


Review  
Pharmacology



# Pharmacokinetics/Pharmacodynamics models of veterinary antimicrobial agents

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 OPEN ACCESS

Received: Jan 29, 2019

Revised: Apr 2, 2019

Accepted: May 21, 2019

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Funding

This work was supported by the National Key Research and Development Program of China (2017YFD0501402) and the National Natural Science Foundation of China (grant No.31772797).

Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

Conceptualization: Luo W, Xie S; Data curation: Chen D, Wu M; Formal analysis: Li Z, Tao Y, Liu Q, Pan Y, Qu W, Yuan Z; Funding acquisition:

## ABSTRACT

Misuse and abuse of veterinary antimicrobial agents have led to an alarming increase in bacterial resistance, clinical treatment failure, and drug residues. To address these problems, consistent and appropriate dosage regimens for veterinary antimicrobial agents are needed. Pharmacokinetics/Pharmacodynamics (PK/PD) models have been widely used to establish rational dosage regimens for veterinary antimicrobial agents that can achieve effective prevention and treatment of bacterial diseases and avoid the development of bacterial resistance. This review introduces building methods for PK/PD models and describes current PK/PD research progress toward rational dosage regimens for veterinary antimicrobial agents. Finally, the challenges and prospects of PK/PD models in the design of dosage regimens for veterinary antimicrobial agents are reviewed. This review will help to increase awareness of PK/PD modeling among veterinarians and hopefully promote its development and future use.

**Keywords:** PK/PD models; dosage regimens; drug residues; bacterial infections; antimicrobial agents

## INTRODUCTION

Worldwide, veterinary antimicrobial agents are the most frequently administered drugs among veterinary drugs [1] used to treat and prevent animal diseases and promote growth performance [2-4]. They have a positive role in animal husbandry and in providing healthy animal-source food for humans. However, overuse of veterinary antibiotics has resulted in a high rate of infectious diseases treatment failure, development of bacterial resistance, and both side and residual effects in livestock. Drug residues in animal-source foodstuff might lead to childhood precocity, obesity, resistance transfer, and other health problems in humans. In addition, residues in excrement and animal carcasses can result in soil and water pollution in the environment (**Fig. 1**) [5]. It is well known that veterinary antimicrobial agents have no effect on animal diseases when applied below the drug's effective dosage; however, when used excessively, such agents can produce toxic reactions and drug residues. The 2014 World Health Organization (WHO) "Antibiotic resistance: global monitoring report" pointed out that the antibiotic resistance is a serious threat and is currently occurring

Xie S; Investigation: Luo W; Methodology: Luo W; Project administration: Xie S; Resources: Xie S; Software: Luo W; Supervision: Luo W; Validation: Chen D, Xie S; Visualization: Xie S; Writing - original draft: Luo W, Xie S; Writing - review & editing: Luo W, Xie S.

around the world; moreover, it can affect everyone, regardless of age or nationality [6]. The development of antibiotic resistance can be very devastating due to its frequent presence in conventional infectious diseases [7]. The high occurrence rate of antibiotic resistance can lead to substantial direct and indirect losses in livestock farming. The Europe, Middle East and Africa (EMEA) has taken some measures to remove growth promoters in veterinary antimicrobial agents from food-producing animal products by imposing restrictions on the pharmaceutical industry [8], but bacterial disease incidence is increasing year by year. Denmark banned the use of antibiotics as growth promoters in 1999, which led to various infections, including those related to diarrhea, and intestinal infections are currently widely prevalent in Denmark, especially among weaned piglets and finishing pigs. The sensitivity of various bacteria to most veterinary antimicrobial agents is decreasing year by year [9] and the widespread use of veterinary antimicrobial agents places considerable pressure on the environment. Researchers have pointed out that a large number of veterinary antimicrobial agents can result in residues in the environment, thus affecting environmental and human health [10].

To solve problems (*e.g.*, inadequate protection of animal and public health) related to the misuse or abuse of veterinary antimicrobial agents, determining reasonable usage rates by optimizing the agent's dosage regimen is essential. Pharmacokinetics/Pharmacodynamics (PK/PD) models are an important investigative tool that can help optimize the dosage regimens of veterinary antimicrobial agents by linking the dosage regimen of a veterinary antimicrobial agent to its clinical effects [11]. At present, PK/PD has been used to establish dosage regimens for eliminating bacteria, reducing carrier status, and slowing the progress

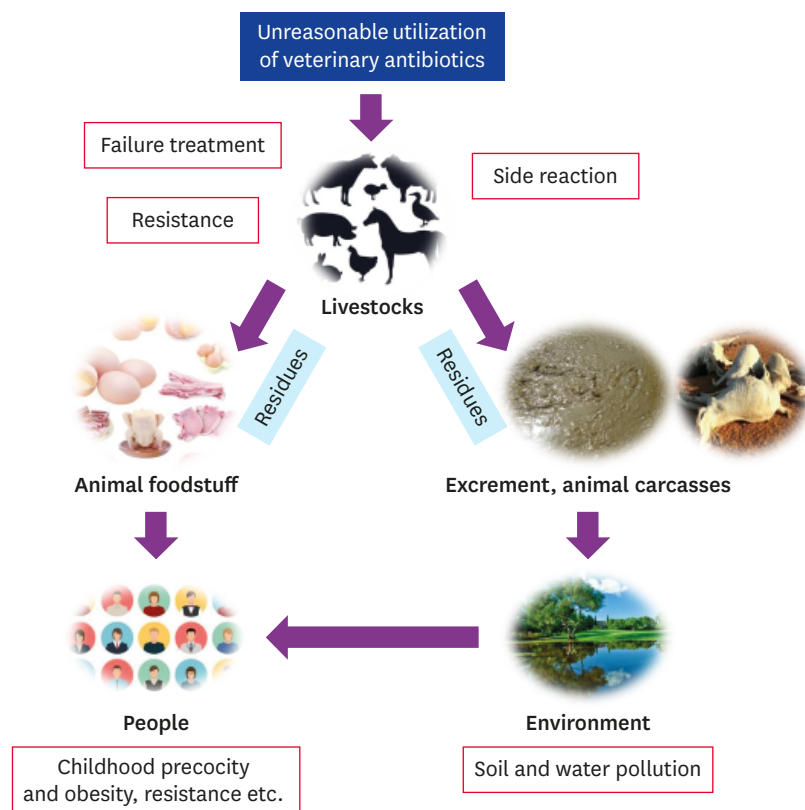


Fig. 1. Effects of inappropriate use of veterinary antibiotics on livestock, animal foodstuff, and the environment.

of bacterial resistance in the veterinary field [12]. Regulatory agencies have suggested that PK/PD-based relationship investigations are necessary during drug development (EMA and Food and Drug Administration [FDA] Guidelines) [13,14].

To increase the understanding of PK/PD and promote its development, this review describes current PK/PD model building methods and reviews research progress in the use of PK/PD for designing dosage regimens for veterinary antimicrobial agents and indicates the challenges and prospects for the future use of PK/PD models.

## PK/PD MODEL BUILDING METHODS

PK/PD model building methods mainly include three approaches: *in vitro*, *in vivo* and *in vivo* PK/PD. Choosing a suitable PK/PD model building method is critical in the determination of dosage regimens. The principles, advantages, and disadvantages of the three approaches are reviewed below and summarized in **Table 1**.

### *In vitro* PK/PD models

*In vitro* PK/PD models investigate the relationship between the concentration of an antibacterial agent and the number of bacteria in a culture system that simulates the environment within an animal's body. The basic method of *in vitro* PK/PD models involves mixing serial concentrations of antimicrobial agents (within a suitable range) with a certain number of bacteria, adding the mixture into a synthetic medium, and determining the changes in bacterial abundance at each antimicrobial agent concentration level at different times during incubation [15]. For example, to determine the minimum inhibitory concentration (MIC) of enrofloxacin against *Escherichia coli* a drug would be diluted to different concentrations (*e.g.*, 32 MIC, 16 MIC, 8 MIC, 4 MIC, 2 MIC, 1 MIC, ½ MIC) and then each concentration is incubated with  $1.5 \times 10^8$  CFU/mL of *E. coli*. During incubation, the number of *E. coli* is calculated after 0, 1, 2, 4, 6, 8, 12, and 24 h at each different concentration of enrofloxacin [16]. The advantage of an *in vitro* PK/PD model is that it can study the relationship between different concentrations of a drug and pathogen at different times without the need to involve a lot of experimental animals, thereby decreasing animal and experimental costs. The concentration range of antimicrobial agents, the type of synthetic medium, and the initial bacterial inoculation level are key factors in the *in vitro* method. The concentration should include the lowest antibacterial agent's concentration that does not kill any bacteria as well as the highest concentration that completely kills the bacteria. Nielsen et al. [17] suggested that an appropriate concentration range for an antibacterial agent should be designed so that it can accurately meet the requirements of the *in vitro* PK/PD models. Regarding the selection of a synthetic medium, it should ensure

**Table 1.** PK/PD model types

PK/PD models	Principles	Advantages	Disadvantages
<i>In vitro</i>	To study the relationship between changes in antibacterial agent concentration and bacteria number in an <i>in vitro</i> system	Accurate determination of relationship between drugs and bacteria; fewer animals used and less cost	Inaccuracy
<i>In vivo</i>	To study the interaction between drugs and bacteria <i>in vivo</i> by establishing an animal disease model	Authenticity	Hard to determine effective drug concentration in target tissues; higher animal use and costs
<i>In ex vivo</i>	To study the interaction between drugs and bacteria by combining PK <i>in vivo</i> PK and <i>in vitro</i> PD	Authenticity; fewer animals used and lower cost	Inaccuracy

PK, Pharmacokinetics; PD, Pharmacodynamics.

the bacteria can grow and can accurately simulate the bacteria's growth condition *in vivo*. Andraud et al. [18] used intestinal contents to replace a synthetic bacteria growth medium to more accurately simulate an actual infection. In addition, Udekwu et al. [19] suggested that the initial bacterial inoculation was a crucial factor in *in vitro* models and could affect MIC determination *in vitro*. A disadvantage of the *in vitro* PK/PD model is that the growth characteristics of the bacteria *in vitro* may not be the same as those *in vivo*. The antibacterial effect determined *in vitro* under simulated conditions may only reflect the antibacterial function of the drug and may ignore the *in vivo* effects related to the body's physiological and psychological states and the influence of external environmental factors. Thus, the antibacterial effect may be more remarkable under *in vivo* conditions.

### ***In vivo* PK/PD models**

PK/PD models *in vivo* use established animal infection models and are mainly used to study the relationship between PK and PD. At present, *in vivo* PK/PD modeling involves the construction of an infected animal model by inoculating a certain number of bacteria. A typical, and the earliest reported, *in vivo* PK/PD model is the mouse thigh infection model built by Gerber et al. [20] in 1982. Subsequently, a large number of infection models, *e.g.*, mouse and rat thigh infection model, pneumonia model, peritonitis infection model, and skin soft tissue infection model, have been reported [21,22]. The advantage of an *in vivo* PK/PD model is that it can truly reflect the progress of drug and bacterial exposure in the animal body. The effect of immune function, virulence, and injection of the test bacterium, and the drug concentration at the target site are the main determining factors in an *in vivo* model. In order to study the antibacterial effect of the drugs without interference from the animal immune system, Gerber et al. [23] and Zuluaga et al. [24] constructed immunosuppressant animal infection models by using intraperitoneal injections of cyclophosphamide at a dose of 250 mg/kg. Xiao et al. [25] established a chicken immunodeficiency animal model involving intraperitoneal injection of cyclophosphamide in order to study the PK/PD of valnemulin against *Mycoplasma gallisepticum in vivo*. It should be noted that the virulence and inoculation of the test bacteria must be appropriate when an immunosuppressant model is constructed [26]. In addition, the appropriate selection of drug concentrations at the target site is essential for effective *in vivo* PK/PD modeling. In the past, a plasma-level drug concentration was mostly used; however, with the development of PK/PD, the drug concentration at the target tissue is now commonly used. For example, Lutsar et al. [27] and Rodvold et al. [28] determined the drug concentration of cerebrospinal fluid in a meningitis model and the concentration of the epithelial fluid in a pneumonia model, respectively, instead of using plasma drug concentrations. Microdialysis and ultrafiltration technology has been used to determine the concentration of the free drug in the intercellular fluid of target tissues as the total drug concentration (including the binding drug concentration) could not accurately reflect the effective concentration at the target site [28]. At the same time, Knudsen et al. [29] used the number of bacteria in infected tissue as a PD index in order to overcome *in vivo* PK/PD model deficiencies. The main disadvantage of *in vivo* PK/PD models is that the drug concentration cannot be quickly and accurately measured because of the combinatory effects of proteins and other ingredients. In addition, it is vital to build a consistent animal infection model for use in *in vivo* PK/PD models since that the physiological and pathological status differences could influence the pharmacokinetics of drug [30]. Therefore, it is important to establish an appropriate and consistent animal infection state by using optimized bacterial isolates and quantities.

### **In ex vivo PK/PD models**

*In ex vivo* PK/PD models are suitable for the study of interactions between the drug and the bacteria as they combine *in vitro* and *in vivo* PK/PD model characteristics. The combination method in an *in ex vivo* PK/PD model involves studying PK in target animals and studying PD in plasma, tissues, and fluids following sampling from the studied animals at different times [31,32]. The advantage of an *in ex vivo* PK/PD models is not only its ability to reflect the real PK process *in vivo* but also its capacity to reduce the number of animals used and the cost of the experiment [33]. At present, *in ex vivo* PK/PD models have become one of the more common methods to study PK/PD of veterinary antimicrobial agents [34]. For example, Wang et al. [16] established an *in ex vivo* PK/PD models of enrofloxacin against swine colibacillosis via combining *in vivo* PK data with *in ex vivo* PD data in pig ileum. Sang et al. [33] used a similar method to establish an *In ex vivo* PK/PD model to determine the appropriate dosage for treating broiler colibacillosis. When using an *in ex vivo* PK/PD model, there is a need to obtain samples from the appropriate target tissue within the infected animals. Sang et al. [33] and Zhou et al. [36] suggested that it is better to select plasma, bronchial lavage, and intestinal fluid for PK and PD study in infected systemic models of a pulmonary infection and a digestive tract infection, respectively. However, determining and measuring drug concentrations and bacteria numbers in target tissues remain a challenge in all three PK/PD models building methods.

## **FORMATION OF A DOSAGE REGIMEN VIA PK/PD MODELS**

PK/PD models are a vital tool in the analysis of the relationship between the time course and antibacterial effects of veterinary antibacterial agents and, thus, in optimizing a therapy regimen. In order to identify the clinically relevant relationship between the dosage interval time and the effect of a drug, PK/PD modeling, an advanced approach to determining a suitable daily dose and dosage interval, may be used [37,38]. Such models have been widely used to establish the dosage regimens of different antimicrobial agents including fluoroquinolones,  $\beta$ -lactam, amphenicols, tetracyclines, aminoglycosides, macrolides, colistin, and valnemulin. Among these, fluoroquinolones and  $\beta$ -lactams have been studied to the greatest extent. In this section, PK/PD research progress related to dosage regimen establishment for different veterinary antibacterial agents are summarized.

### **Fluoroquinolones**

Fluoroquinolones are broad-spectrum antimicrobial agents with strong bacteriostatic effects on Gram-negative and Gram-positive bacteria, as well as on mycoplasma and some caustic bacteria [8]. Fluoroquinolones can achieve high drug concentrations in tissues and sera [39-42]. However, misuse and abuse of fluoroquinolones have resulted in high failure rates in infectious disease treatments, as well as increased bacterial resistance and residue levels. Therefore, formulation of a safe and reasonable dosage regimen is urgently needed. The rational dosage regimens of different members of fluoroquinolones including enrofloxacin, danofloxacin, sarafloxacin, and marbofloxacin against some main pathogenic bacteria (e.g., *Mannheimia haemolytica*, *E. coli*, *Pasteurella multocida*, *Haemophilus parasuis*, *Streptococcus suis*, *Streptococcus pneumoniae*, and *Salmonella typhimurium*) have been formulated by using PK/PD models to increase the therapeutic effect while decreasing adverse effects and the development of bacterial resistance (**Table 2**). For example, Wang et al. [16], Sang et al. [33], and Balaje et al. [43] optimized the prevention, treatment, and rational dose regimens of enrofloxacin against *E. coli* in pigs and broilers and against *P. multocida* in buffalo calves,

**Table 2.** Current PK/PD models for fluoroquinolone-based treatments

Drug	Bacteria	Animal	Parameter	Models	Dosage regimen
Enrofloxacin	<i>E. coli</i>	Pigs	AUC/MIC $C_{max}/MIC$	<i>In ex vivo</i>	1.96 mg/kg by intramuscular administration
Enrofloxacin	<i>E. coli</i>	Broilers	AUC/MIC $C_{max}/MIC$	<i>In ex vivo</i>	11.9 mg/kg by oral administration
Enrofloxacin	<i>P. multocida</i>	Buffalo calves	AUC/MIC $C_{max}/MIC$	<i>In ex vivo</i>	12 mg/kg by intramuscular administration
Danofloxacin	<i>M. haemolytica</i>	Calves	AUC/MIC $C_{max}/MIC$	<i>In ex vivo</i>	0.738 mg/kg by a single intravenous bolus
Danofloxacin	<i>S. typhimurium</i>	Rabbits	AUC/MIC $C_{max}/MIC$	<i>In ex vivo</i>	10 mg/kg by oral administration
Danofloxacin	<i>E. coli</i>	Camel	AUC/MIC $C_{max}/MIC$	<i>In ex vivo</i>	4 mg/kg by intramuscular administration
Marbofloxacin	<i>P. multocida</i>	Piglets	AUC/MIC $C_{max}/MIC$	<i>In ex vivo</i>	2.5 mg/kg by intramuscular administration
Marbofloxacin	<i>P. multocida</i>	Calves	AUC/MIC $C_{max}/MIC$	<i>In ex vivo</i>	2 mg/kg by intramuscular administration
Marbofloxacin	<i>H. parasuis</i>	Pigs	AUC/MIC $C_{max}/MIC$	<i>In ex vivo</i>	16 mg/kg by intramuscular administration
Marbofloxacin	<i>E. coli</i>	Pigs	AUC/MIC $C_{max}/MIC$	<i>In ex vivo</i>	2 mg/kg by oral administration
Marbofloxacin	<i>S. suis</i>	Pigs	AUC/MIC $C_{max}/MIC$	<i>In ex vivo</i>	12.35 mg/kg by oral administration

PK/PD, Pharmacokinetics/Pharmacodynamics; AUC/MIC, the area under the concentration time curve/the minimal inhibitory concentration;  $C_{max}/MIC$ , the maximum concentration/the minimal inhibitory concentration.

respectively, by applying *in-ex vivo* PK/PD models. The optimized dosage regimens had great therapeutic significance and their application confirmed that dosage regimens formulated by PK/PD models present a low risk for the emergence of resistance [44]. For fluoroquinolones, the maximum concentration/the minimal inhibitory concentration ( $C_{max}/MIC$ ) and the area under the concentration time curve (AUC)/MIC have often been used as parameters to formulate dosage regimens related to the concentration-dependent bactericidal effect of fluoroquinolones. Dosage regimens vary depending on the types of drugs, animals, and bacteria. For example, the optimized dose regimens for danofloxacin against *M. haemolytica* in calves was 0.738 mg/kg administered by a single intravenous (IV) bolus, while against *S. typhimurium* in rabbits the regimen was daily oral administration of 10 mg/kg for 3 days, and against *E. coli* in camels was 4 mg/kg by intramuscular administration [31,45,46]. Moreover, the same drug can have a different dosing regimen against the same bacterial infection in different animals. For example, the optimized dose regimens of marbofloxacin against *P. multocida* in piglets and calves were 2.5 and 2 mg/kg intramuscular administration, respectively [47,48]. Even, the same drug can have a different dosing regimen against a different bacterial infection in the same animal. Dose regimens for fluoroquinolones are more accurate when obtained via PK/PD models that are specific to the bacterium and the animal species. For example, the dosage regimen of marbofloxacin against *H. parasuis*, *E. coli*, and *S. suis* in pigs was 16 mg/kg by intramuscular administration, 2 mg/kg by oral administration, and 12.35 mg/kg by oral administration for a 90% target attainment ratio [49-51]. Based on the aforementioned reports, the type of animal studied has less effect on the dosage regimen than the type of bacteria or drug. Also, different administration routes (*e.g.*, oral or intramuscular administration) may have an impact on dosage regimen. Thus, the kind of drug, the animal and bacterium of interest, and the route of administration must be considered when formulating an optimal dosage regimen. The abovementioned studies have shown that the dosage regimens for fluoroquinolones are more effective when obtained via PK/PD modeling.

### $\beta$ -lactams

Among the various veterinary antimicrobial agents,  $\beta$ -lactams have been widely used in veterinary clinics due to their broad antibacterial spectra and remarkable antibacterial activities [52]. At present, the dosage regimens of  $\beta$ -lactam antibiotics have been studied via PK/PD models to avoid their misuse and abuse. The  $\beta$ -lactam dosage regimen depends on the types of animals and bacteria. Appropriate dosage regimens for different  $\beta$ -lactams, including cefquinome and amoxicillin, against some key pathogenic bacteria (*e.g.*, *E. coli*, *S. pneumoniae*, *S. suis*, and *Actinobacillus pleuropneumoniae*) have been formulated via PK/PD modeling (Table 3). For example, the recommended therapeutic regimen of cefquinome against *E. coli* in pigs was 1.33 mg/kg every 24 h based on *In ex vivo* PK/PD models [48], whereas that for clinical treatment of mouse mastitis caused by *Staphylococcus aureus* infection was 75 mg/kg every 12 h based on an *in vivo* PK/PD model [53]. However, for lactating mice infected by *E. coli*, the formulated dose was 200  $\mu$ g per mammary gland once daily based on *in vivo* PK/PD model results [54]. In addition, the recommended therapeutic regimen for amoxicillin against *S. pneumoniae* in a gerbil model of acute otitis media was 5 mg/kg via intramuscular administration as determined by an *in vivo* PK/PD model [55]. For  $\beta$ -lactam antibiotics, the % cumulative time that the concentration exceeds the minimal inhibitory concentration (% T > MIC) parameter is often used to formulate the dosage regimen as it reflects a time-dependent bactericidal effect. For example, the antibacterial activity of cefquinome against *S. aureus* in a catheter-associated biofilm infection model and *A. pleuropneumoniae* in a piglet tissue cage infection model exhibited time-dependence in both *in ex vivo* or *in vivo* PK/PD models [36,56]. Based on the above examples, both the type of animal and the bacterium species are important considerations in PK/PD models being used to formulate optimal dosage regimens for  $\beta$ -lactams. Interestingly, based on the above examples, the dose of cefquinome was less than that for enrofloxacin in the treatment of *E. coli* in pigs; however, the difference was not marked [35,48], indicating that cefquinome has higher bioavailability than enrofloxacin in the treatment of *E. coli* in pigs.

### Amphenicols

Florfenicol, a member of the amphenicol drug family, is widely used in veterinary clinics. For amphenicols, determination of the %T>MIC parameter is often used to formulate the dosage regimen due to their time-dependent bactericidal effects. The dosage regimens of florfenicol against *A. pleuropneumoniae* and *P. multocida* in pigs were formulated by using an *in ex vivo* PK/PD model. The calculated daily dosages to achieve a 90% target attainment rate (TAR) for bacteriostatic and bactericidal effects were 6.2 and 9.6 mg/kg, respectively, for *P. multocida* and 18.2 and 35.2 mg/kg, respectively, for *A. pleuropneumoniae* [57]. The recommended therapeutic regimen of florfenicol against *S. suis* in pigs was 25.02 mg/kg by intramuscular

**Table 3.** Current PK/PD models for  $\beta$ -lactam-based treatments

Drug	Bacteria	Animal	Parameter	Models	Dosage regimen
Cefquinome	<i>E. coli</i>	Porcine	%T>MIC	<i>In ex vivo</i>	1.33 mg/kg by intramuscular administration
Cefquinome	<i>S. aureus</i>	Mouse	%T>MIC	<i>In vivo</i>	75 mg/kg/12 h by intramuscular administration
Cefquinome	<i>E. coli</i>	Mouse	%T>MIC	<i>In vivo</i>	200 $\mu$ g/gland by intramuscular administration
Amoxicillin	<i>S. pneumoniae</i>	Mouse	%T>MIC	<i>In vivo</i>	5 mg/kg by intramuscular administration
Cefquinome	<i>S. aureus</i>	Mice	%T>MIC	<i>In ex vivo</i>	
Cefquinome	<i>A. pleuropneumoniae</i>	Piglets	%T>MIC	<i>In vivo</i>	

PK/PD, Pharmacokinetics/Pharmacodynamics; % T > MIC, cumulative time that the concentration exceeds the minimal inhibitory concentration.

administration as derived by an *in ex vivo* PK/PD model [58]. In addition, the estimated daily dose of florfenicol against *M. haemolytica* and *P. multocida* in calves to achieve a 90% TAR were formulated through *in ex vivo* PK/PD models as 14.1 mg/kg for *M. haemolytica* and 4.2 mg/kg for *P. multocida* [32]. Dosage regimens formulated by PK/PD models will be helpful in reducing the emergence of bacterial resistance to florfenicol. The above examples show that PK/PD dosages for fluoroquinolones are less than those for florfenicol in the treatment of *P. multocida*, *M. haemolytica*, and *S. suis*, indicating that fluoroquinolones have a higher bioavailability than florfenicol in the treatment of *P. multocida*, *M. haemolytica*, and *S. suis*.

### Tetracyclines

Appropriate dosage regimens for different tetracyclines, including doxycycline and oxytetracycline, against some key pathogenic bacteria (*e.g.*, *M. gallisepticum*) have been formulated for use in chickens and pigs by using *In ex vivo* PK/PD models. The estimated %T>MIC values after a single IV dose of 10 mg/kg for 0 log<sub>10</sub> (CFU/mL), 2 log<sub>10</sub> (CFU/mL), and 3 log<sub>10</sub> (CFU/mL) reductions were 32.48%, 45.68%, and 54.36%, respectively. When the %T>MIC time is 45.68%, the most effective dosage regimens can be obtained [59]. Additionally, these results provide guidance for obtaining optimal dosing strategies for doxycycline in *M. gallisepticum* infections. Doxycycline was observed to be a time-dependent kinetic at low serum concentrations but a concentration-dependent kinetic at high serum concentrations against *E. coli*, *S. aureus*, *P. multocida*, and *S. pneumoniae* [21]. However, the results showed that doxycycline had time-dependent characteristics against *M. gallisepticum*; this difference may be caused by differences within the target microorganism.

### Aminoglycosides

Aminoglycosides are highly potent, broad-spectrum antibiotics with many desirable properties for their application in the treatment of serious infections. The C<sub>max</sub>/MIC and AUC/MIC parameters are often used during the formulation of dosage regimens for aminoglycosides due to their concentration-dependent bactericidal effects. An appropriate dosage regimen for amikacin has been formulated by using PK/PD models. Staneva et al. [44] found that the therapeutic effect of an intramuscular daily dose of 10 mg/kg amikacin against *Pseudomonas aeruginosa* sepsis in rabbits was greater than that from a daily dose of 20 mg/kg; the daily dose of 10 mg/kg was able to reduce drug toxicity and achieve better clinical results. Aminoglycoside toxicity is related to the duration of drug treatment. Once-daily dosing and selection of the most appropriate time of the day may help in achieving improved chronotherapeutic results and reduced drug toxicity.

### Macrolides

Macrolides are characterized by their ability to extensively partition into tissues, where they are then observed to have multi-fold higher concentrations compared to the concentration in plasma. The %T>MIC parameter has often been used to formulate the dosage regimen of macrolides due to their time-dependent bactericidal effect. Nan et al. [60] optimized the dosage regimen of acetylkidasamycin against *Clostridium perfringens* in pigs by using an *in ex vivo* PK/PD model. A dosage regimen of 18.63 mg/kg body weight (B.W) every 12 h was sufficient for the prevention of *C. perfringens* infection, and the therapeutic dosage regimen for *C. perfringens* infection was 51.36 mg/kg every 12 h for 3 days. In that study, a novel PK method (liquid chromatography and tandem mass spectrometry) was successfully developed to study the holistic PK properties of acetylkidasamycin and was validated for PK study through an *in vivo* experiment. Such dosage regimens developed by novel PK/PD models could, to some extent, decrease the risk of emergence of macrolide resistance.



### Colistin

Colistin is an antimicrobial member of the polymyxin antibiotic group and has been used widely in veterinary clinics since the formulation of an appropriate dosage regimen. The daily dosage regimen of colistin for gastrointestinal tract disease in swine based on *in ex vivo* PK/PD models was 50,000 IU/kg at 12 h intervals according to the  $C_{max}$ /MIC and AUC/MIC results [61]. For colistin, the AUC/MIC was deemed the most appropriate parameter based on studies into the pulmonary delivery of colistin against *P. aeruginosa* in a mouse lung infection model and the administration of colistin and imipenem against a *P. aeruginosa* biofilm infection [35,62]. The developed dosage regimen for swine was enough to provide a bacteriological cure while minimizing opportunities for the emergence of colistin resistance.

### Valnemulin

Valnemulin is widely used in veterinary clinics to treat various infectious diseases following the formulation of an appropriate dosage regimen. AUC/MIC is the most appropriate parameter for assessment of valnemulin effects due to its concentration-dependent bactericidal characteristic. Xiao et al. [25] optimized its dosage regimen against a mixed infection of *M. gallisepticum* S6 in chickens by using an *in ex vivo* PK/PD model. The optimal daily dosage levels for the therapy and eradication of *M. gallisepticum* S6 in chickens were 12.4 mg/kg and 18.3 mg/kg, respectively. The therapy portion of their experiment demonstrated that valnemulin could effectively treat and eradicate *M. gallisepticum* S6 infections when using the formulated dosage regimen. However, the breed of chicken as well as their age, gender, physical status, and other factors, may affect the dosage predicted as such factors can influence the PK parameters. Thus, a population-based PK approach should be taken in the future. As the dosages were based on the MIC of one bacterial strain, it would be better to calculate valnemulin dosages based on the MIC distribution for the bacterial species rather than for a strain. Such a species-based approach would include the strain-specific variation in susceptibility to the drug.

## CHALLENGES AND PROSPECTS

PK/PD models have become an important tool for the development and assessment of new veterinary antimicrobial agents, and model results can help to ensure the safe and efficient use of veterinary antimicrobial agents. Moreover, their use can reduce or eliminate misperceptions about the risks associated with veterinary antimicrobial agent usage by consumers, veterinarians, animal and food producers, and veterinary pharmaceutical companies. At present, there are some remaining challenges and prospects associated with PK/PD models. Some of the challenges that urgently need to be overcome are listed in the following and summarized in **Table 4**. 1) How to select the most appropriate PK/PD index to evaluate the efficacy of a veterinary antimicrobial agent. The effects of many veterinary antimicrobial agents *in vivo* cannot be measured directly and continuously, which can lead to measurement inaccuracies, thus the need to select the best PK/PD index. 2) How to correctly determine the connection and correlation between the PK/PD model index and the status and process of the relevant infection. 3) How to accurately determine the concentration of the drug and the number of bacteria in the target tissue. Determination of the appropriate PK/PD index, especially for drug concentrations in the target tissues of an animal, is not easy. In addition, there is a need to consider the residual effects of the drug *in vivo*. 4) How to accurately simulate the animal disease model, the antibacterial effect of the host immune system, and influences of the animal's body and mental state, health state, and

**Table 4.** Advantages of, challenges to, and prospects for PK/PD models

Advantages	Challenges	Prospects
1. Optimizes the dosage regimen.	1. Selecting the appropriate PK/PD index.	1. Determine PK/PD index via software programs.
2. Ensures safe and efficient use of veterinary antimicrobial agents.	2. Correctly determining the connection and correlation between PK/PD model index and the state and process of the disease.	2. Use modern technology (microanalysis and ultrafiltration).
3. Avoids drug resistance.	3. Getting an accurate concentration of drugs and number of bacteria.	3. Use appropriate immunosuppressants.
4. Reduces animal husbandry losses.	4. Accurate simulation of target animal.	4. Determine PK/PD parameter indices separately for multi-target and multi-component drugs.
5. Avoids effects on human health and avoids causing environmental pollution.	5. Selecting an appropriate target animal.	5. Establish additional PK/PD models for existing and new antibacterial agents.
	6. Developing PK/PD models for multi-target and multi-component drugs.	
	7. Improve equations for time-dependent antibacterial agents.	

PK/PD, Pharmacokinetics/Pharmacodynamics.

the external environment. Diseases can often affect the function of specific organs and the disposition of the drugs *in vivo*; consequently, attaining the desired dosage may be difficult due to the severity of the infection and several other factors. Therefore, construction of an animal infection model that is similar to a natural infection is difficult. 5) How to select the appropriate target animal, physiology and pathology of animals, and the scientific indicator is very difficult when constructing animal infection models. Bacterial species, appropriate dose, and virulence strength are not easily selected. In the establishment of an effective animal infection model, the bacterial infection should provide obvious clinical symptoms without producing death among the test animals. Based on the characteristics of the selected bacterium, a suitable dose should allow PK/PD modeling of the animal infection without death of the subject animals. In addition, the model should consider whether the inoculated bacteria are sensitive by examining their MIC<sub>50</sub> or MIC<sub>90</sub> values. 6) Current PK/PD models are only suitable for drugs that have a single composition and that have an exact mechanism of action. Therefore, there is a need to establish PK/PD models that allow the determination of dosages for multi-target and multi-component drugs, *e.g.*, compound preparations and Chinese herbal medicines containing many effective components. 7) The data-fitting equations in PK/PD models mainly focus on concentration-dependent antibacterial drugs, *e.g.*, fluoroquinolones; thus the fitting of equations for time-dependent antibacterial agents need further study. 8) During the treatment of animal diseases, public health problems (*i.e.*, drug residues, drug resistance, environmental pollution, etc.) and animal safety problems (*e.g.*, nephrotoxicity, etc.) should be prevented. For overcoming the above challenges, researchers should make full use of advanced and new technologies during the development of PK/PD models.

The following and the summary in **Table 4** presents some of the prospects for improving existing or developing new PK/PD models. 1) Complex PK/PD relationships need to incorporate more computer simulation-based techniques that can assist in improving clinical efficacy and can help in the quantitative characterization of the time course of a veterinary antimicrobial agent's effects, thereby achieving a “more optimal” drug therapy dosage. Thus, research on PK/PD models needs to incorporate software programs that can help determine parameters such as %T>MIC, AUC<sub>0-24h</sub>/MIC, and C<sub>max</sub>/MIC. Examples of such software programs that already have these provisions are NONLIN PK/PD modeling software (NONLIN, PCNONLIN, and WINNONLIN), Kinetica, ADAPT, NONMEN, as well as several other PK/PD applicable software programs (TOPFIT, NONMEN, PKAnalyst, RSTIR, STELLA, DIFFEQ, MKMODEL, NPEM2, and SAS). The use of more precise mathematical models to

predict the connection and correlation between PK/PD index and disease status/process should be encouraged. 2) Modern technology related to microanalysis and ultrafiltration can be used to obtain accurate and precise estimates of drug concentrations. Similarly, their use would allow bacteria concentrations to be measured accurately at different times. The use of such advanced technologies will improve the accuracy of PK/PD dosage regimens. 3) Appropriate immunosuppressants should be used to inhibit the immune response of animals, thus allowing the PK/PD model to assess a natural infection that is highly stimulated. However, the type of animal, operating techniques, feeding environments, and other factors can affect the immunosuppression of the animal model and may even produce death among study subjects. Therefore, there is an urgent need to construct simple and effective immunosuppressive animal models. In addition, mechanism-based PK/PD models should pay close attention to eliminating, as much as possible, influences related to the animal's mental state, health status, and external environment. 4) PK/PD models for a variety of antibacterial agents used by veterinarian clinics still need to be established, and optimal administration dosages formulated to reduce the potential development of bacterial resistance to those agents.

In summary, PK/PD models are important tools for formulating rational dose regimens for a variety of veterinary antimicrobial agents. Such models can be significant guides for the development and safe use of new veterinary antimicrobial agents. Further development and increased use of PK/PD models for antimicrobial agents will continue to be important in eliminating bacterial invasion, reducing bacteria-carrier status, slowing the progress of bacterial resistance, and enhancing animal-source food safety.

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