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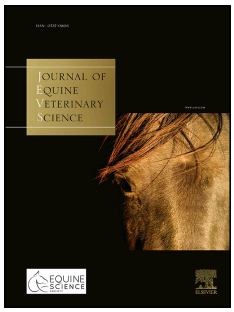

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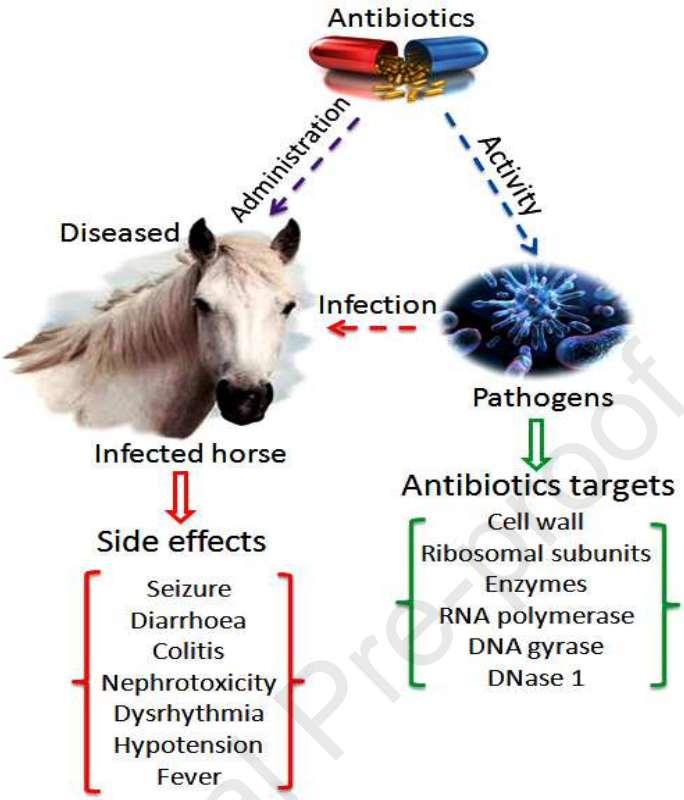
Graphical abstract



Adverse effect of antibiotics administration on horse health: An overview

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Abstract

Antibiotics-based therapy plays a paramount role in equine medicine due to their potential pharmacokinetics and pharmacodynamics properties. Conventional antibiotics show bacteriostatic and bactericidal properties by interfering bacterial cell wall and protein synthesis as well as inhibiting RNA polymerase, DNase 1, and DNA gyrase. Antibiotics are extensively used not only for the treatment of varied bacterial infections but also the prevention of post-operative and secondary infections. Surprisingly, antibiotics such as sulfonamides or trimethoprim/sulphonamide combinations, benzylpenicillin, cefquinome, fluphenazine, enrofloxacin, and sodium ceftriaxone cause detrimental effects on horses' health viz. diarrhoea, colitis, nephrotoxicity, ototoxicity, dysrhythmia, arthropathy, ataxia, anorexia, seizures, peripheral neuropathy, and certain neurological abnormalities. Therefore, in equine practice, it is essential to optimize and analyze the combinations, formulations, route of administration, and dosages of certain antibiotics before administration. This review overviews the mode of actions and pharmacological attributes of certain antibiotics, commonly used towards the treatment of disparate horse diseases. Most importantly, special emphasis was given to spotlight the potential adverse effects encountered during the administration of antibiotics as therapeutics in horses.

Key words: Antibiotics; Horses, Pharmacological traits; Side effects, Therapeutics

1. Introduction

Horses are classified as one of the most important herbivorous equines which have played quintessential socioeconomic role in the developing countries [1, 2]. Most horses are companion animals and show close bonding with humans. They have been used not only as a ride in ancient wars but also as a mode of transport in this century. These animals played a crucial role in the development of first antidote for the treatment of diphtheria in the late 19th century [3] and anti-venom for snake bite [4]. Since then, horses are being used for animal-assisted diversified therapies. In addition, horses were employed as model for viral infections, respiratory problems, and orthopaedic diseases [5].

In spite of the versatile role of horses in our daily life, their mortality due to disparate deadly diseases has often been a colossal concern for veterinarians. Microbial infections have shown drastic impact upon working horses, thereby causing huge economic loss to the equine industries at present [6, 7]. In order to combat deadly infections, antibiotic therapy is considered as one of the leading options in equine industries [8]. As a matter of fact, the administration of varied classes of antibiotics or antimicrobial drugs is extensively known to treat primary and secondary bacterial infections. On the other hand, antibiotics are used as feed supplements too for improving growth performance and other biochemical parameters of horses [9]. Unfortunately, reduced feed intake, allergies, and diarrhoea are the most common adverse impact observed in horses due to the use of antibiotics as feed additive [10]. In addition, the overexploitation of antibiotics caused the emergence of drug resistant microorganisms, indicating the desperate essentiality to control antibiotics use in livestock industries.

Considering the detrimental influence in nutritional aspects, several countries have already banned the exploitation of antibiotics as growth promoters in animals. However, diversified classes of antibiotics are being administrated for the preventions of plethora of

diseases in horses which showed severe side effects. Generally, antibiotics disrupt normal microflora present inside the body, and thus, allow the overgrowth of potential pathogens [11]. In view of the overexploitation of antimicrobials for past few decades in equine veterinary sciences, the present review highlights the effect of conventional antibiotics on the horses' health.

2. Antibiotics against horses' infection: Mode of action and pharmacological traits

A variety of bacterial diseases are being treated in horses using antibiotic therapy. Antibiotics based treatment can cause not only reduced mortalities but also lower possibilities for disease transmission from animal-to-animal or animal-to-human [12]. In fact, it is central for the treatment of primary and secondary infections in horses. Hence, it is imperative to select effectual antibiotics considering its dosage, mode of actions, and possible adverse effects [13]. Mode of action and pharmacological traits of some commonly used antibiotics for horse's infections are summarized in Table 1.

3. Effect of antibiotics administration on horses' health

In spite of the beneficial attributes for treating plethora of diseases, antibiotics cause severe side effects to the horses' health. Reports have also suggested that the use of antibiotics in equines leads to the emergence of antibiotic resistant microbes associated infections in humans [14]. Effect of commonly used antibiotics as therapeutics on horses' health is discussed below:

3.1. Sulfonamides or Trimethoprim/sulphonamide combinations

Potentiated sulfonamides along with trimethoprim or pyri-methamine are extensively used as antimicrobial agents in equines [15]. Diarrhoea, hematuria, folate deficiency, colitis, hemolytic anaemia, immune-mediated diseases, abortion, neurologic signs, crystalluria, congenital defects, obstruction of renal tubuli, and pruritus are common side effects of sulfonamides when administrated alone or in combination with trimethoprim [16]. The

treatment of four-year-old Quarter Horse mare with trimethoprim-sulfadiazine showed fever, respiratory infection with productive cough, disorientation, and bilateral anterior uveitis with discharge. Stevens-Johnson syndrome is associated with the administration of sulphonamide [17]. The administration of sulfonamide causes hypersensitivity reactions and type I anaphylactic IgE antibody reactions. Anaphylaxis is clinically expressed as low blood pressure and collapse. Cardio-vascular collapse may lead to multi-organ slow-flow, causing infarction with multi-organ failure. Antibiotic administration showed cerebral infarction in the brain computed tomography (CT) scan. This was attributed to a cerebral slow-flow during cardiovascular collapse. Study observed a limited right occipital cortico-subcortical lesion in the visual cortex, interpreted as an ischemic scar in the watershed area related to hemodynamic infarction [18].

3.2. Benzylpenicillin

In equine therapy, benzylpenicillin is the most commonly used penicillin as highly hydrophilic sodium or potassium salts or as a procaine salt with low hydrophilic trait. These salts are often administrated intravenously, while procaine salt is injected intramuscular. Olsen et al. [19] studied the adverse effects of procaine benzylpenicillin or sodium or potassium benzylpenicillin in horses. In the study, 2 horses were administrated sodium or potassium benzylpenicillin intravenously, while the remaining 57 horses were injected with procaine benzylpenicillin intramuscularly. Initially, allergic reactions were observed due to the administration of sodium or potassium benzylpenicillin and procaine benzylpenicillin. In most of the horses, locomotor and behavioural changes were observed as the most common clinical signs. In general, procaine is easily hydrolyzed to non-toxic metabolites by the action of plasma esterases. However, the high doses of procaine enter the circulation and lead to the enhanced hydrolyzing ability, thereby showing toxicity. Likewise, low esterase activity may induce procaine toxicity and reveal another risk factor.

3.3. Cefquinome

Cefquinome (2-amino-5-thiazolyl) is used as veterinary medicine and belongs to fourth generation of cephalosporins [20]. It is known to exhibit antibacterial activity against equine bacterial pathogens, particularly *Streptococcus zooepidemicus*, *Staphylococcus* spp., *Actinobacillus equuli*, *Rhodococcus* spp., *Pseudomonas* spp., *E. coli*, and other *Enterobacteriaceae* [21]. It is generally recommended to treat respiratory diseases, septicaemia, and other bacterial infections of horses [22]. Altan et al. [23] evaluated the impact of various doses (1-6 mg/kg) of cefquinome on haematological (white blood corpuscles, lymphocytes, monocytes, granulocytes, red blood corpuscles, haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, red cell dispersion width, and platelets) and biochemical parameters (albumin, total bilirubin, cholesterol, triglyceride, gamma glutamyl transferase, alanine aminotransferase, creatinine, lactate dehydrogenase, alkaline phosphatase, aspartate aminotransferase, total protein, and blood urea nitrogen) of horses. Results showed no significant differences in serum biochemical parameters amongst the tested groups. On the other hand, significant differences were found in certain haematological parameters such as monocytes, granulocytes, red blood corpuscles, haemoglobin, haematocrit, mean corpuscular haemoglobin, and platelets were significantly affected amongst the groups. Findings suggested lack of clinically significant effect on the blood parameters of horses when administrated with cefquinome within the range of 1-6 mg/kg.

3.4. Fluphenazine

Fluphenazine is a phenothiazine derivative neuroleptic which is mainly used for the treatment of schizophrenia and other psychoses in humans. In general, it suppresses aggressive behaviour by blocking postsynaptic D2 receptors and presynaptic D2 autoreceptors, thereby reducing the synthesis and activity of dopamine [24]. The major side

effects of fluphenazine include tardive dyskinesia, akathisia, and hyperreflexia [25] which are initially originated from the extrapyramidal system of the brain, where D2 receptors are inhibitory [26]. Since, horses have a more extensive extrapyramidal system than humans, hence, horses are considered more susceptible to the severe side effects of fluphenazine. Baird et al. [27] observed behavioural abnormalities in four racehorses (4-year old) after the administration (both intramuscular and intravenous) of fluphenazine decanoate (25-50 mg). The clinical signs observed were: profuse sweating, aimless circling, intense pawing and striking with the thoracic limbs, and rhythmic swinging of the head and neck alternating with episodes of severe stupor. Fluphenazine was found in the serum samples obtained from all 4 horses. However, three horses were recovered following intensive care and returned to racing, but the remaining horse showed severe neurological signs and respiratory failure, indicating that horses may be more sensitive to the side effects of fluphenazine decanoate administration. In another study, the administration of 25 mg of fluphenazine decanoate in four-year-old, castrated, male Thoroughbred horse showed seizure-like activity which was further controlled by administrating xylazine [28].

3.5. Enrofloxacin

Enrofloxacin belongs to fluoroquinolone antimicrobials which is bactericidal in nature and shows effectiveness at lower doses (5 mg/kg of body weight) against equine pathogens. It is generally administered orally or by injection [29, 30]. Report has shown that the oral administration of enrofloxacin develops cartilage lesions in horses [31]. In another study, horses were administrated enrofloxacin (5, 15, and 25 mg/kg of body weight) intravenously for 21 days and joint angles, cross-sectional area of superficial and deep digital flexor and calcaneal tendons, carpal or tarsal osteophytes or lucency, and midcarpal, and tarsocrural articular cartilage lesions were observed. Results showed that the administration of enrofloxacin did not alter most of the variables for 7 days. However, in 1 horse, the

administration of enrofloxacin at 15 mg/kg showed lameness and cellulitis around the tarsal plantar ligament during the last week. Likewise, 1 horse (dosage, 15 mg/kg) showed superficial digital flexor tendinitis. On the other hand, the administration of enrofloxacin at 25 mg/kg in 1 horse showed tarsal sheath effusion without lameness after 3 days. The administration of enrofloxacin at 15 and 25 mg/kg by bolus injection developed transient neurological signs. In contrary, the intravenous administration of low dose of enrofloxacin (5 mg/kg) showed no adverse effects, suggesting lower doses of enrofloxacin administration a safer approach [32].

Antimicrobials based therapy is used for treating different bacterial diseases such as pneumonia, septic arthritis, peritonitis, and placentitis during pregnancy. *In vitro* and *in vivo* investigations showed that enrofloxacin caused tendonitis and arthropathies in young and growing horses [33-35]. Fluoroquinolone antibiotics are generally avoided in pregnant mares due to its chondrotoxic nature towards the foetus [36]. In contrary, recent reports suggested that the administration of enrofloxacin in late pregnancy might not affect the foetus or foal [37, 38]. However, it is assumed that toxicity may appear when organogenesis and the development of limb begin in the first trimester [39].

Ellerbrock et al. [40] assessed the influence of enrofloxacin for 2 weeks on the equine foetus between 46 and 60-days gestation. Results suggested that the administration of enrofloxacin to the early pregnant mare might not cause gross or histological lesions in the foetus. It can be used for treating bacterial infections in pregnant mares. The administration of enrofloxacin should be avoided for those bacteria that showed resistance towards first-line antimicrobial agents.

Transportation through vehicles affects the health of horses. The transportation stress and adverse environment of vehicles induce fever which is mainly observed after 20 h or more after the beginning of the transportation [41]. The shipping fever in horses is primarily

caused by *Streptococcus equi* subsp. *zooepidemicus* (*S. zooepidemicus*) which generally affects horse's bronchoalveolar region [42]. Endo et al. [43] assessed the effect of single dose of enrofloxacin (5 mg/kg) on fever and blood properties in 68 Thoroughbred racehorses after long-distance transportation for 21 h. Horses were administrated enrofloxacin ≤1 h before transportation. Clinical examinations and hematologic analyses revealed significant reduction in the rectal temperatures, white blood cell counts, and serum amyloid A concentration in enrofloxacin administrated group as compared to the control group. Findings suggested that the administration of enrofloxacin just before transportation can certainly prevent transportation-associated fever in adult Thoroughbred racehorses.

3.6. Other antibiotics

Equine recurrent uveitis (ERU) is an immune-mediated disease characterized by recurrent bouts of ocular inflammation [44]. Fischer et al. [45] investigated the effect of intravitreal administration of gentamicin in ERU infected horses of different ages, breeds, and gender. Horses were treated with intravitreal injection of 4 mg of undiluted gentamicin (100 mg/mL in 35 horses) and preservative-free gentamicin (80 mg/mL in 52 horses) under sedation. Results showed that intravitreal injection of low-dose gentamicin controlled different types and stages of uveitis.

Lyme borreliosis is a tick transmitted disease of horses which is caused by spirochete *Borrelia burgdorferi*. Symptoms include lameness, arthritis, carditis, dermatitis, and neurological abnormalities. The intradermal and subcutaneous administration of sodium ceftriaxone induced anaphylactoid reactions in horses infected by *B. burgdorferi*, which further evolved into colic syndrome, laminitis and emergence of opportunistic infections [46]. In addition, adverse effects of some commonly used antibiotics on horses' health are summarized in Table 2.

4. Conclusions and future perspective

In summary, antibiotics are of immense significance in antimicrobials-based therapy for horses. Commonly used antibiotics in equine industries showed bacteriostatic and bactericidal properties by interfering bacterial cell wall and protein synthesis as well as inhibiting RNA polymerase, DNAase 1, and DNA gyrase. However, antibiotics such as sulfonamides or trimethoprim/sulphonamide combinations, benzylpenicillin, cefquinome, fluphenazine, enrofloxacin, and sodium ceftriaxone have shown certain limitation in terms of revealing adverse effects on horses' health. Thus, there is desperate essentiality to strengthen the laws and policies towards the usage of antibiotics in equine industries. In addition, it is imperative to optimize and analyze the combinations, formulations, route of administration, and dosages of antibiotics used in order to avoid the adverse effects on horses' health in future.

Conflict of interest

Authors declare that they have no conflict of interest.

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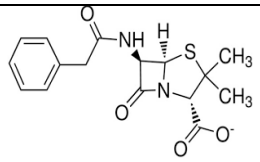
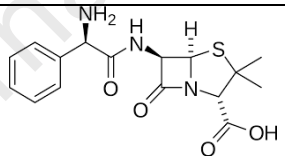
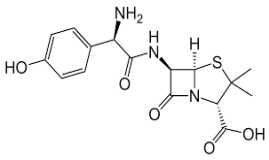
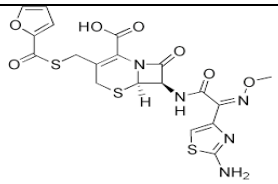
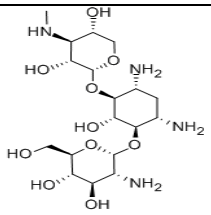
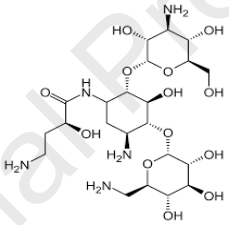
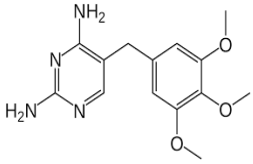
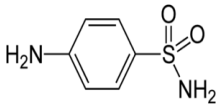
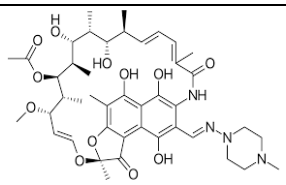
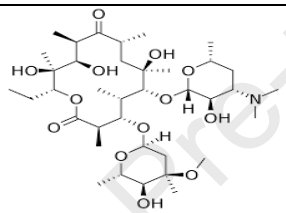
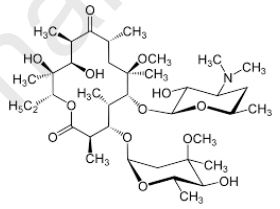
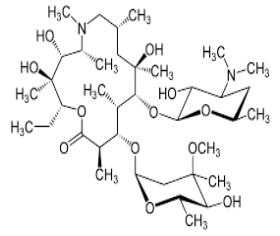
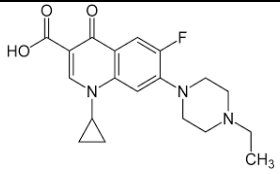
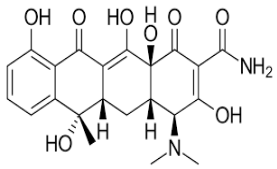
Table 1: Mode of action and pharmacological traits of commonly used antibiotics for horse's infections (adapted from [13]).

Antibiotics	Formula	Structure	Mode of action	Pharmacological properties
Penicillin G	$C_{16}H_{18}N_2O_4S$		Interferes with the synthesis of bacterial cell wall by binding to transpeptidase and other penicillin-binding proteins.	Distributes widely throughout plasma but shows poor penetration into the biological membranes due to low lipid solubility. It does not penetrate abscesses or sites of tissue necrosis well. Elimination occurs via active renal tubular secretion. Shows antibacterial activities in a time-dependent manner.
Ampicillin and amoxicillin	Ampicillin ($C_{16}H_{18}N_3NaO_4S$) Amoxicillin ($C_{16}H_{19}N_3O_5S$)	 Ampicillin  Amoxicillin	Interferes with the synthesis of bacterial cell wall by binding to transpeptidase and other penicillin-binding proteins.	Distributes widely throughout plasma but shows poor penetration into the biological membranes due to low lipid solubility. Elimination occurs predominantly by the renal route (primarily tubular secretion). Shows antibacterial activities in a time-dependent manner.
Ceftiofur	$C_{19}H_{17}N_5O_7S_3$		Prevents the synthesis of bacterial cell wall by binding	Hydrolysed by the liver to desfuroylceftiofur. It penetrates into body

			to penicillin-binding proteins.	fluids but does not enter the cerebrospinal fluid in efficient doses. Elimination occurs via glomerular filtration and active tubular secretion. Shows antibacterial activities in a time-dependent manner.
Aminoglycosides (gentamicin and amikacin)	Gentamicin ($C_{21}H_{43}N_5O_7$) Amikacin ($C_{22}H_{43}N_5O_{13}$)	 Gentamicin  Amikacin	Interferes with the protein synthesis by binding to the 30S ribosomal subunit.	Distributes in a volume similar to the extracellular fluid volume. Elimination occurs by glomerular filtration. Shows antibacterial activities in a time-dependent manner.
Trimethoprim-sulphonamide combinations	Trimethoprim ($C_{14}H_{18}N_4O_3$) Sulphonamide (RSO_2NH_2)	 Trimethoprim  Sulphonamide	Sulphonamides prevent incorporation of para-aminobenzoic acid into folic acid in bacterial cells. Trimethoprim inhibits dihydrofolate reductase (enzyme responsible for folate synthesis)	It is lipophilic in nature and distributes effectively. They cross the blood-brain barrier. Elimination occurs by renal excretion. Shows antimicrobial activities in a time-dependent manner.

Rifampin	$C_{43}H_{58}N_4O_{12}$		Inhibits RNA polymerase	It is highly lipophilic in nature. It has a wide volume of distribution, and excellent penetration into cells. The exact mechanism of elimination of rifampin in horses is not well understood, but it is considered to be excreted via bile with some minor urinary excretion.
Erythromycin, clarithromycin, and azithromycin	Erythromycin ($C_{37}H_{67}NO_{13}$) Clarithromycin ($C_{38}H_{69}NO_{13}$) Azithromycin ($C_{38}H_{72}N_2O_{12}$)	 Erythromycin  Clarithromycin  Azithromycin	Inhibits bacterial protein synthesis by reversibly binding to the 50S ribosomal subunit.	It is high lipophilic in nature. It is widely distributed in the body and shows excellent penetration into cells. Elimination occurs predominantly via bile.
Enrofloxacin	$C_{19}H_{22}FN_3O_3$		Inhibits DNA gyrase.	It is high lipophilic in nature. High doses are found in liver, spleen and kidney; moderate concentrations in skin, muscle, heart, stomach,

				intestine, uterus, mammary gland, bone and bladder; and mild concentrations in cerebrospinal fluid and eyes. Elimination occurs predominantly in the urine.
Tetracyclines	$C_{22}H_{24}N_2O_8$		Inhibit bacterial protein synthesis by reversible binding to the 30S ribosomal subunit	It is well distributed to most of the tissues, except central nervous system. After intravenous administration of oxytetracycline, therapeutic concentrations are detected in peritoneal and synovial fluid and urine. After oral administration of doxcycline, therapeutic levels are found in peritoneal and synovial fluids, as well as in broncho-alveolar lavage cells and urine. Elimination of oxytetracycline occurs in the urine via glomerular filtration while doxycycline is eliminated in the faeces.

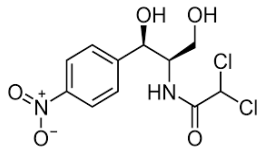
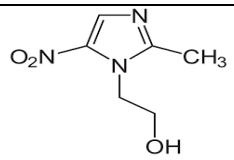
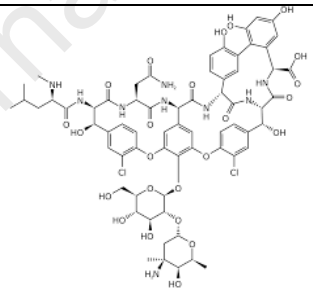
Chloramphenicol	$C_{11}H_{12}Cl_2N_2O_5$		Inhibits the synthesis of protein by binding irreversibly to the 50S ribosomal subunit.	It is highly lipophilic and distributes efficiently throughout the body. Therapeutic doses are found in liver, kidney, synovial fluid, peritoneal fluid. Elimination occurs in the urine.
Metronidazole	$C_6H_9N_3O_3$		Inhibits DNase 1	It is widely distributed in the body and penetrates tissues well. Metronidazole can be detected in bone, peritoneal and synovial fluid, abscesses, and the central nervous system. Elimination occurs in urine.
Vancomycin	$C_{66}H_{75}Cl_2N_9O_{24}$		Inhibits the synthesis of bacterial cell wall peptidoglycan.	It shows poor tissue distribution. Therapeutic concentrations are detected in synovial fluid after intravenous administration. Elimination occurs via glomerular filtration.

Table 2: Adverse effects of commonly used antibiotics on horses' health (adapted from [13]).

Antibiotics	Nature of activity	Indicator pathogens	Side effects
Penicillin G	Bactericidal	Promising activities against Gram-positive bacteria, with the exception of some *Staphylococcus* spp., and *Rhodococcus equi*. Limited activities against Gram-negative bacteria.	Excitement, seizure-like activity, muscle soreness, focal myositis, respiratory difficulty, diarrhoea, head shaking, teeth grinding, salivation, lacrimation, high borborygmus, mild colic, passage of soft faeces, and colitis.
Ampicillin and amoxicillin	Bactericidal	Promising activities against Gram-negative bacteria such as *E. coli*, *Proteus* spp. and *Salmonella* spp.	Irritation and antimicrobial-associated colitis.
Ceftiofur	Bactericidal	Broad spectrum activities against Gram-positive and Gram-negative aerobes and many anaerobes. Pronounced activity against *Pasteurella* spp.	Discomfort, irritation, diarrhoea, and colitis.
Aminoglycosides (gentamicin and amikacin)	Bactericidal	Shows limited activities against aerobic Gram-negative bacteria, *Mycoplasma* spp., and *Mycobacteria* spp.	Nephrotoxicity, ototoxicity, and muscle irritation.
Trimethoprim-sulphonamide combinations	Bactericidal and bacteriostatic	Broad-spectrum activities against many Gram-positive and Gram-negative aerobic bacteria.	Affect the gastrointestinal flora, cause colitis and diarrhoea occasionally, tremor, excitement, ataxia, collapse, dysrhythmia, and

			hypotension.
Rifampin	Bactericidal	Narrow spectrum antimicrobial activities against Gram-positive aerobes, some Gram-negative non-enteric aerobes, and most anaerobes. Broad spectrum activities against *Staphylococcus aureus*, *R. equi*, *Mycobacterium* spp., *Corynebacterium* spp., and *Streptococcus* spp.	Rusty orange staining of urine, anorexia, benign faecal softening, and false elevation in liver enzymes.
Erythromycin, clarithromycin, and azithromycin	Bactericidal and bacteriostatic	Broad spectrum activities against Gram-positive aerobes such as *R. equi*. Moderate activities against some Gram-negative non-enteric aerobes and few anaerobes.	Colitis, diarrhoea, fever, and hepatobiliary toxicity.
Enrofloxacin	Bactericidal	Broad spectrum activities against Gram negative aerobes, including Enterobacteriaceae and *Pseudomonas aeruginosa*, and against *Mycoplasma* spp., *Rickettsia* spp. and *Ehrlichia* spp. Moderate activities against Gram positive and anaerobes bacteria.	Non-inflammatory arthropathy, weakening and rupture of tendons, ataxia, severe oral ulceration, colitis, and neurological behaviours.
Tetracyclines	Bactericidal and bacteriostatic	Broad spectrum activities against Gram-positive and Gram-negative aerobes, except *Proteus* spp. and *Pseudomonas* spp.	Renal tubular necrosis, hypotension, and antimicrobial-associated colitis.

Chloramphenicol	Bacteriostatic	Broad spectrum activities against Gram-positive and Gram-negative aerobes and anaerobes.	Anaemia and pancytopenia.
Metronidazole	Bactericidal	Narrow spectrum activities against anaerobic bacteria and protozoa.	Depression, weakness, ataxia, vestibular signs, seizures, peripheral neuropathy, and anorexia.
Vancomycin	Bactericidal	Narrow spectrum activities against Gram-positive aerobic bacteria.	Irritation.

Highlights

1. Antibiotics are equine medicines which are used to treat varied infections in horses.
2. Antibiotics show bacteriostatic and bactericidal traits through varied mode of actions.
3. Certain conventional antibiotics cause detrimental effects on horses' health.
4. Diarrhoea, colitis, seizures, and neurological abnormalities are common side effects.
5. Analyzing the administration route and antibiotics dosage in equines is suggested.

Ethical statement

Not applicable.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: