Streptococcus* and *Staphylococcus* spp, enteric pathogens such as *Escherichia coli* and *Enterobacter* spp, and environmental pathogens could all be expected to play a role in surgical site infections in cattle. Levels of resistance in isolates of *E. coli* from cattle in Australia are very low (Abraham and others 2015; Barlow and others 2015) as they are in many parts of Europe (de Jong and others 2012), but data on other pathogens are lacking.

Evidence from human medicine suggests that surgical antimicrobial prophylaxis for longer than 24 hours provides no benefit compared to administration for less than 24 hours (McDonald and others 1998). Similarly, in bovine surgery there has been no difference detected between single dose prophylaxis and 7-day postoperative therapy following
rumenotomy (Hartnack and others 2015) or correction of a caecal torsion (Klein and others 1994). In addition, there were no surgical site infection reported in a series of uncomplicated hernia repairs even though 30% of these cases did not receive any prophylactic antimicrobial therapy (Klein and Firth 1988). Antimicrobial use guidelines for companion animals (Holloway and others 2013) and equids (British Equine Veterinary Association 2016) also recommend discontinuing therapy within 24 hours. Clearly, despite the challenging environmental conditions, cattle surgery can be performed in a way that minimises the need for extended courses of prophylactic antimicrobials. In this survey, most respondents suggested that they used antimicrobial therapy for longer than 24 hours in all surgical scenarios, with 1-3 days and 4-7 days of therapy being most frequently selected in all but two scenarios posed (eye ablation and repair of umbilical hernia, where therapy for less than 24 hours was most frequently selected). Although relatively few practitioners indicated that they used antimicrobials for longer than seven days for uncomplicated eye ablation, umbilical hernia repair and caesarean section, such usage is concerning, as it is likely to be both excessive and unnecessary.

There are several features of this study that may have influenced the results. Recall bias may occur with questionnaire based surveys when respondents are asked to remember events that have occurred in the past. Hypothetical scenarios were posed rather than asking clinicians to recall specific cases in order to minimise this. Respondents were self-selected in this study and many were recruited at conferences, so selection bias may also be present. This may have biased the results towards practitioners who were more likely to complete continuing education, and who had more awareness of recommended prescribing practices. The survey was anonymous, to minimise response bias.
In conclusion, this survey has shown that, while antimicrobials were commonly used for surgical prophylaxis in bovine practice in Australia, the choice of antimicrobial agent was generally appropriate for the surgical scenario, with mainly procaine penicillin and oxytetracycline administered and very little use of critically important antimicrobials. Education is warranted to improve drug dosing and timing of administration prior to surgery. Further investigation into the appropriate duration of antimicrobial therapy to prevent surgical site infections in cattle is needed. Finally, further research into minimum inhibitory concentrations of common bovine pathogens and a subsequent review of drug labelling is needed to ensure that suppliers are encouraged to revise their labels to reflect the current understanding of antimicrobial pharmacokinetics and pharmacodynamics and to ensure advice about with-holding periods for meat and milk is accurate.

Acknowledgments

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Table 1. Survey respondent demographics

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NA; not available
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Figure 1. Frequency of prophylactic antimicrobial usage in cattle for different surgical scenarios.

Figure 2. Overall proportion of antimicrobials used for surgical prophylaxis across all scenarios.

*TMS: Trimethoprim sulphonamide

Figure 3. Proportions of different classes of antimicrobials for surgical prophylaxis in specific scenarios.

*LIRA: Other low importance rating antimicrobials

Figure 4. Proportions of respondents indicating differing durations of antimicrobial prophylactic therapy for specific surgical scenarios.