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Effect of antimicrobial dosing factors on competitive growth of strains

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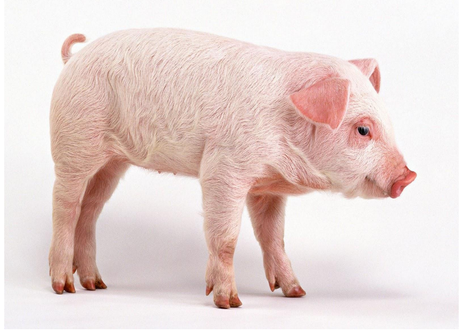
- Increased antimicrobial resistance calls for better use of antibiotics
- Pharmacokinetic-pharmacodynamic (PK-PD) models are useful to design the optimal treatment strategies that minimise resistance development.



Study Subjects:

- Tetracycline - known for wide-spread antimicrobial resistance
- *Escherichia coli (E. coli)* – good indicator bacterium of antimicrobial resistance in animals.

OBJECTIVES

Purpose: Optimize intramuscular treatment to minimize level of antimicrobial resistance in a pig. Primary objectives were to use a mathematical model to:

(1) Predict competitive growth of randomly selected *E. coli* strains in a pig treated intramuscularly.

(2) Assess the optimal dose, dosing frequency and treatment duration to suppress or delay the growth of resistant strains.

(3) Analyse the effect of multiple competing bacterial strains on resistance development.

MATERIALS AND METHODS

Plasma concentrations of tetracycline in pigs modeled using data from literature.

Competitive growth of 3, 6 and 12 randomly selected strains under

- Same daily dose of 20mg/kg
- Treatment durations (3, 5, 8 days)
- Dosing frequencies (1/2days, 1/day, 2/day)
- One-third proportion of strains was sampled to be resistant.

Growth of *E. coli* strains in the presence of tetracycline assessed using PD E_{max}-*model*

$$\alpha(c) = \alpha_{max} - \frac{\alpha_{max}\left(\frac{c}{EC_{50}}\right)^{\gamma}}{1+\left(\frac{c}{EC_{50}}\right)^{\gamma}}$$

Where α is net bacterial growth rate, and c is Tetracycline concentration

Changes in bacterial counts of individual bacterial strains in a pig were modeled using ordinary different equation

$$\frac{dN_i}{dt} = \left(\alpha_{max} - \frac{\alpha_{max}c^{\gamma}}{EC_{50}{}^{\gamma}+c^{\gamma}}\right)\left(\frac{N_{max}-N_i}{N_{max}}\right)\left(\frac{N_{max}-\sum N_i}{N_{max}}\right)N_i - \varphi N_i$$

where N_{max} is carrying capacity, and φ is strains flow-out rate

RESULTS

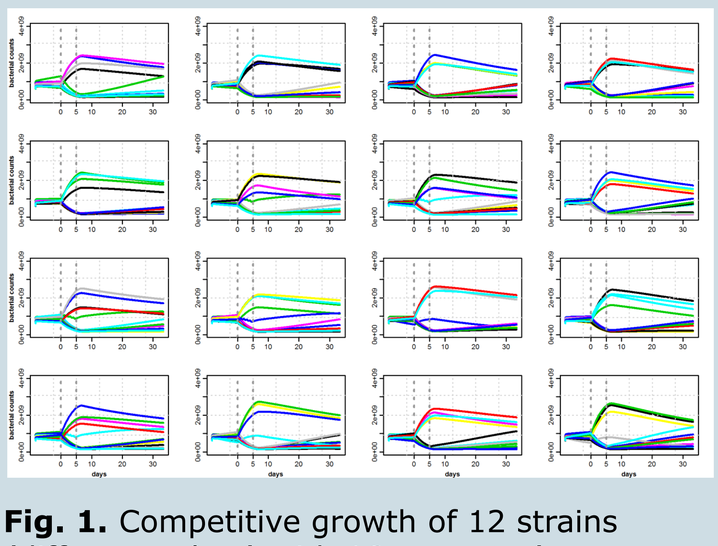


Fig. 1. Competitive growth of 12 strains (different colors) with 16 repeats (one per plot) and a different composition of 12 strains in each repeat.

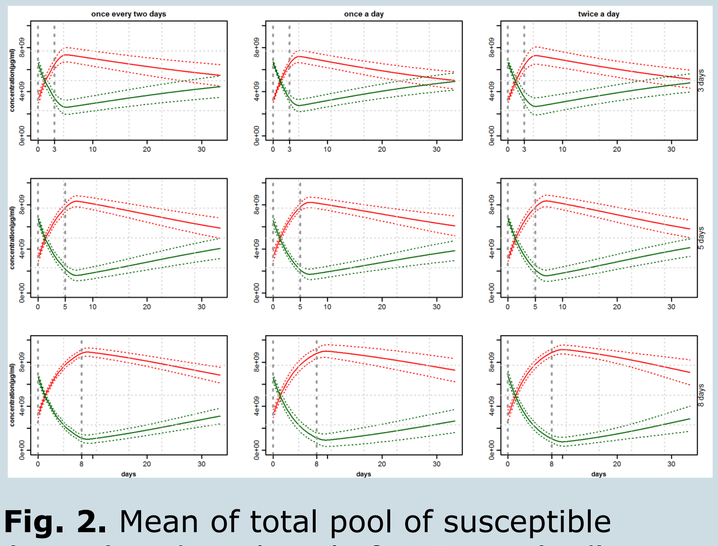


Fig. 2. Mean of total pool of susceptible (green) and total pool of resistant (red) bacterial counts at nine combinations of treatment duration and dosing frequency

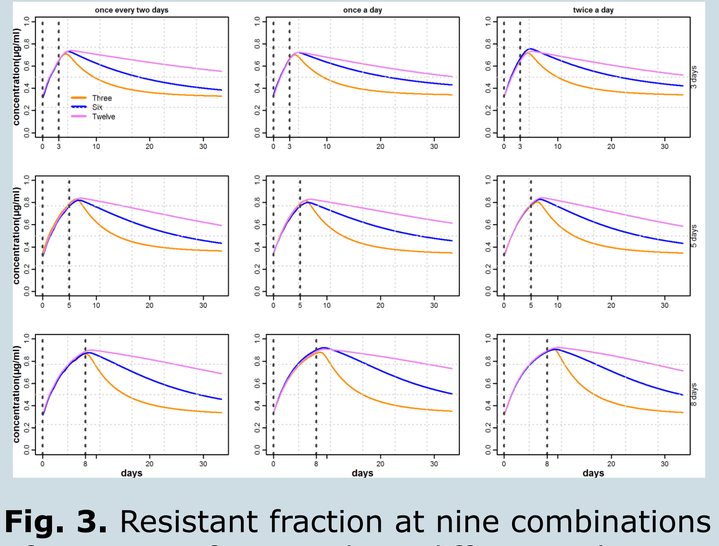


Fig. 3. Resistant fraction at nine combinations of treatment factors where different colors represent number of competing strains (i.e. 3, 6 and 12).

(1) Four out of 12 competing strains showed clear growth advantage during the treatment period across all 16 repeats regardless of different strains composition.

(2) Very little effect of dosing frequency. A more prolonged treatment duration resulted in increased resistance and consequently took longer to return to equilibrium.

(3) Fewer competing strains in a pig resulted in less time to return to the initial equilibrium level.

DISCUSSION AND CONCLUSIONS

Less time under antimicrobial pressure less time taken for susceptible strains to overcome competition from the resistant ones.
This could have arisen because of the large difference between susceptibility levels.

The longer the period before return to equilibrium the greater the risk of transmission of resistant strains to other pigs. The number of competing strains is an important determinant of the return time to equilibrium.

Predictions from this study could be used to redesign dosing regimens.
Accounting for the number of strains and their composition would help to improve the design of treatment protocols.