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Abstract

Fecal excretion of antibiotics and resistant bacteria in the environment are major public health threats associated with extensive farming and modern medical care. Innovative strategies that can reduce the intestinal antibiotic concentrations during treatments are in development. However, the effect of lower exposure on the amount of resistant enterobacteria excreted has not been quantified, making it difficult to anticipate the impact of these strategies. Here, we introduce a bacterial kinetic model to capture the complex relationships between drug exposure, loss of susceptible enterobacteria and growth of resistant strains in the feces of piglets receiving placebo, 1.5 or 15 mg/kg/day ciprofloxacin, a fluoroquinolone, for 5 days. The model could well describe the kinetics of drug susceptible and resistant enterobacteria observed during treatment, and up to 22 days after treatment cessation. Next, the model was used to predict the expected amount of resistant enterobacteria excreted over an average piglet's lifetime (150 days) when varying drug exposure and treatment duration. For the clinically relevant dose of 15 mg/kg/day for 5 days, the total amount of resistant enterobacteria excreted was predicted to be reduced by 75% and 98% when reducing treatment duration to 3 and 1 day treatment, respectively. Alternatively, for a fixed 5-days treatment, the level of resistance excreted could be reduced by 18%, 33%, 57.5% and 97% if 3, 5, 10 and 30 times lower levels of colonic drug concentrations were achieved, respectively. This characterization on *in vivo* data of the dynamics of resistance to antibiotics in the colonic flora could provide new insights into the mechanism of dissemination of resistance and can be used to design strategies aiming to reduce it.

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Introduction

Antibiotics are widely used in animal farming for curative, prophylaxis and metaphylaxis purposes. This results in massive excretion of antibiotics [1,2] and resistant bacteria with the feces of the animals during treatments [3]. It impacts the ecology of the environment and ultimately contributes to increase resistance in bacteria infecting humans [4], making resistance of human bacteria to antibiotics one of the major threats to public health in the next decade [5,6].

In particular, fluroquinolones (FQ) are widely used in animals, including in pets and farm animals for respiratory, urinary tract and skin infections, and have also been categorized as critical for human use (see the WHO list of Critically Important Antimicrobials [7]). Unfortunately resistance to FQ has regularly increased over the last decades and has reached a level that jeopardizes the treatment of common human infections caused by members of the *Enterobacteriaceae* family (enterobacteria), in particular *Escherichia coli* and *Klebsiella spp*, such as gastrointestinal and urinary tract infections [8,9]. Besides causing infections, enterobacteria are also naturally present in the intestinal commensal flora of humans and several animal species [10,11]. When a subject is treated with FQ, either by the oral or the parenteral route, a fraction of the dose administered is eliminated in the intestine after biliary and intestinal excretion [12]. These residual concentrations may be sufficient to eliminate FQ-susceptible species but not to act against resistant enterobacteria [13,14]. Consequently, resistant enterobacteria can multiply in these free niches and reach high concentrations before being excreted in the feces [15]. This set of events is believed to be a major driver of emergence and dissemination of bacterial resistance [16] and this is why innovative strategies, such as charcoal-based adsorbent, are now being developed to reduce intestinal antibiotic residues [17,18]. However, the effect of lower

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