Modeling within-host and on-farm dynamics of plasmid-mediated resistance to cephalosporin ceftiofur in commensal *Escherichia coli* in cattle

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Enteric bacteria of food animals are a reservoir of antimicrobial-resistance genes. Antimicrobial pressure on these bacteria from enteric drug metabolites is poorly understood. Ceftiofur resistance in *Escherichia coli* in cattle is primarily mediated by a plasmidic blaCMY-2 gene. We built deterministic compartmental mathematical models to evaluate how the parameters of pharmacodynamics of ceftiofur enteric metabolites against *E. coli*, and the bacterial ecology impact on the frequency of resistance in enteric *E. coli*, and overall in the meta-population of commensal *E. coli* on a beef farm. The models showed that a low fraction of resistant enteric *E. coli* could persist without ceftiofur pressure, being influenced by ecological parameters: frequency of blaCMY-2 horizontal transfer, rate of replacement of enteric *E. coli* by ingested *E. coli*, and frequency of resistance in the latter. During therapy, irrespective of whether drug formulation was sustained-release or not, resistant *E. coli* expanded in absolute number and relative frequency; this was determined by pharmacodynamics (e.g. MIC values). However 4 weeks after therapy and beyond, the ecological parameters were again most important. There was a substantial uncertainty in the outcome during and post therapy. On-farm dynamics of ceftiofur resistance in commensal *E. coli* depended on housing system (feedlot vs pasture), and other factors.