Author/s:
Hardefeldt, LY;Gilkerson, JR;Billman-Jacobe, H;Stevenson, MA;Thursky, K;Browning, GF;Bailey, KE

Title:
Antimicrobial labelling in Australia: a threat to antimicrobial stewardship?

Date:
2018-05-01

Citation:
Hardefeldt, L. Y., Gilkerson, J. R., Billman-Jacobe, H., Stevenson, M. A., Thursky, K., Browning, G. F. & Bailey, K. E. (2018). Antimicrobial labelling in Australia: a threat to antimicrobial stewardship?. Australian Veterinary Journal, 96 (5), pp.151-154. https://doi.org/10.1111/avj.12677.

Persistent Link:
https://hdl.handle.net/11343/283885

Hardefeldt Laura (Orcid ID: 0000-0001-5780-7567)
Browning Glenn (Orcid ID: 0000-0002-0903-2469)

PRODUCTION NOTES

Corresponding author

Name: Laura Hardefeldt

Email: Laura.Hardefeldt@unimelb.edu.au
Article Type: Short contribution

Journal Section: Education, ethics and welfare

Layout Instructions

Figures: 2

Tables: 2

Word Count (approx.): 2975

Antimicrobial labelling in Australia: a threat to antimicrobial stewardship?

LY Hardefeldt,[a,b]* JR Gilkerson,[a,b] H Billman-Jacobe,[a,b] MA Stevenson,[a,b] K Thursky,[c] GF Browning[a,b†] and KE Bailey[a,b†]
*Corresponding author.
[†]Contributed equally to this work.
[a]Asia-Pacific Centre for Animal Health, Melbourne Veterinary School, Faculty of Veterinary and Agricultural Sciences, University of Melbourne, Parkville, Victoria, Australia; Laura.Hardefeldt@unimelb.edu.au
[b]National Centre for Antimicrobial Stewardship, Melbourne Veterinary School, Faculty of Veterinary and Agricultural Sciences, University of Melbourne, Parkville, VIC, Australia
[c]National Centre for Antimicrobial Stewardship, Peter Doherty Institute, Carlton, VIC, Australia
[†]Contributed equally to this work

[Anne: short contributions have unstructured abstract = 100 words; currently 249 words]
Antimicrobial resistance is a public health emergency, placing veterinary antimicrobial use under growing scrutiny. Antimicrobial stewardship, through appropriate use of antimicrobials, is a response to this threat. The need for antimicrobial stewardship in Australian veterinary practices has had limited investigation. A 2016 survey undertaken to investigate antimicrobial usage patterns by Australian veterinarians found that antimicrobial dose rates were varied and often inappropriate. Doses of procaine penicillin in horses and cattle were often low, with 68% and 90% of respondents, respectively, reporting doses that were unlikely to result in plasma concentrations above minimum inhibitory concentrations for common equine and bovine pathogens. Frequency of penicillin administration was also often inappropriate. Gentamicin doses in horses were largely appropriate (89% of dose rates appropriate), but 9% of respondents reported twice daily dosing. Amoxycillin and amoxycillin-clavulanate were administered at the appropriate doses, or above, to dogs and cats by 54% and 70% of respondents, respectively. Here, we explore the potential reasons for inappropriate antimicrobial dose regimens and report that antimicrobial labels often recommend incorrect dose rates and thus may be contributing to poor prescribing practices. Changes to legislation are needed to ensure that antimicrobial drug labels are regularly

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/avj.12677

updated to reflect the dose needed to effectively and safely treat common veterinary pathogens. This will be especially true if changes in legislation restrict antimicrobial use by veterinarians to the uses and doses specified on the label, thus hampering the current momentum towards improved antimicrobial stewardship.

Keywords antimicrobial resistance; cattle; dose rates; guidelines; horses; penicillin; stewardship

Abbreviation AMR, antimicrobial resistance

Antimicrobial resistance (AMR) is regarded as a worldwide public health emergency.[1] In 2016, a review of AMR commissioned by the UK government suggested that approximately 700,000 people have died because of multidrug resistant infections and predicted that by 2050 the mortality rate may exceed 10 million people.[2] Antimicrobials are an essential part of veterinary medicine and their use ensures both the welfare of animals under veterinary care and the ongoing security and safety of food. The misuse of antimicrobials cannot be justified. Antimicrobial stewardship encompasses the full range of measures used to promote appropriate antimicrobial prescribing and reduce the selective pressure for development of AMR.

In 2016, a series of surveys were undertaken to investigate antimicrobial usage patterns by Australian veterinarians.[3-5] In total, 721 members of the veterinary profession completed the companion animal practice questions, 337 completed the equine practice questions and 212 completed the bovine practice questions. Respondents indicated that they used predominantly low-importance-rating antimicrobials, as defined by the Australian Strategic Technical Advisory Group on AMR.[6] The classes of antimicrobials most frequently administered for prophylaxis during small animal surgery were aminopenicillins (53%), predominantly amoxicillin-clavulanate (40%), and first-generation cephalosporins (36%).[3] For equine surgery, the most common class of antimicrobials administered was penicillins, with procaine penicillin selected by 66% of respondents and long-acting penicillins selected by 3.3% of respondents.[4] Other antimicrobials commonly administered to horses were trimethoprim-sulfonamide (17%) and gentamicin (12%).[4] In cattle, penicillins (39% procaine penicillin, 5% long-acting penicillin formulations) and tetracyclines (46% oxytetracycline) were the antimicrobials most commonly administered for surgical prophylaxis.[5]

There are multiple sources of information about dose rates that may be used by practitioners, including educational and training materials, authoritative text books and the label recommendations provided by the manufacturers of the drugs (and approved by the Australian Pesticides and Veterinary Medicines Authority).[3-5] At the time of the survey, guidelines for antimicrobial use were available for companion animals,[7, 8] but not for horses or cattle, although guidelines for these species have been released recently in Australia.[8] The current best-practice dose rate required for procaine penicillin to achieve appropriate plasma concentrations of penicillin in horses is 22,000 IU/kg every 12 h (Table 1)[9-11] and in cattle 22,000 IU/kg every 12–24 h (Table 2).[12] However, the label for procaine penicillin for both cattle and horses recommends an intramuscular dose of 20 mL/500 kg (12,000 IU/kg) every 24 h.[13] Similarly, current recommended dose rates for gentamicin in horses are 7.7–9.7 mg/kg once daily,[14] but the labels for gentamicin recommend a dose of 1.5 mg/kg[15] or 2 mg/kg[16] three times daily. The current best evidence suggests that dose regimens for amoxycillin of

15 mg/kg every 12 h[17] and for amoxycillin-clavulanate of 12.5 mg/kg every 12 h[18] are appropriate for dogs, but the respective labels recommend 7 mg/kg[19] and 8.75 mg/kg.[20] This commentary aims to explore antimicrobial dose rates used by Australian veterinarians for small animals, cattle and horses based on surveys of antimicrobial usage patterns by Australian veterinarians.

Antimicrobial Usage Patterns

Surveys were undertaken using an online questionnaire to collect information about the respondents, the frequency with which antibiotics were used for specific surgical conditions (including the dose, timing and duration of therapy) and practice policies on antimicrobial use and sources of information on antimicrobials and their use.[3] An aspect of the results that has not been reported previously was the range of dose rates used by equine and companion animal veterinarians.

Equine practitioners prescribed procaine penicillin in doses that varied widely, with 12,000, 15,000 and 22,000 IU/kg most frequently reported (Figure 1). Doses reported were less than the recommended dose in 65% of responses. Procaine penicillin was administered twice daily by 74% of respondents and once daily by 26% of respondents. Trimethoprim-sulfonamide was administered most commonly at 15 or 30 mg/kg (Figure 1) and was administered twice daily by 94% of respondents, with 6% reporting once-daily dosing. Reported trimethoprim-sulfonamide dose rates were less than the recommended dose in 70% of cases. Gentamicin was most commonly administered at 6.6 mg/kg (Figure 1) and once daily by 92% of respondents, with 9% reporting twice-daily dosing. Only 6% of respondents indicated using gentamicin at a dose lower than is commonly recommended.

Companion animal veterinarians most commonly prescribed amoxycillin at a dose rate of 15 mg/kg (Figure 2) and the frequency of administration was most commonly twice daily (99%). Doses reported were lower than the recommended dose in 46% of cases. Amoxycillin-clavulanate was most commonly administered at 12.5 mg/kg or 8.75 mg/kg (Figure 2) and the frequency of administration was most commonly twice daily (99%). Reported doses were lower than the recommended dose in 29% of cases.

Dose rates used by bovine practitioners have been previously reported.[5] The dose of procaine penicillin administered ranged from 7.5 to 24 mg/kg, with the most frequent dose rates being 12.5 mg/kg and 15 mg/kg.[5] Reported doses were lower than the recommended dose in 90% of cases. Procaine penicillin was administered once daily by 96% of respondents using a short-acting formulation and twice daily by 5% of respondents.[5] 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 and 10 mg/kg.[5] Reported doses were lower than the recommended dose in 59% of cases. Most respondents reported administering oxytetracycline once daily when using a short-acting formulation (97%), with the remainder reporting that they administered it every 12 h (2.8%).[5]

Discussion

The survey identified a wide range of dose rates in use for common antimicrobials used in horses, consistent with previous findings described in cattle.[21] Of concern is a predominant use of dose rates lower than those required to result in plasma concentrations of the antimicrobial greater than the minimum inhibitory concentrations required for efficacy against common equine and bovine pathogens.[22] The recommended dose and inter-dosing

interval for horses and cattle are shown in Tables 1 and 2, respectively. Comparatively, the dose rates in use for common antimicrobials used in companion animal medicine were mostly at or above those recommended in the literature.[20, 23]

Poor teaching of veterinary undergraduates is one potential reason for failure of veterinarians to administer appropriate doses of antimicrobial agents. Veterinary pharmacology is taught as a stand-alone subject in five of the seven veterinary schools in Australia[24, 25] (CS, MW, SR, JM, CP, RC, TN, pers. comm. 2017). It is integrated into other courses at the University of Melbourne and James Cook University (RT, pers. comm. 2017). Integration of pharmacology may lead to reduced emphasis and requirement for knowledge in this area. However, appropriate drug doses are taught at all Australian veterinary schools,[4] which is consistent with the data showing Australian university equine veterinarians had 3.2-fold higher odds of compliance with guidelines than general practitioners in the 2016 survey.[4] Thus, it seems unlikely that inappropriate university teaching is the primary reason for under-dosing of antimicrobial agents in equine and bovine practice.

A second potential contributor to inappropriate dosing is the labelling of antimicrobials. Some of the doses recommended on the labels for antimicrobials fall below those now recognised as appropriate. Recommended doses on the labels for procaine penicillin, gentamicin, amoxycillin and amoxycillin-clavulanate are all lower than the current recommendations in the literature.[9-11, 14, 17, 18] In addition, the label for gentamicin in horses recommends administration three times daily, which is likely to increase the risk of renal toxicity in treated horses.[26] The gentamicin label also carries a 'do not use' clause that prohibits use unless sensitivity testing indicates that other antimicrobials are ineffective. In most jurisdictions in Australia, this clause is legally binding and off-label use in the absence of sensitivity data is, therefore, illegal. Despite this, the majority of practitioners appear to use gentamicin as part of a broader spectrum empirical approach to therapy, including for prophylaxis in compromised surgical scenarios. Although this use would clearly be contrary to the off-label use restrictions, as culture and sensitivity have not been performed prior to use, it is a preferable approach to administration of third-generation cephalosporins or fluoroquinolones as these are both antimicrobial classes with a high-importance rating. Thus, this label restriction could drive practitioners towards less appropriate therapeutic options if enforced. Inappropriate labels are likely to influence bovine prescribing where the withholding periods for meat and milk declared on the label are only applicable for the labelled dose. Improvements in the accuracy of labels would enable the use of appropriate doses in this species.

Although the dose recommended by the label is likely to be a factor influencing some veterinarians, the label is clearly not the only factor leading to inappropriate antimicrobial dosing. Respondents to our equine survey frequently used off-label (appropriate) doses of gentamicin in horses (89% of dose rates appropriate), but often used labelled (inappropriate) doses of procaine penicillin (32% of dose rates appropriate). The doses of amoxycillin-clavulanate also reflect this, with 23% of companion animal practitioners using the labelled (inappropriate) dose and 50% using an off-label (appropriate) dose. A change in legislation to make off-label use of antimicrobials illegal, without ensuring regular updates to the labelling of veterinary medicines, would clearly be detrimental to the aim of improved antimicrobial stewardship.

The risk of side effects associated with using gentamicin at the labelled dose and inter-dosing interval may have led to an emphasis on the appropriate dosing of this drug, whereas the risk of under-dosing procaine penicillin and oxytetracycline is insidious. However, the use of amoxycillin and amoxycillin-clavulanate is largely at an appropriate (off-label) dose and risks of under-dosing of these drugs are also not immediately obvious. It is possible that these differences between companion animal and large animal practitioners are influenced by differences in the source of continuing education or differing opportunities to attend continuing education. The culture within veterinary practices may also contribute to the dose rates used by veterinarians. This may be especially true for recent graduates, who are likely to rely more heavily on the experience of colleagues to guide clinical decision making, or for veterinarians who are not predominantly working in equine or bovine practice and for whom dose rates for these species may not be easily recalled. However, we have not yet evaluated the role of these factors.

Conclusion

Changes to legislation are recommended to ensure that antimicrobial drug labels are regularly updated to reflect the dose needed to effectively and safely treat common veterinary pathogens, as well as to ensure that label restrictions are not driving selection of inappropriate antimicrobials for therapy. This will especially be true if changes in legislation restrict antimicrobial use by veterinarians to that directed by the label. This change would hamper the current momentum towards improved antimicrobial stewardship. Development of evidence-based antimicrobial use guidelines may also improve dose rates used by veterinarians in Australia.

Acknowledgments

This research was funded by the National Health and Medical Research Council through the Centres of Research Excellence program, grant no. 1079625. LYH was a recipient of an Australian Postgraduate Award scholarship.

References

1. World Health Organisation. United Nations high-level meeting on antimicrobial resistance. WHO, 2016. http://www.who.int/antimicrobial-resistance/events/UNGA-meeting-amr-sept2016/en/. Accessed September 2017.
2. O'Neill J. Tackling drug-resistant infections globally: Final report and recommendations. *Rev Antimicrob Resistance* https://amr-review.org/sites/default/files/160525_Final paper_with cover.pdf, 2016.
3. Hardefeldt LY, Browning GF, Thursky K et al. Antimicrobials used for surgical prophylaxis by companion animal veterinarians in Australia. *Vet Microbiol* 2017;203:301–307.
4. Hardefeldt LY, Browning GF, Thursky K et al. Antimicrobials used for surgical prophylaxis by equine veterinary practitioners in Australia. *Equine Vet J* 2017 doi: 10.1111/evj.12709. [Epub ahead of print].
5. Hardefeldt LY, Browning GF, Thursky KA et al. Cross-sectional study of antimicrobials used for surgical prophylaxis by bovine veterinary practitioners in Australia. *Vet Rec* 2017;181:426.
6. Australian Strategic and Technical Advisory Group on Antimicrobial Resistance. *Importance rating and summary of antibacterials used in human health in Australia*.

Commonweath of Australia, 2015. http://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-amr.htm. Accessed????
7. Holloway S, Trott DJ, Shipstone M et al. *Antibiotic prescribing: detailed guidelines*. Australasian Infectious Diseases Advisory Panel, 2013. www.ava.com.au/sites/default/files/AVA_website/pdfs/AIDAP guidelines.pdf. Accessed????
8. Asia Pacific Centre for Animal Health, National Centre for Antimicrobial Stewardship. *Australian veterinary prescribing guidelines*. 2017. Accessed September 2017.
9. Uboh CE, Soma LR, Luo Y et al. Pharmacokinetics of penicillin G procaine versus penicillin G potassium and procaine hydrochloride in horses. *Am J Vet Res* 2000;61:811–815.
10. Firth EC, Nouws JF, Driessens F et al. Effect of the injection site on the pharmacokinetics of procaine penicillin G in horses. *Am J Vet Res* 1986;47:2380–2384.
11. Love DN, Rose RJ, Martin IC et al. Serum concentrations of penicillin in the horse after administration of a variety of penicillin preparations. *Equine Vet J* 1983;15:43–48.
12. Dubreuil P, Daigneault J, Couture Y et al. Penicillin concentrations in serum, milk, and urine following intramuscular and subcutaneous administration of increasing doses of procaine penicillin G in lactating dairy cows. *Can J Vet Res* 2001;65:173–180.
13. MSD Animal Health. Depocillin procaine penicillin 300 ng/mL injection. www.infopest.com.au. Accessed March 2017.
14. Bauquier JR, Boston RC, Sweeney RW et al. Plasma peak and trough gentamicin concentrations in hospitalized horses receiving intravenously administered gentamicin. *J Vet Intern Med* 2015;29:1660–1666.
15. Nature Vet PtyLtd. Gentamax 100. http://websvr.infopest.com.au/LabelRouter?LabelType=L&Mode=1&ProductCode=55873. Accessed September 2017.
16. Troy Laboratories Pty Ltd. Gentam 100. www.infopest.com.au. Accessed April 2017.
17. ten Voorde G, Broeze J, Hartman EG et al. The influence of the injection site on the bioavailability of ampicillin and amoxycillin in beagles. *Vet Q* 1990;12:73–79.
18. Bywater RJ, Palmer GH, Buswell JF et al. Clavulanate-potentiated amoxycillin: activity in vitro and bioavailability in the dog. *Vet Rec* 1985;116:33–36.
19. Jurox. Moxylan ready-to-use injection 150 mg/mL. www.infopest.com.au. Accessed June 2017.
20. Norbrook Laboratories Australia. Noroclav injection for dogs and cats. www.infopest.com.au. Accessed June 2017.
21. Hardefeldt LY, Browning GF, Thursky K et al. Antimicrobials used for surgical prophylaxis by bovine veterinary practitioners in Australia. *Vet Rec* 2017 In press.
22. Prescott JF. Beta-lactam antibiotics: penam penicillins. In: Giguere S, Prescott JF, Dowling PM, editors. *Antimicrobial therapy in veterinary medicine*. 5th edn. Wiley-Blackwell, USA, 2013.
23. Norbrook Laboratories Australia. Betamox injection. www.infopest.com.au. Accessed June 2017.
24. University of Queensland. Bachelor of Veterinary Science Study Planner. 2017. Accessed September 2017.
25. University of Adelaide. Doctor of Veterinary Medicine. 2017. Accessed September 2017.

26. van der Harst MR, Bull S, Laffont CM et al. Gentamicin nephrotoxicity: a comparison of in vitro findings with in vivo experiments in equines. *Vet Res Commun* 2005;29:247–261.
27. Gustafsson A, Baverud V, Franklin A et al. Repeated administration of trimethoprim/sulfadiazine in the horse: pharmacokinetics, plasma protein binding and influence on the intestinal microflora. *J Vet Pharmacol Ther* 1999;22:20–26.
28. Mevius DJ, Nouws JF, Breukink HJ et al. Comparative pharmacokinetics, bioavailability and renal clearance of five parenteral oxytetracycline-20% formulations in dairy cows. *Vet Q* 1986;8:285–294.

(Accepted for publication 22 November 2017)

Figure 1. Doses of antimicrobials reported by equine practitioners for (a) procaine penicillin (1000 IU/kg), (b) trimethoprim-sulfonamide (mg/kg) and (c) gentamicin (mg/kg). Arrows indicate recommended dose.

Figure 2. Doses of antimicrobials reported by companion animal practitioners for (a) amoxycillin (mg/kg) and (b) amoxycillin-clavulanate (mg/kg). Arrows indicate recommended dose.

Table 1. Recommended doses and inter-dosing intervals for antimicrobials in horses

Drug	Dose	Inter-dosing interval	Route	Reference
Procaine penicillin	22,000 IU/kg	12 h	IM	[9-11]
Trimethoprim-sulfonamide	30 mg/kg	12 h	IV/PO	27
Gentamicin	7.7–9.7 mg/kg	24 h	IM/IV	14

IM, intramuscular; IV, intravenous; PO, oral.

Table 2. Recommended doses and inter-dosing intervals for antimicrobials in cattle

Drug	Dose	Inter-dosing interval	Route	Reference
Procaine penicillin	22,000 IU/kg	12–24 h	IM	12
Oxytetracycline	10 mg/kg	24 h	IV/IM	28

IM, intramuscular; IV, intravenous

1. World Health Organisation. United Nations high-level meeting on antimicrobial resistance. 2016. Retrieved 13/9/17 http://www.who.int/antimicrobial-resistance/events/UNGA-meeting-amr-sept2016/en/.
2. O'Neill J. Tackling drug-resistant infections globally: Final report and recommendations. *The Review on Antimicrobial Resistance*, https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf, 2016.
3. Hardefeldt LY, Browning GF, Thursky K et al. Antimicrobials used for surgical prophylaxis by companion animal veterinarians in Australia. *Veterinary Microbiology* 2017;203:301-307.
4. Hardefeldt LY, Browning GF, Thursky K et al. Antimicrobials used for surgical prophylaxis by equine veterinary practitioners in Australia. *Equine Vet J* 2017.
5. Hardefeldt LY, Browning GF, Thursky KA et al. Cross-sectional study of antimicrobials used for surgical prophylaxis by bovine veterinary practitioners in Australia. *Vet Rec* 2017.
6. Australian Strategic and Technical Advisory Group on Antimicrobial Resistance. Importance rating and summary of antibacterials used in human health in Australia. Commonweath of Australia, http://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-amr.htm, 2015.
7. Holloway S, Trott DJ, Shipstone M et al. Antibiotic Prescribing detailed guidelines. Australasian Infectious Diseases Advisory Panel, www.ava.com.au/sites/default/files/AVA_website/pdfs/AIDAP%20guidelines.pdf, 2013.
8. Asia Pacific Centre for Animal Health, National Centre for Antimicrobial Stewardship. Australian Veterinary Prescribing Guidelines. 2017. Retrieved 13/9/17.
9. Uboh CE, Soma LR, Luo Y et al. Pharmacokinetics of penicillin G procaine versus penicillin G potassium and procaine hydrochloride in horses. *Am J Vet Res* 2000;61:811-815.
10. Firth EC, Nouws JF, Driessens F et al. Effect of the injection site on the pharmacokinetics of procaine penicillin G in horses. *Am J Vet Res* 1986;47:2380-2384.
11. Love DN, Rose RJ, Martin IC, Bailey M. Serum concentrations of penicillin in the horse after administration of a variety of penicillin preparations. *Equine Vet J* 1983;15:43-48.
12. Dubreuil P, Daigneault J, Couture Y, Guay P, Landry D. Penicillin concentrations in serum, milk, and urine following intramuscular and subcutaneous administration of increasing doses of procaine penicillin G in lactating dairy cows. *Can J Vet Res* 2001;65:173-180.
13. MSD Animal Health. Depocillin Procaine Penicillin 300ng/ml Injection. www.infopest.com.au. Retrieved 10/3/17.

14. Bauquier JR, Boston RC, Sweeney RW, Wilkins PA, Nolen-Walston RD. Plasma Peak and Trough Gentamicin Concentrations in Hospitalized Horses Receiving Intravenously Administered Gentamicin. *J Vet Intern Med* 2015;29:1660-1666.
15. Nature Vet PtyLtd. Gentamax 100. http://websvr.infopest.com.au/LabelRouter?LabelType=L&Mode=1&ProductCode=55873. Retrieved 15/9/17.
16. Troy Laboratories PTY LTD. Gentam 100. www.infopest.com.au. Retrieved 26/4/17.
17. ten Voorde G, Broeze J, Hartman EG, van Gogh H. The influence of the injection site on the bioavailability of ampicillin and amoxycillin in beagles. *Vet Q* 1990;12:73-79.
18. Bywater RJ, Palmer GH, Buswell JF, Stanton A. Clavulanate-potentiated amoxycillin: activity in vitro and bioavailability in the dog. *Vet Rec* 1985;116:33-36.
19. Jurox. Moxylan ready-to-use injection 150mg/ml. www.infopest.com.au. Retrieved 1/6/17.
20. Norbrook Laboratories Australia. Noroclav injection for dogs and cats. www.infopest.com.au. Retrieved 1/6/17.
21. Hardefeldt LY, Browning GF, Thursky K et al. Antimicrobials used for surgical prophylaxis by bovine veterinary practitioners in Australia. *Veterinary Record* 2017;In press.
22. Prescott JF. Beta-lactam antibiotics: Penam Penicillins. In: Giguere S, Prescott JF, Dowling PM, editors. *Antimicrobial Therapy in Veterinary Medicine*. 5th edn. Wiley Blackwell, Iowa, USA, 2013.
23. Norbrook Laboratories Australia. Betamox injection. www.infopest.com.au. Retrieved 1/6/17.
24. University of Queensland. Bachelor of Veterinary Science Study Planner. 2017. Retrieved 22/9/17.
25. University of Adelaide. Doctor of Veterinary Medicine. 2017. Retrieved 22/9/17.
26. van der Harst MR, Bull S, Laffont CM, Klein WR. Gentamicin nephrotoxicity--a comparison of in vitro findings with in vivo experiments in equines. *Vet Res Commun* 2005;29:247-261.
27. Gustafsson A, Baverud V, Franklin A et al. Repeated administration of trimethoprim/sulfadiazine in the horse--pharmacokinetics, plasma protein binding and influence on the intestinal microflora. *J Vet Pharmacol Ther* 1999;22:20-26.
28. Mevius DJ, Nouws JF, Breukink HJ et al. Comparative pharmacokinetics, bioavailability and renal clearance of five parenteral oxytetracycline-20% formulations in dairy cows. *Vet Q* 1986;8:285-294.