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Use of aminoglycoside antibiotics in equine clinical practice; a questionnaire-based study of current use

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Abstract

Veterinary use of the aminoglycoside antibiotics is under increasing scrutiny. This questionnaire-based study aimed to document the use of aminoglycosides with a particular focus on gentamicin. An online questionnaire was delivered to generalist equine veterinary surgeons and specialists in internal medicine to determine the perceived importance, frequency of use and routes of administration of the aminoglycoside antibiotics. A series of hypothetical scenarios were also evaluated regarding gentamicin. Data were compared to evaluate the impact of the level of specialisation on prescribing practices for different antibiotics using Chi-squared and Fischer's exact tests. Data were analysed from 111 responses. Gentamicin was commonly used empirically without culture and susceptibility testing. Generalists were more likely to use gentamicin only after susceptibility testing than specialists in a variety of clinical presentations including respiratory diseases, septic peritonitis, acute febrile diarrhoea, cellulitis and contaminated limb wounds ($p < 0.01$). Intravenous administration of gentamicin was most common, although inhaled and regional administration of gentamicin and amikacin were also described. Amikacin was most commonly used by intra-articular administration. Gentamicin was more likely to be used in high-risk procedures or contaminated surgeries (86% and 74%, respectively) compared with clean surgery (32%; $p < 0.0001$). Gentamicin was often used perioperatively in horses undergoing exploratory celiotomy and more commonly used in horses undergoing an enterotomy (90%) than without and enterotomy (79%; $p = 0.04$). Most respondents (86%) used gentamicin at a dose of 6.6 mg/kg in adults, with few changing their dosing strategies based on the presence of sepsis, although higher doses were more reported in foals (7–15 mg/kg) irrespective of the presence of sepsis. Aminoglycosides are widely used in equine practice and use outside current EU marketing authorisations is common. Stewardship of the aminoglycoside antibiotics could be enhanced in both generalists and specialists through the more frequent use of susceptibility testing, regional administration and dose adjustment, especially in foals.

KEYWORDS
aminoglycosides, antibiotic resistance, equine medicine

1 | INTRODUCTION

Aminoglycoside antibiotics are commonly used for the management of bacterial infections and for perioperative prophylaxis in the horse (Dowling, 2013; Freeman et al., 2011; Haggett & Wilson, 2008; Isgren et al., 2016; Santschi, 2006). They are usually combined with beta-lactam antibiotics due to their synergistic effects making the combination effective against a range of common bacterial pathogens. However, emerging bacterial resistance is described in horses, and the impact of this on the contemporary prescribing practices of veterinary surgeons treating horses is unknown.

Due to the human health risks of bacterial resistance, the aminoglycoside antibiotics have been reclassified by the World Health Organisation (WHO) as Critically Important Antibiotics (CIA) (WHO, 2019). This classification is related to their use in the treatment of human infections where there is evidence of transmission of resistant bacteria or transmission of resistance genes from non-human sources, in particular *Enterococcus spp.*, *Enterobacteriaceae* and *Mycobacterium* spp. In 2013, the European Medicines Agency (EMA) issued a consultation to develop advice on the impact of using antimicrobials in animals (DG SANCO, 2013). Part of that consultation set out to establish whether classes of antibiotics should be reclassified such that future legislation could restrict their use in veterinary medicine. This included the potential for limiting use outside of marketing authorisations. Several aminoglycoside antibiotics are authorised for use in horses and other species in the EU.[1] The authorised indications for gentamicin were harmonised across the EU, limiting its use to management of lower respiratory tract infection caused by gram-negative bacteria (EMA, 2015).[2] Neomycin and streptomycin have broader marketing authorisations and are formulated with procaine penicillin.[3] Framycetin is authorised for parenteral administration in cattle with mastitis.[4] There are no authorised veterinary formulations of amikacin in the EU.[5]

The aims of this study were to document the perceived importance and current use of aminoglycoside antibiotics and to identify the clinical scenarios where veterinary surgeons select gentamicin in their clinical practice and the dosing strategies employed. The study was undertaken on behalf of the Board of the Federation of European Equine Veterinary Associations.

2 | MATERIALS AND METHODS

A survey to establish prescribing practices was developed and piloted by four equine internal medicine specialists. Based on feedback, four clinical scenarios were removed to shorten the overall length of the survey. The questions established the participants' demographics and perceived importance, frequency of current usage and routes of administration of gentamicin, amikacin, neomycin, streptomycin and framycetin. Respondents were also questioned on the use of gentamicin in a range of clinical scenarios and whether this use was their routine first-line (empirical) antibiotic in each condition, whether it was preserved for use following treatment failure with other antibiotics or only used based on results of bacterial culture and susceptibility testing. The dose rates and dosing frequencies of gentamicin used by respondents were also evaluated in adult horses and neonates without systemic disease, with sepsis (without hypovolaemia) and with septic shock (with increased plasma creatinine and/or lactate concentrations). Finally, respondents were asked whether therapeutic drug monitoring was routine in their practice and were invited to submit any further comments. The survey was delivered through an online platform (esurveycreator.co.uk; Enuvo GmbH, Switzerland) and was distributed through electronic mail discussion forums used by general practitioners in the UK and practitioners across Europe via equine veterinary associations and globally to equine internal medicine specialists through the ACVIM portal. The total pool of potential respondents is difficult to predict, and thus a response rate was not calculated. No non-demographic questions were compulsory, and respondents were able to skip individual questions throughout the survey.

2.1 | Statistical analysis

Data were screened and coded by response. Entire responses were excluded from individuals who failed to provide demographical data or where no more than two questions about antibiotic usage were answered. Data were coded to recognise respondents from the EU or the rest of the world. Postgraduate qualifications were coded so that data from general practitioners and advanced veterinary practitioners (equivalent to level 6 or 7 of the UK Higher Education Framework[6]) were considered together as 'generalists', whereas those with specialist qualifications (equivalent to the UK higher education framework level 8 qualifications) and those undertaking specialist training (residencies) or PhDs were considered together as "specialists". Given the distribution of the responses by geographical region and specialisation, further comparisons were only made based on postgraduate training. 'Frequent use' was defined as a medicine that was used daily or multiple times per day. 'Infrequent use' was defined as being used weekly or less frequently. Comparisons were made between the category of respondents (generalist vs. specialist), and between the use of different aminoglycoside antibiotics using the Chi-squared test or the Fisher's exact test as appropriate. Results of respondents' opinions of the importance of each aminoglycoside were pooled and "very important" and "important" were compared with "unimportant" and "very unimportant". Odds ratios (OR) and 95% confidence intervals (CI) were reported for binomial data. Differences were considered significant where $p < 0.05$. All statistical comparisons were performed using GraphPad Prism version 8.00 for Mac (GraphPad Software, www.graphpad.com).

3 | RESULTS

Responses were returned from 166 respondents; 55 were excluded based on inconsistency in completion of questions, leaving

111 responses that were included in the statistical analysis. Most of the respondents who were generalists worked within Europe (94%; OR 18.4; CI 2.55–65.4; $p < 0.0001$), whereas specialists were more evenly divided between Europe and the rest of the world (Table 1).

The reported frequencies of use of the different aminoglycoside antibiotics are shown in Table 2. Gentamicin was the most frequently used aminoglycoside, with frequent use being reported more commonly by specialists (51%) compared with generalists (3%; OR 35.6 CI:5.9–376.0; $p < 0.0001$). Frequent use was reported more often for gentamicin than for amikacin, irrespective of specialisation of respondents (7% compared to 35% of respondents; OR 7.12; CI 3.00 to 17.7; $p < 0.0001$). Streptomycin was used frequently by 6% of generalists, but no specialists and only 24% of respondents ever used this antibiotic. Neomycin was only used infrequently with only 42% using this antibiotic. Framycetin was only used by 10% of respondents and all use was infrequent.

Respondents' opinions regarding the importance of the aminoglycoside antibiotics are shown in Table 3. Gentamicin was most frequently considered to be very important to equine clinical practice (90% of respondents) and was rated as very important or important more frequently than amikacin (99% compared to 92%: OR 9.18; OR 1.13–74.8; $p < 0.02$). Amikacin was considered to be very important or important more frequently than neomycin (92% compared to 35%; OR 20.04; CI 8.49–47.3; $p < 0.0001$). Neomycin was considered to be very important or important more frequently than streptomycin (35% compared to 16%; OR 2.79; CI 1.30–5.78; $p = 0.01$). Most respondents (91%) considered framycetin to be unimportant (unimportant or very unimportant) to equine clinical practice. Generalists more frequently considered streptomycin as very important or important compared with specialists (31% compared to 8%; OR 5.18; CI 1.53–16.2; $p = 0.01$), however, there was no other difference in the considered importance of the aminoglycosides by generalists and specialists.

Routes of administration of the aminoglycoside antibiotics are shown in Table 4. Gentamicin (98% of respondents) and amikacin (52%) were both used by intravenous and, infrequently, by intramuscular administration. Specialists more commonly reported systemic administration (intravenous and intramuscular) of amikacin than generalists (55% compared to 22%; OR 9.28; CI 3.67–23.8;

TABLE 1 Distribution of responses by region and specialisation

Country	Number of generalist veterinary surgeons	Number of specialist veterinary surgeons
Europe	34	30
North America	2	40
Australasia/ Asia	0	5

Note: Generalists were defined as those having a veterinary qualification equivalent to level 6 or 7 of the UK Higher Education Framework, Specialists as level 8 qualifications and those actively engaged in residency training programmes. More of the generalist veterinary surgeons practised within Europe (94%) compared with the rest of the world (2%; OR 18.4; CI 2.55 to 65.4; $p < 0.0001$).

TABLE 2 Distribution of responses regarding frequency of use of the different aminoglycoside antibiotics (> DAILY – more than once daily, DAILY – once daily, WEEKLY – at least weekly, LESS – Occasional use and NEVER)

	Specialists						Generalists					
	Frequent		Infrequent				Frequent		Infrequent			
	>Daily	Daily	Weekly	Less	Never	Total responses	>Daily	Daily	Weekly	Less	Never	Total responses
Gentamicin	25 (33%)	13 (17%)	28 (37%)	9 (12%)	0	75	0	1 (3%)	11 (31%)	24 (67%)	0	36
Amikacin	2 (3%)	3 (4%)	18 (24%)	46 (62%)	5 (7%)	74	0	2 (6%)	8 (24%)	20 (61%)	3 (9%)	33
Streptomycin	0	0	2 (3%)	8 (11%)	61 (86%)	71	1 (3%)	1 (3%)	4 (11%)	9 (26%)	20 (57%)	35
Neomycin	0	0	6 (8%)	23 (32%)	43 (60%)	72	0	0	3 (9%)	12 (38%)	17 (53%)	32
Framycetin	0	0	2 (3%)	3 (4%)	66 (93%)	71	0	0	2 (7%)	3 (10%)	25 (83%)	30

Note: Data were pooled for frequent use (daily or more than once daily) and infrequent use (weekly or less frequently) as shown. Generalists were defined as those having a veterinary qualification equivalent to level 6 or 7 of the UK Higher Education Framework. Specialists as level 8 qualifications and those actively engaged in residency training programmes. Number of respondents shown for each question. Where percentages do not equal 100%, this is a result of rounding, rather than incomplete responses.

TABLE 3 Distribution of responses regarding importance of the antibiotics to clinical practice

	Specialists					Generalists				
	Very important	Important	Unimportant	Very unimportant	Total responses	Very important	Important	Unimportant	Very unimportant	Total responses
Gentamicin	66 (96%)	3 (4%)	0	0	69	26 (78%)	6 (18%)	1 (3%)	0	33
Amikacin	41 (62%)	23 (34%)	1 (2%)	1 (2%)	66	15 (50%)	9 (30%)	5 (17%)	1 (3%)	30
Streptomycin	1 (2%)	3 (6%)	10 (20%)	36 (72%)	50	3 (10%)	6 (21%)	7 (24%)	13 (45%)	29
Neomycin	4 (8%)	13 (25%)	10 (19%)	26 (49%)	53	1 (4%)	10 (38%)	6 (23%)	9 (35%)	26
Framycetin	1 (2%)	1 (2%)	9 (18%)	39 (78%)	50	1 (4%)	4 (16%)	5 (20%)	15 (60%)	25

Note: Generalists were defined as those having a veterinary qualification equivalent to level 6 or 7 of the UK Higher Education Framework, Specialists as level 8 qualifications and those actively engaged in residency training programmes. NUMBER of respondents shown for each question. Where percentages do not equal 100%, this is a result of rounding, rather than incomplete responses.

TABLE 4 Distribution of responses regarding routes of administration of the aminoglycoside antibiotics

	Specialist n = 75							Generalist n = 36						
	Intravenous	Intramuscular	Intra-articular	Regional perfusion	Inhaled	Intra-uterine	Other	Intravenous	Intramuscular	Intra-articular	Regional perfusion	Inhaled	Intra-uterine	Other
Gentamicin	75	18	28	36	28	15	7	34	9	12	11	3	5	3
Amikacin	48	7	57	26	6	0	4	7	1	29	6	0	0	1
Streptomycin	0	6	0	0	0	0	2	1	13	0	0	0	3	1
Neomycin	0	9	0	0	0	1	7	1	9	1	0	0	2	23
Framycetin	0	0	0	0	0	3	1	0	0	0	0	0	3	1

Note: Generalists were defined as those having a veterinary qualification equivalent to level 6 or 7 of the UK Higher Education Framework, Specialists as level 8 qualifications and those actively engaged in residency training programmes. Other routes include topical, oral administration. Respondents could select multiple routes of administration.

$p < 0.0001$). Neomycin and streptomycin were predominantly used by intramuscular administration, although oral administration was reported by a small number of respondents (<5%). Gentamicin and amikacin were both used by regional administration (intra-articularly and intravenous regional perfusion (IVRP)) for orthopaedic disease. Specialists used gentamicin regionally for orthopaedic disease more than generalists (85% compared to 64%; OR 3.28; CI 1.32–8.61; $p = 0.01$). Amikacin was used intra-articularly more commonly than gentamicin (77% compared to 36%; OR 6.11; CI 3.38–11.02; $p < 0.0001$), but this route of administration was similar between specialists and generalists for both amikacin (76% compared to 81%; OR 0.76; CI 0.29–2.04; $p = 0.64$) and gentamicin (37% compared to 33%; OR 1.19; CI 0.52–2.75; $p = 0.68$). Gentamicin was more commonly used by inhalational administration by specialists than generalists (37% compared to 8%: OR 6.55; CI 1.96–21.60; $p = 0.0013$). A small number of specialists reported inhalational use of amikacin (8%). Intrauterine administration of gentamicin was reported by 18% of respondents; and this was similar for specialists and generalists (20% compared to 13%; OR 0.65; CI 0.24–1.92; $p = 0.60$). One respondent reported the use of neomycin by intrauterine administration and one by intra-articular administration. Small numbers of respondents used other aminoglycosides by intrauterine administration or topically in wounds.

The hypothetical use of gentamicin in different clinical settings is shown in Table 5. Gentamicin was reported for the management of different lower respiratory tract infections. In the management of primary pneumonia/pleuropneumonia, 70% used this empirically without bacterial culture and susceptibility testing. Gentamicin was more frequently reported to be used empirically by specialists (80%) than generalists (45%; OR 4.815; CI 1.98–11.7; $p = 0.0005$). Gentamicin was less likely to be used in horses with pneumonia secondary to other diseases (e.g. in equine asthma); it was used empirically by only 13% of respondents and following culture and susceptibility testing by 31% (OR 0.10; CI 0.046–0.24; $p < 0.0001$). In horses with aspiration pneumonia, gentamicin was used empirically by 58% of respondents, being used empirically more frequently by specialists (72%) than generalists (29%; OR 4.81; CI 1.98–11.7; $p < 0.0004$). Gentamicin was commonly used empirically in the management of septic peritonitis (70%). Empirical use was more common for the management of septic peritonitis by specialists (81%) compared with generalists (47%; OR 4.05; CI 1.56–10.5; $p < 0.005$). Only 21% of respondents used gentamicin empirically for the management of acute febrile diarrhoea, with 58% of respondents rarely or never using it in this presentation, and 14% of respondents using only based on susceptibility testing results. Specialists (30%) were more likely to use gentamicin empirically in horses with acute febrile diarrhoea than generalists (3%; OR 11.0 CI; 1.88–119.3; $p = 0.0052$).

Gentamicin was used as a first-line empirical antibiotic in several perioperative procedures. It was more likely to be used in high-risk or contaminated surgeries (86% and 74%, respectively) compared with clean surgeries (32%; OR 64.5; CI 10.7–669.8 and OR 26.6; CI 7.47–85.6, respectively, $p < 0.0001$). It was used more commonly in horses undergoing exploratory celiotomy when involving an enterotomy (90%) compared with those without (78%; OR 2.51; CI 1.01–6.21; $p = 0.04$). In horses with wounds of the limbs, its empirical use was more common when there was synovial sepsis present (82%) than contaminated wounds without synovial sepsis (48%; OR 4.72; CI 2.44–9.05; $p < 0.0001$). Specialists were more likely to use gentamicin empirically in the management of cellulitis and contaminated wounds without synovial sepsis (46% and 58%, respectively) compared with generalists (6%; OR 13.54; CI 3.18–59.8; $p < 0.0001$ and 29%; OR 3.38; CI 1.42–8.51; $p = 0.01$, respectively).

The majority ($n = 76;86\%$) of respondents reported using gentamicin at the authorised dose (6.6 mg/kg ± 10%) once daily, with the remainder administering up to 10 mg/kg once daily (median 8.8 mg/kg) in systemically healthy horses, defined as those with clinical evidence of infection without significant cardiovascular compromise. There was no difference in the reported dose used by specialists or generalists, with the authorised dose being used by 84% ($n = 52$) and 97% ($n = 24$) of respondents, respectively (OR 0.20; CI 0.024–1.61; $p = 0.17$). Few respondents increased their dose in adult horses with sepsis without ($n = 2$; 3%) or with hypotension ($n = 3$; 4%), whereas three respondents (6%) reduced their dose in the presence of sepsis and hypotension (4.4–6.6 mg/kg once daily; median 5.2 mg/kg), and a single respondent used a lower dose more frequently (4 mg/kg twice daily). Higher doses of gentamicin were used in systemically healthy foals, defined in the same way as for adult horses, with 43% ($n = 22$) of respondents using 6.6 (±10%) mg/kg once daily. Of those using higher doses, the median dose was 12 mg/kg (range 7.7–15 mg/kg) with specialists ($n = 28;68\%$) being more likely to use these higher doses than generalists ($n = 1;10\%$; OR 19.30; CI 2.22–170; $p = .001$). Dosing interval was mostly the same for foals as for adult horses, with 70% ($n = 37$) of respondents reporting once daily use. Those using higher doses of 11 mg/kg or above mostly used gentamicin every 36 hr. Higher doses were no more likely to be used in foals in sepsis with 66% ($n = 33$) selecting doses above using 6.6 (±10%) mg/kg once daily (OR 1.47; CI 0.65–3.29; $p = 0.4$) or those with sepsis and hypotension with 75% ($n = 23$) using higher doses (OR 2.18; CI 0.82–5.80; p-0.16) in this clinical scenario.

Therapeutic drug monitoring (TDM) was used routinely by only four respondents (4%), although 9 (8%) had used this previously and a further 39 respondents (35%) would use this in selected cases. Nineteen respondents (17%) selected drug dosing based on TDM results from other centres. Seventeen respondents (15%) provided free-text comments. Of these, six (35%) commented on the essential value of aminoglycosides in treating clinical disease in horses. A further six (35%) respondents commented that restrictions placed on aminoglycosides could encourage practitioners to use alternative agents that may have a higher priority to human health. Other comments related to indications about when they would use antibiotics in certain conditions, for example, two commented that they only would use aminoglycoside antibiotics in horses with acute febrile diarrhoea in the face of severe neutropenia. Absence of timely TDM in certain regions was also highlighted.

TABLE 5 List of conditions/surgical types to determine how gentamicin was used in theoretic scenarios in a questionnaire of equine veterinary generalists and specialists

Clinical condition	Specialist						Generalist					
	First line (empirical)	After treatment failure	Only following susceptibility testing	Rarely used in this condition	Never	Number of responses by specialisation	First line (empirical)	After treatment failure	Only following susceptibility testing	Rarely used in this condition	Never	Number of responses by specialisation
Primary pneumonia/pleuropneumonia	58 (80%)	4 (6%)	9 (12%)	1 (1%)	0	72	15 (45%)	5 (15%)	8 (24%)	5 (15%)	0	33
Secondary pneumonia	10 (15%)	4 (6%)	20 (30%)	10 (15%)	23 (34%)	67	3 (10%)	4 (13%)	10 (32%)	6 (19%)	8 (26%)	31
Aspiration pneumonia	52 (72%)	9 (12%)	7 (10%)	3 (4%)	1 (1%)	72	10 (29%)	4 (12%)	7 (21%)	10 (29%)	3 (9%)	34
Septic peritonitis	56 (81%)	4 (6%)	5 (7%)	4 (6%)	0	69	17 (47%)	5 (14%)	8 (22%)	4 (11%)	2 (6%)	36
Periapical dental disease	8 (14%)	4 (7%)	13 (23%)	17 (30%)	15 (26%)	57	2 (6%)	5 (16%)	9 (28%)	7 (22%)	9 (28%)	32
Bacterial cholangiohepatitis	20 (29%)	7 (10%)	24 (35%)	13 (19%)	5 (7%)	69	4 (15%)	4 (15%)	6 (22%)	5 (18%)	8 (30%)	27
Acute febrile diarrhoea	21 (30%)	4 (6%)	5 (7%)	30 (43%)	10 (14%)	70	1 (3%)	3 (9%)	9 (27%)	8 (24%)	12 (36%)	33
Bacterial endocarditis	35 (51%)	6 (9%)	17 (25%)	7 (10%)	3 (4%)	68	7 (30%)	5 (22%)	5 (22%)	2 (9%)	4 (17%)	23
Endometritis	16 (32%)	2 (4%)	23 (46%)	4 (8%)	5 (10%)	50	9 (26%)	2 (6%)	13 (38%)	6 (18%)	4 (12%)	34
Cellulitis	33 (46%)	12 (17%)	11 (15%)	11 (15%)	5 (7%)	72	2 (6%)	13 (38%)	8 (24%)	8 (24%)	3 (9%)	34
Osteomyelitis	29 (51%)	2 (4%)	19 (33%)	6 (11%)	1 (2%)	57	11 (38%)	8 (28%)	7 (24%)	3 (10%)	0	29
Contaminated limb wounds without synovial sepsis	38 (58%)	5 (8%)	12 (18%)	7 (11%)	3 (5%)	65	10 (29%)	8 (24%)	9 (26%)	5 (15%)	2 (6%)	34
Wounds with synovial sepsis	55 (85%)	3 (5%)	5 (8%)	1 (2%)	1 (2%)	65	25 (76%)	3 (9%)	4 (12%)	1 (3%)	0	33
Surgical prophylaxis												
Clean surgery	25 (41%)	5 (8%)	0	12 (20%)	19 (31%)	61	4 (14%)	1 (3%)	1 (3%)	8 (28%)	15 (52%)	29
High risk surgery (e.g. fracture)	45 (86%)	3 (6%)	2 (4%)	2 (4%)	0	52	10 (83%)	0	1 (8%)	1 (8%)	0	12
Contaminated surgery	56 (85%)	2 (3%)	3 (5%)	4 (6%)	1 (2%)	66	12 (46%)	4 (15%)	5 (19%)	3 (12%)	2 (8%)	26
Exploratory celiotomy (with enterotomy)	63 (94%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)	67	9 (69%)	1 (8%)	2 (15%)	1 (8%)	0	13
Exploratory celiotomy (without enterotomy)	55 (83%)	4 (6%)	1 (2%)	3 (5%)	3 (5%)	66	6 (50%)	1 (8%)	2 (17%)	3 (25%)	0	12

Note: Generalists were defined as those having a veterinary qualification equivalent to level 6 or 7 of the UK Higher Education Framework, Specialists were as level 8 qualifications and those actively engaged in residency training programmes. Percentage responses for each question by qualification as some conditions not relevant to all individuals. Number of respondents shown for each question. Where percentages do not equal 100%, this is a result of rounding, rather than incomplete responses.

4 | DISCUSSION

The outcomes of the study highlight the frequent use and perceived importance of the aminoglycoside antibiotics, especially gentamicin and amikacin, in equine clinical practice. Gentamicin was more frequently used by specialists than generalists and their use of gentamicin was more frequently instituted prior susceptibility testing in a range of conditions. The order of ranked importance matched the order of frequency of use in the study, highlighting that perceived importance might simply reflect clinical practice rather than clinical importance. Without widespread bacterial susceptibility testing of pathogenic bacteria from clinical isolates, the actual importance of these agents cannot be determined. Indeed, individuals will often be influenced by the published literature, where aminoglycoside antibiotics, especially gentamicin, are widely recommended in clinical textbooks and research publications (Durham, 2018; Hardefeldt et al., 2018; Lescun et al., 2006; Robinson et al., 2016) and are cited as first-line antibiotics in published clinical guidelines (Bowen and Slater 2012). As is commonly recommended in these texts, gentamicin was reported to be frequently used in conditions beyond its authorised indication in the EU (EMA, 2015) and amikacin without an authorised veterinary product in the EU. Proposed legislative change to prevent unauthorised use of this class of antibiotic would, therefore, impact upon current protocols in equine practice. This study was not designed to determine whether restricting the use of these antibiotics would impact on clinical outcomes, and research to determine the susceptibility of common bacterial isolates would help to guide policymakers. Given the concern of a small number of respondents that restrictive prescribing could promote the use of antibiotics with broader authorised use, but more significant importance to human health, any change in legislation should be reinforced by updated clinical guidelines to avoid such unwanted consequences.

The widespread use of the aminoglycoside antibiotics, especially gentamicin, persists in equine practice despite numerous studies demonstrating the emergence of antimicrobial resistance in bacteria isolated from horses (Chipangura et al., 2017; Cummings et al., 2016; Hardefeldt et al., 2019; Kaszanyitzky et al., 2003; Robinson et al., 2016; Sauer et al., 2003; Spijk et al., 2017; Theelen et al., 2013; Toombs-Ruane et al., 2015; van Duijkeren et al., 1995). This continued use suggests that bacterial resistance does not impact on the clinical outcomes of these cases as treatment failure would inevitably result in changes in clinical practice. However, the impact of resistance may not only affect clinically relevant pathogens, and resistance to gentamicin in faecal *E coli* has been shown to increase during periods of hospitalisation, suggesting that hospital use of antimicrobials selects for antibiotic resistance (Dunowska et al., 2006). Although the prevalence of faecal *E coli* bacteria that were resistant to gentamicin was low in one study of companion animals in Spain (Sáenz et al., 2001), it was higher (17% in total) in a study from the UK that focussed on horses (Maddox et al., 2011). An important mechanism of aminoglycoside resistance is through the action of aminoglycoside-modifying enzymes. Of these, the AAC(6′)

enzymes are the most ubiquitous, being produced by gram-positive and gram-negative bacteria (Ramirez & Tolmasky, 2010) and genes encoding for these enzymes may transfer between bacteria by plasmid-mediated routes to other bacterial types. These factors highlight the impact of using antibiotics on bacterial resistance beyond the individual animal and the potential for impacts on human health with their continued widespread use.

Respondents rarely reported using bacterial culture and susceptibility testing prior to gentamicin use in this study; indeed, generalists were more likely to use gentamicin only after culture and susceptibility testing than specialists. This might reflect the need for parenteral, often intravenous, administration, which places an obstacle to its use in ambulatory clinical practice that may drive clinical decision making. This pattern of gentamicin use by generalists is supported by other studies that have evaluated hypothetical choice of antibiotics in different scenarios (Hughes et al., 2012) and those evaluating antibiotic use based on clinical records (Barr et al., 2012). A small number of respondents reported intramuscular use of gentamicin, and this route of administration has been evaluated in the horse (Magdesian et al., 1998) and could provide an alternative route of administration in ambulatory practice, albeit outside the currently authorised use. These data demonstrate areas where stewardship of the aminoglycoside antibiotics could be enhanced, especially among veterinary specialists, through the promotion of susceptibility testing as has previously been recommended (Morley et al., 2005).

Regional administration of the aminoglycoside antibiotics included intra-articular, intravenous regional, inhaled and intra-uterine use. Local use of antibiotics has the advantage of creating high peak local concentrations at the site of therapy, with limited systemic concentrations, thereby reducing selection pressure for resistance in other areas of the body (Horspool et al., 1994). This has particular benefit in reducing exposure of the aminoglycosides to *Enterobacteriaceae* in the gastrointestinal tract. Of these routes, intra-articular administration was reported most commonly. Amikacin was used more frequently by the intra-articular route than was gentamicin, despite evidence that it causes synovitis (Dykgraaf et al., 2007) and apoptosis of chondrocytes and synovial cells (Pezzanite et al., 2020), suggesting potential for articular injury with its use by this route. However, there are no studies comparing intra-synovial inflammatory effects of amikacin and gentamicin to suggest superiority of either product. IVRP achieves higher intra-synovial concentrations of gentamicin than systemic dosing (Lescun et al., 2006; Whitehair et al., 1992) and is another method used to promote targeted antibiotic use predominantly by specialists. Although authorised for, and widely used in the management of respiratory tract infections in this study, the penetration into respiratory secretions following intravenous administration is poor compared with inhalation (McKenzie & Murray, 2000). The use of inhaled gentamicin by internal medicine specialists demonstrates another potential area of enhanced antibiotic stewardship when using these agents. However, the environmental and personal safety aspects of using inhaled antibiotics should be evaluated, as inappropriate human exposure may be exacerbating selection pressures for

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resistance in personnel involved in this process. If these risks can be mitigated, then these responses demonstrate that antibiotic stewardship can be further enhanced by promoting more targeted administration through local administration of these antibiotics.

Another area for potential improvement concerning stewardship of the aminoglycoside antibiotics was with perioperative use. Gentamicin was widely used in the perioperative period of horses undergoing elective and emergency surgery. Perioperative use was lower in clean surgeries but still undertaken by almost one third of respondents. Furthermore, in horses undergoing celiotomy without an enterotomy, use of gentamicin remained common, in a procedure during which no contamination should occur. These demonstrate perioperative use of gentamicin likely in excess of clinical need, representing an area for further scrutiny of their use (Durward-Akhurst et al., 2012; Freeman et al., 2011; Santschi, 2006; Schaer et al., 2012). An evidence base for the use of the aminoglycosides in these settings is lacking, and the development of robust clinical guidelines for perioperative use of antibiotics in horses is overdue (Morley et al., 2005).

Most respondents used gentamicin in adult horses at the authorised dose and did not adjust doses in the face of sepsis or septic shock. As concentration-dependent antibiotics, achieving high peak plasma concentrations, 8–12 times higher than the minimum inhibitory concentrations of pathogens is important for the efficacy of the aminoglycoside antibiotics (Bauquier et al., 2015). Previous studies have also demonstrated limited dose modification when using gentamicin by equine practitioners (Hardefeldt et al., 2019). It has been suggested that doses of 7.7–9.7 mg/kg are necessary to achieve peak plasma concentrations over 32 µg/ml in adult horses (Bauquier et al., 2015). Although a more recent study suggested that, in the UK, 97% of bacterial isolates had MICs below 2 µg/ml, suggesting that dosing at 6.6 mg/kg would be sufficient to achieve 10 times the MIC in many cases (Durham, 2018). Although median plasma concentrations were 21.4 µg/ml in this study, the range of plasma concentrations (4.4–42.6 µg/ml) reported highlights that many horses would not achieve the required concentrations of when given gentamicin at the authorised dose. Furthermore, it has been shown that sepsis affects total circulating volume and therefore may result in sub-therapeutic concentrations in the most severely affected horses (Sweeney et al., 1992; van der Harst et al., 2005), but rarely resulted in increased doses by respondents in this study. Similarly, critically ill human patients, treated with standard doses of aminoglycosides, often fail to achieve optimal plasma concentrations (Rea et al., 2008). As such, greater access to TDM could enhance outcomes and reduce opportunities for the development of gentamicin resistance (Koterba et al., 1986; Sojka & Brown, 1986). In foals, gentamicin dose should be increased to reflect the differences in total body water and used at doses above 10 mg/kg (Corley & Hollis, 2009). The responses from this study demonstrate considerable inconsistency with dosing in the neonate, especially among generalists as well as a lack of use and availability of TDM in selecting drug doses in the adult or neonate.

The results of this study indicate the perceived importance of the aminoglycoside antibiotics in equine practice. However, it must be reiterated that the opinions of these respondents may not directly imply importance, but understanding these perceptions is essential if changes in prescribing practices are to be introduced. Although this survey generated a relatively small number of responses, the strategy of targeting specific groups of practitioners was developed to reduce the likelihood of receiving multiple responses from the same practice or hospital. However, it is acknowledged that the total number of completed responses may affect the validity of these data. Furthermore, as the study was targeted at internal medicine specialists over other specialists, this may not be reflective of all practices being undertaken in an individual veterinary hospital. However, in our experience, internal medicine specialists are often involved in the development of infection control policies within veterinary hospitals and, therefore, were expected to be able to answer on behalf of the entire hospital. As this was a survey-based study, the results may not be truly reflective of practices undertaken in each centre. A more substantial and more widespread study may overcome some of the reporting biases that this study design may have encouraged. Responses were excluded from a relatively large number of respondents, as they only answered one or two of the clinical questions. This was considered appropriate as they may have returned to complete the full set of questions at another time or did not fully engage with the questionnaire. Not all respondents in this study work in the EU, including some in Europe, not influenced by EU law. As such, some respondents may be affected by different legislation and may use products with different marketing authorisation and the potential for geographical differences impacting on the responses should not be overlooked. These data were analysed by specialisation, not the geographical area to reflect the geographical bases of these different groups. Furthermore, graduates with PhDs were included alongside those with clinical qualifications, as these all meet the same educational priorities and intellectual skills. However, different classification may have influenced these results.

5 | CONCLUSIONS AND CLINICAL RELEVANCE

The aminoglycoside antibiotics are commonly used in equine practice and are widely used both in accordance with and outside their marketing authorisation within Europe. Restrictions to cascade use of these agents would result in changes to prescribing practices in clinical practice. Opportunities to promote more targeted use of the aminoglycosides should concentrate on increasing regional antibiotic use, optimising their dosing, developing better guidance around perioperative use of antibiotics and the use of bacterial culture and susceptibility testing. Opportunities to enhance antibiotic stewardship exist in populations of generalist and specialist veterinary surgeons.

AUTHOR CONTRIBUTION

Adam Redpath: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Writing-original draft. **Gayle Hallowell:** Formal analysis; Methodology; Writing-review & editing. **Mark Bowen:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Supervision; Writing-review & editing.

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ENDNOTES

[1] http://vet.eudrapharm.eu

[2] https://www.ema.europa.eu/en/documents/referral/gentamicin-article-35-opinion-following-article-35-referral-veterinary-medicinal-products-containing_en.pdf

[3] Summary of Product Characteristics Pen & Strep Suspension for Injection (Norbrook Laboratories (GB) Ltd), Streptacare Suspension for Injection (Animalcare Ltd, UK) and Duphapen + Strep Procaine Penicillin 200 mg & Dihydrostreptomycin Sulphate 250 mg Suspension for Injection (Zoetis UK Ltd). Neopen Suspension for Injection (Intervet UK Ltd).

[4] Summary of Product Characteristics Framomycin 150 mg/ml Solution for Injection (Elanco UK Animal Health).

[5] http://vet.eudrapharm.eu

[6] https://www.qaa.ac.uk/docs/qaa/quality-code/qualifications-frameworks.pdf

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