Modelling the impact of antimicrobials on the chicken gut microbiome and the dynamics of resistance genes – example of colistin

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TAKE HOME MESSAGE

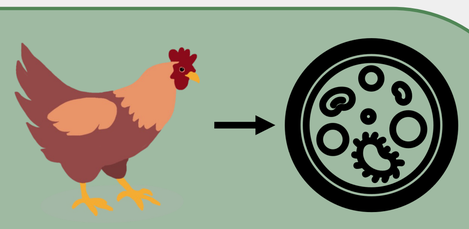
Timing, duration, and dose of antimicrobial drug administration impacts the dynamics of resistance genes over the poultry production cycle.

INTRODUCTION

- The use of antimicrobial drugs (AMDs) within poultry production has been a topic of concern over recent years due to their impact on **Global One Health**.
- The One Health Poultry Hub aims to investigate further these concerns in South and South East Asia
- Increased use of and exposure to colistin within the poultry setting can lead to the rise of AMR (antimicrobial resistant) genes, specifically *mcr*-1 (mediated colistin resistance).
- Understanding the impact of AMDs on the presence of resistance genes in the gut microbiome of poultry is important to advise policy surrounding their use, specifically in the current research in South and Southeast Asia.

METHODS

EXPERIMENT
An experimental poultry flock[1]
- Exposed to oral colistin for 72 hours
- 8 chickens removed and culled at given time points
- 8 *E. coli* isolates sampled per bird
- *mcr*-1 gene screening on resistant bacteria



MODEL
Adaptation of SIR compartmental models with poultry and environmental states, with the transmission rate (β), shedding rate (λ), decay rate (θ), treatment dose (t), and treatment coverage (f) parameters.

DATA FITTING
Data[1] was fit to the models using the log-likelihood.

PARAMETER ESTIMATION
Markov Chain Monte Carlo (MCMC) simulations using a random walk (Metropolis Hasting's) algorithm were conducted to estimate parameters.

AIMS AND OBJECTIVES

To model the impact of colistin on resistance gene (*mcr*-1) dynamics in chickens

Use published data to fit to compartmental models on antimicrobial resistance (AMR)

DATA

The results from the *in vivo* study can be seen in figure 2**.** MCR-1 prevalence increases with colistin use and decreases once administration stops.

MODEL
The model (Figure 1) is a system of differential equations simulating the change of uncolonized (**U**), wildtype (**W**), resistant (**R**), dually wildtype/resistant (**WW/RR**) and dually wildtype and resistant (**WR**) chickens over time. The force of infection comes from the environment ($\mathbf{E_R}$/$\mathbf{E_W}$).

$$\frac{dU}{dt} = -\beta_W\left(\frac{E_W}{ENV_t}\right)U - \beta_R\left(\frac{E_R}{ENV_t}\right)U + tfW$$
$$\frac{dW}{dt} = \beta_W\left(\frac{E_W}{ENV_t}\right)U - \beta_W\left(\frac{E_W}{ENV_t}\right)W - \beta_R\left(\frac{E_R}{ENV_t}\right)W + tf(WW - W)$$
$$\frac{dR}{dt} = \beta_R\left(\frac{E_R}{ENV_t}\right)U - \beta_R\left(\frac{E_R}{ENV_t}\right)R - tfWR$$
$$\frac{dWW}{dt} = \beta_W\left(\frac{E_W}{ENV_t}\right)W - tfWW - 2\beta_R\left(\frac{E_R}{ENV_t}\right)WW$$
$$\frac{dRR}{dt} = \beta_R\left(\frac{E_W}{ENV_t}\right)R - 2\beta_R\left(\frac{E_R}{ENV_t}\right)WW + \beta_R\left(\frac{E_R}{ENV_t}\right)WR$$
$$\frac{dWR}{dt} = \beta_W\left(\frac{E_W}{ENV_t}\right)W + 2\beta_R\left(\frac{E_R}{ENV_t}\right)WW - 2\beta_R\left(\frac{E_R}{ENV_t}\right)WR - tfWR$$

The simulated data with estimated parameters was fit to the data, an example can be seen in figure 3 (β_W=0.3 β_R=0.1, $\theta = \lambda = 0.2$). This was then fit using a binomial distribution:

$$Pn_i = \binom{8}{n_i} p_x^{n_i}(1-px)^{8-n_i} = B(n_i, 8, px)$$

We used Bayesian inference via MCMC to fit an estimate the parameters for the model described above. This is the current progress of the research project.

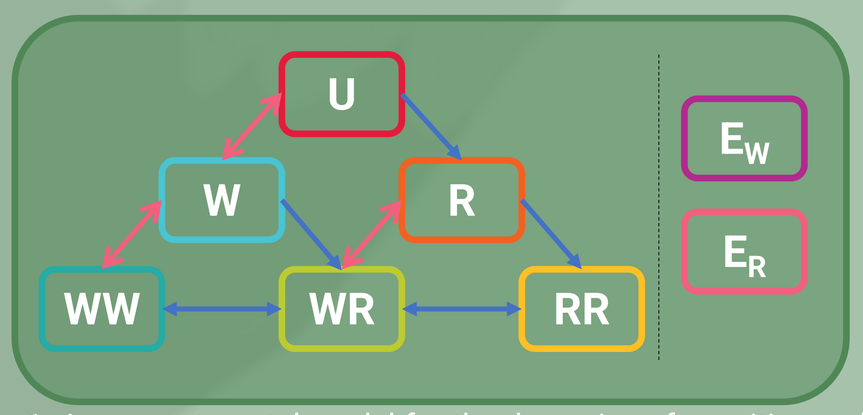


Figure 1: A compartmental model for the dynamics of sensitive and resistant strain bacteria via environmental transmission over time. The pink arrows show dynamics under AMD use. (Adapted from Colijn *et al.* 2010[2]).

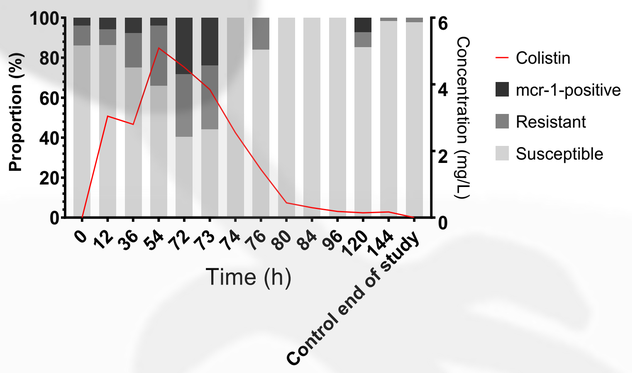


Figure 2: The proportion of mcr-1 positive *E.coli* isolates (black) at each time point within the *in vivo* study from Mead *et al.* 2021[1].

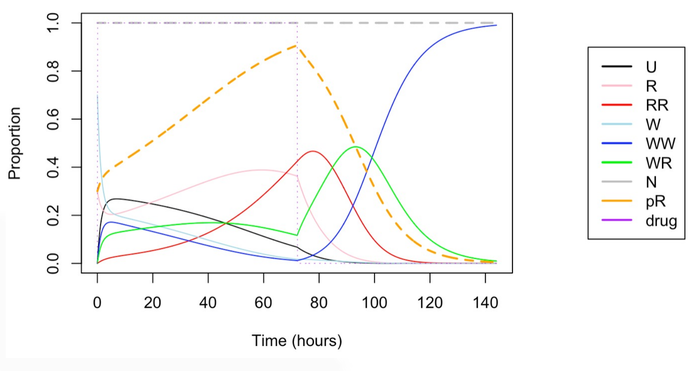


Figure 3: The simulated proportion of chickens in each compartment over time under colistin administration to be fitted to the *in vivo* study. pR= the proportion of resistance in the flock.

DISCUSSION

- Administration of antimicrobial drugs such as colistin leads to an increase in the prevalence of resistance genes in poultry production systems.
- *In vivo* studies are amenable to Bayesian statistical analysis using mechanistic models.
- Simulations can predict the dynamics of resistant genes over the production cycle, and infer efficacious farming methods to reduce the impact of AMR on global one health.

Further Work

- Continued parameter estimation for colistin and *E. coli*
- Poultry Hub data on AMD use, residues, and resistance genes via questionnaires, novel analytical methods, and sequences respectively.
- Expanding to country specific AMDs based on gut microbiome sequence data and antimicrobial residue data

[1] Mead *et al.* 2021: https://doi.org/10.3389/fvets.2021.698135
[2] Colijn *et al.* 2010: https://doi.org/10.1098/rsif.2009.0400

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