**Modelling the effects of livestock antibiotic usage on human foodborne disease**

**ABSTRACT**

Livestock antibiotic usage has been proposed as a major driver of antimicrobial resistance in human populations. This has contributed to the implementation of antibiotic stewardship programs aiming to curtail usage of livestock antibiotics. However, the possible consequences of livestock antibiotic curtailment on human health are poorly understood. In particular, there is the potential for increases in the carriage of foodborne pathogens in livestock due to a loss of antibiotic pressure, and subsequent increase in human foodborne disease. Here we use a mathematical model to explore the impact of curtailing livestock antibiotic usage on both antibiotic-sensitive and antibiotic-resistant foodborne disease in humans.

The model identified increases in the daily incidence of human foodborne disease and a decrease in resistant human foodborne disease following livestock antibiotic curtailment. However, these effects can be mitigated through interventions to reduce animal-to-human transmission by targeting the farm-to-fork pathway. The magnitude of interventions needed to mitigate increases in human foodborne disease were found to vary across different case studies, suggesting that a “one-size fits all approach” across different agricultural settings, livestock hosts, and drug/bug combinations will likely not be efficacious.

This study provides a motivating example of one of many plausible scenarios following livestock antibiotic curtailment and identifies that even if increases in human foodborne disease are observed, existing agricultural biosecurity measures could successfully mitigate the negative human health consequences of livestock antibiotic curtailment.

**INTRODUCTION**

Antimicrobial resistance (AMR) is currently one of the largest threats to human health, with a growing number of key antibiotic therapeutics being rendered ineffective by resistant bacterial pathogens. Livestock antibiotic usage has been identified as a potentially important driver of AMR in human populations, with cross-species transmission of resistant bacteria and resistance determinants potentially occurring at the livestock/human interface (1). This has led to calls to curtail the usage of livestock antibiotics, with legislature such as the 2006 European Union ban and 2017 US Food Drug Administration regulation on antibiotic growth promotion, aiming to safeguard the efficacy of clinical antibiotics and reduce the potential for transmission of resistant pathogens to human populations (2, 3).

A range of beneficial outcomes have been reported as a consequence of livestock antibiotic curtailment, including decreased faecal *Enterococci* resistance rates in Denmark and Germany resulting from the 2006 growth promotion ban (2, 4, 5). Transient increases in the carriage of other resistant pathogens, increases in livestock carriage of foodborne pathogens and increases in therapeutic livestock antibiotic usage following antibiotic curtailment have been identified in AMR literature (6). These negative consequences have been suggested to be attributable to increases in livestock production in the years following the European ban on antibiotic-mediated growth promotion and due to other resistance-related genetic factors (7, 8). However, the unforeseen nature of these potential consequences highlights the risks of introducing interventions into highly complex and poorly understood systems as part of a “precautionary principle” based approach (9). The need to better understand the potential long-term impacts of future AMR policy is also likely to increase in coming years, with new EU legislation strictly controlling the use of livestock antibiotics for metaphylaxis or prophylaxis by 2022 (10). However, the precise relationship between livestock antibiotic usage and antibiotic-resistant/sensitive human foodborne disease remains poorly understood (5).

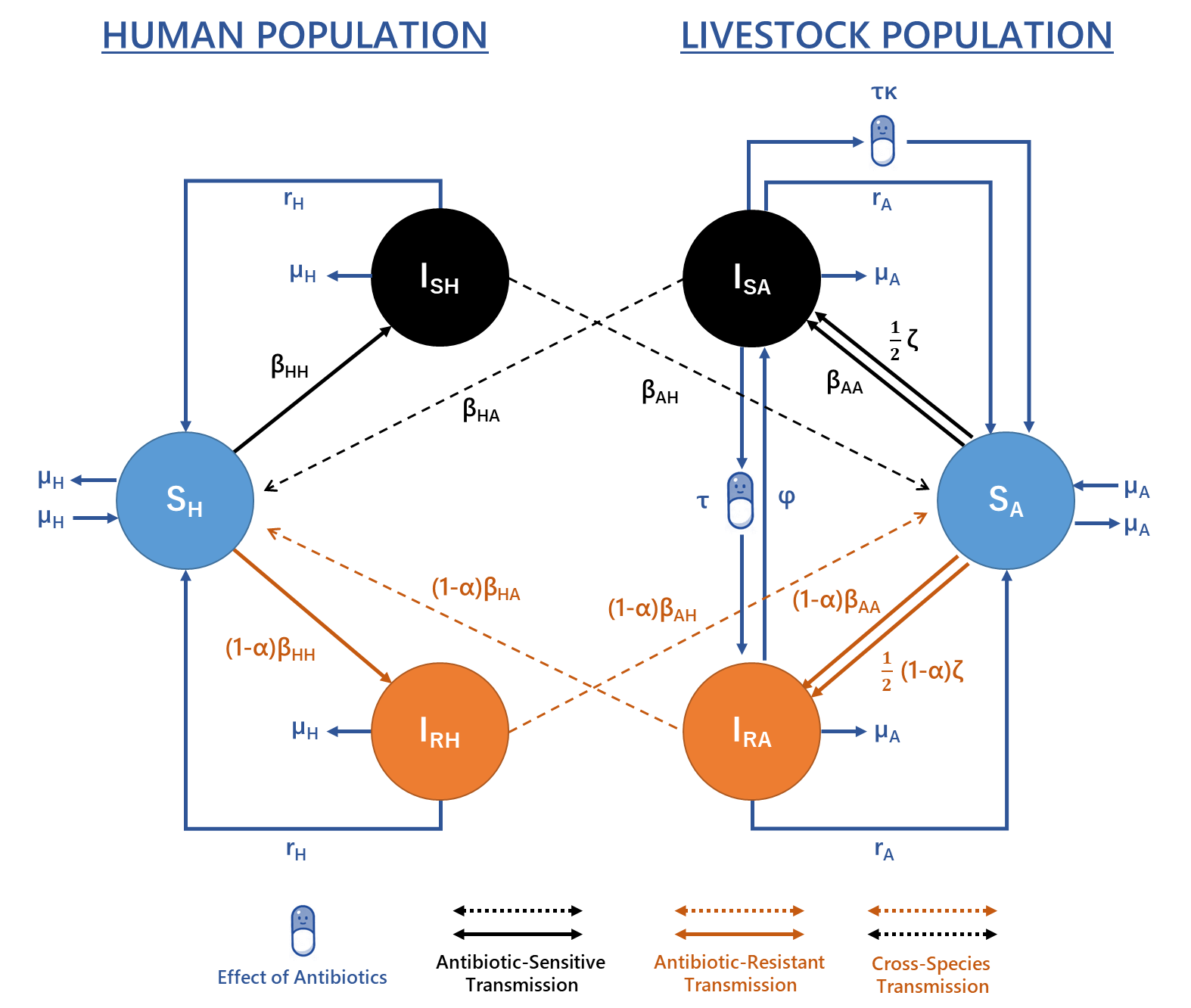
One approach to better understand the complexities of livestock antibiotic usage includes the use of mathematical models. These models can help by testing uncertainties, especially regarding the potential effects of livestock antibiotic usage on human health and the extent of AMR transmission at the livestock/human interface. However, there is a severe dearth of models which quantitatively explore these uncertainties (11). Existing frameworks include predictive risk assessment models and a small number of generalised deterministic models (12-17). Nevertheless, significant knowledge gaps still exist, including a lack of understanding of the potential consequences resulting from livestock antibiotic curtailment and the impact of different mitigating scenarios on altering these outcomes (18).

To address some of the gaps in AMR modelling literature, a deterministic mathematical model was developed to explore the effects of livestock antibiotic curtailment on common foodborne infections in humans across a range of scenarios. By explicitly modelling both livestock/human populations and various assumptions regarding the effects of livestock antibiotic usage, we explore the potential long-term consequences of livestock antibiotic curtailment, including alterations to the overall incidence of human foodborne disease and the antibiotic-resistant fraction of infections. Additionally, we explore the effects and feasibility of introducing interventions to mitigate the potential negative consequences of livestock antibiotic curtailment.

**METHODOLOGY**

**Model Structure and Description**

A deterministic compartmental model was developed to describe the transmission of antibiotic-resistant and antibiotic-sensitive foodborne bacteria within and between livestock and human populations (Figure 1) (19). Each host population can be stratified based on their respective infection status: susceptible humans (SH), humans infected with antibiotic-sensitive bacteria (ISH), humans infected with antibiotic-resistant bacteria (IRH), susceptible livestock food-animals (SA), livestock food-animals infected with antibiotic-sensitive bacteria (ISA) and livestock food-animals infected with antibiotic-resistant bacteria (IRA).



**Figure 1. Model structure describing the transmission of foodborne pathogens between/within livestock and human populations.** Model equations and parameters can be found described in the supplementary material (Table S2).

Transmission is simplified into four transmission routes: animal-to-animal (βAA), human-to-human (βHH), animal-to-human (βHA) and human-to-animal (βAH) transmission, with each β parameter linearly describing both indirect and direct transmission between compartments for model tractability. A background rate of transmission in the livestock population was also modelled (ζ); representing infection/contamination of livestock hosts from sources other than livestock or humans. This background transmission rate was scaled by a factor of 0.5 to ensure an equal influence of ζ on both antibiotic-sensitive and resistant transmission routes. This value was chosen due to a lack of *a priori* information on potential differences in background livestock contamination rate for antibiotic-sensitive/resistant strains. Natural recovery from antibiotic-sensitive/resistant infection occurs in both human/livestock populations at rate rH and rArespectively. Per capita birth/death rates are represented by µA in livestock and µH in human populations.

We use a parameter (τ) to describe the selective pressure and therapeutic effect of livestock antibiotic usage. We model the selective pressure of livestock antibiotics as a single transition rate, encompassing a range of evolutionary and biological phenomena that convert livestock between antibiotic-sensitive to resistant states. One plausible mechanism includes an implicit majority-minority relationship in each infected state, with livestock in each infected compartment possessing a small proportion of bacteria belonging to the other susceptibility class. Subsequent antibiotic usage may therefore clear antibiotic-sensitive bacteria (ISA) and allow the minority antibiotic-resistant strain to proliferate and dominate (IRA) (12). We similarly model a single reversion parameter (φ) to encompass a range of different biologically plausible phenomena that may cause reversion of antibiotic-resistant (IRA) to sensitive strains (ISA). This includes the potential for resistant strains to gain acquire of develop de novo compensatory mutations to reduce fitness costs (20).

To reduce the linearity associated with livestock antibiotic usage on both livestock recovery and antibiotic-resistance conversion, a scaling parameter was introduced (κ) to model the relative efficacy of antibiotic mediated recovery in livestock. Transmission-related fitness costs associated with antibiotic-resistance were included and assumed to reduce the rate of transmission for antibiotic-resistant bacteria as a scaling factor (α).

**Primary outcome measures**

Two primary outcome measures were considered in this study: 1) the daily incidence of human non-typhoidal salmonellosis per 100,000 population in the EU, defined as the sum of the daily incidence of antibiotic-sensitive and resistant infections at the long-term non-zero steady state. This was calculated directly from model output as the daily proportion of newly infected humans multiplied by the EU population size and then scaled by 100,000 (**cite**). 2) The fraction of antibiotic-resistant human non-typhoidal salmonellosis (I\*­RHProp) (defined as IRH / (ISH+IRH) at the long-term non-zero steady state.

The long-term non-zero steady state of the two previously defined quantities was calculated using the “rootSolve” package. Although we note that it is likely that the current “real-world” dynamics of AMR are in flux due to the influence of interventions, population dynamics etc., studying it at equilibrium is a useful indication of the long-term dynamics of the AMR and where the system is heading. This is especially the case for resistant *Salmonella* spp. infections, with a short duration of infectious human carriage (1/rH), facilitating a rapid approach to equilibrium. This approach is also justified with temporal surveillance data suggesting the proportion of antibiotic resistance in livestock populations has stabilised at roughly constant levels in recent years (Figure S7-8).

**Model parameterisation and case studies**

An approximate Bayesian computation sequential Monte-Carlo (ABC-SMC) approach was used for parameter estimation. Summary statistics and distance functions were used to estimate the posterior probability distribution of model parameters given the data, . Detailed methodology for the ABC-SMC approach can be found in Toni et al, (2009) (21).

We note that while the primary outcome measures are relevant for humans (incidence and I\*­RHProp), the model also simulates the relationship between livestock antibiotic usage and the fraction of antibiotic-resistant livestock infection. As a key part of our model is to assess dynamics following a withdrawal in livestock antibiotic usage, it is critical that the model is able to reproduce the relationship between livestock antibiotic usage and resistance. Therefore, we fit this livestock portion of the model to this relationship between usage and resistance using surveillance data. Resistance data was obtained from the European Food Safety Authority (EFSA) summary reports. The proportion of isolates resistant to the specific antibiotic class from carcasses of broiler poultry/fattening pigs was extracted from the respective EFSA datasets (22-27). Antibiotic sales data was obtained from European surveillance of veterinary consumption (ESVAC) reports (28-32). ESVAC antibiotic sales data is found averaged for all livestock species in each country in the original surveillance report. A scaling calculation was therefore required to convert the generic antibiotic sales to a value specific to the modelled livestock host with sales described as grams per population correction unit, g/PCU. Details of this can be found in the supplementary information. Note that due to a lack of accurate country-level antibiotic usage data, sales were assumed to be a proxy for usage. Mentions of “usage” are therefore in reference to the ESVAC sales data.

Four case studies were chosen to aid model parameterisation and to ground the model with EU epidemiological surveillance data. These case studies were: 1) ampicillin-resistant non-typhoidal salmonella in broiler poultry to humans from 2014-2018, 2) tetracycline-resistant non-typhoidal salmonella in broiler poultry to humans from 2014-2018, 3) ampicillin-resistant non-typhoidal salmonella in fattening pigs to humans from 2015-2018 and 4) tetracycline-resistant non-typhoidal salmonella in fattening pigs to humans from 2015-2018 (**Figure SX…**).

These four case studies were chosen due to the high level of usage (both historical and current) of tetracycline and ampicillin in broiler poultry and fattening pigs, and the availability of resistance data for these two livestock species (28-33). We use the relationship between sales/usage and resistance for these four case studies as the basis for the model fitting and parameterisation in this study, consistent with the observed statistically significant relationship between the two variables for three out of four included case studies, with one case study exhibiting a borderline significant relationship (Figure 2).

**Datasets and livestock parameterisation**

Yearly ESVAC data for livestock antibiotic sales and EFSA data on the proportion of *Salmonella* spp. isolates obtained from livestock species carcasses resistant to the tetracycline/ampicillin were used to create usage/sales and livestock resistance pairs for each country in each respective case study (22-32). These pairs spanned across multiple years for each country (Figure S7-8). Therefore, for any one country, there may be multiple usage/resistance pairs corresponding to different years in the dataset. These pairs were used to determine the observed relationship between livestock antibiotic sales/usage and the fraction of antibiotic-resistant livestock infection in European countries between 2014-2018 for each respective livestock species.

It is important to note that the stratification of each country into their respective yearly data for each data point introduces an assumption that the level of antibiotic usage will also be representative of resistance for a particular year. Due to the existence of lag between the effects of antibiotic stewardship interventions and alterations in either human or livestock resistance (34), it is important to ensure that there are relative levels of stability in the yearly usage and resistance for each country. We note that for the majority of included countries, this temporal stability for each country across included yearly data points was observed (Figure S7-10), therefore we can be confident that resistance will still correspond to usage in the explored time period.

**Distance Measures/ Summary Statistics**

A simulated dataset for each case study was generated by modelling the fraction of antibiotic resistant livestock infections for each country/year observation, for each of the observed levels of antibiotic sales included in the dataset. A sum of squared errors distance function was then used to calculate the distance between the simulated and observed fraction of antibiotic-resistant livestock infection for each country/year data point. In accordance with the EFSA methodology, countries with <10 isolates in the respective EFSA dataset for a particular year were omitted from the dataset (22-27).

Two additional summary statistics were also used: 1) minimise the difference between the modelled daily EU incidence of human salmonellosis at baseline antibiotic usage and the observed ECDC daily EU incidence of human salmonellosis currently observed (0.593 per 100,000), 2) minimise the difference between the model estimated proportion of resistant human salmonellosis at baseline antibiotic usage and the EFSA averaged European proportion of resistant human salmonellosis specific for each case study. The baseline antibiotic usage for each case study was considered the unweighted average tetracycline/ampicillin usage across each included antibiotic country/year data point. 1) Ampicillin-resistance in broiler poultry (0.314 at 0.0049 g/PCU), 2) tetracycline-resistance in broiler poultry (0.316 at 0.0069 g/PCU), 3) ampicillin-resistance in fattening pigs (0.345 at 0.0125 g/PCU) and 4) tetracycline-resistance in fattening pigs (0.340 at 0.01305 g/PCU).

**ABC-SMC model fitting**

An ABC-SMC approach was used estimate the marginal posterior probability distribution for six model parameters (θ) given the data (21, 35). Other model parameters were not fitted as estimates with high levels of certainty were available (rH, rA, μA and μH), or due to the relative nature of other transmission parameters with respect to βAA, βHA and ζ (βHH and βAH). βHH and βAH were instead held at values of 0.0001. These low values were chosen due to the negligible impact of these transmission routes on Salmonella spp. transmission (cite – 94% study salmonellosis in humans). Prior distributions for each fitted parameter can be found in the supplementary material (Table S3).

The ABC-SMC model fit was run for ten generations, with each generation running until the acceptance of 1000 particles. Acceptance thresholds (ε) were required for each of the three summary statistics for each generation, calculating the difference between the modelled summary statistic and the data. These thresholds can be found in thesupplementary material (Table S4). A multivariate normal distribution was chosen for the ABC-SMC perturbation kernel (21), with the randomly sampled mean and covariance matrix calculated from the previously accepted generation of accepted particles. An intersection metric was used to ensure that accepted particles satisfied tolerance values set for the distance measure for each calculated for each summary statistic per generation.

Mean point estimates from the approximated marginal posterior probability distributions of the 10th accepted generation were used as the final parameter sets for each respective case study. Point estimates and calculated 95% HDIs from the marginal posterior distribution for each model parameter can be found in the supplementary material (Table S2).

**Sensitivity Analysis**

A Fourier amplitude sensitivity test (FAST) approach was used to conduct a sensitivity analysis of the model system to the model parameters with regards to two outcome measures (36): 1) the daily incidence of human foodborne infection and 2) proportion of resistant human infection. The parameter space range chosen for the sensitivity analysis was limited to an order of magnitude above and below the parameterised values. For fitted model parameters, this range was taken as an order of magnitude above and below the fitted mean point estimate for each parameter across each considered case study.

The FAST approach was also used to identify the sensitivity of the model system to two intervention related outcome measures: 1) Relative changes in daily incidence when livestock antibiotics were curtailed (*τ* = 0 g/PCU), compared to daily incidence at mean baseline livestock antibiotic usage across the four case studies (*τ* = 0.00934 g/PCU) and 2) Relative changes in daily incidence under antibiotic curtailment (0 g/PCU) relative to the observed daily incidence with current levels of antibiotic usage (0.593 per 100,000). An in-depth description of this sensitivity analysis can be found in the supplementary material.

**RESULTS**

Observed country-level antibiotic usage and livestock tetracycline/ampicillin-resistance surveillance data was plotted for all four case studies, with the model output overlaid (Figure 3). It is important to note that the ζ parameter (ζ > 0) is necessary to prevent I\*RHProp decreasing to 0 upon livestock antibiotic curtailment (τ = 0 g/PCU). Inclusion of the ζ parameter was shown to provide a better fit to the model compared to a null model with ζ = 0 (Figure S1). Approximated marginal posterior probability distributions for the fitted model parameters from the ABC-SMC approach and the respective diagnostics can be found in the supplementary material (Figure S2-6; Figure S11).

Chart, line chart

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**Figure 3. Observed and estimated relationship between livestock antibiotic usage data and antimicrobial-resistant salmonellosis in humans. A) Ampicillin-resistance in broiler poultry, B) tetracycline-resistance in broiler poultry, C) ampicillin-resistance in fattening pigs and D) tetracycline-resistance in fattening pigs.** Solid red lines and ribbons represent model fit resulting from the approximated posterior distribution using ABC-SMC and the corresponding 95%. Country-specific 95% confidence intervals for the observed data (dots) were calculated for each case study using a 1-sample proportion test with continuity correction.

The FAST analysis identified animal-to-human transmission (βHA) as the most influential parameter for the daily incidence of salmonellosis, with other parameters having a substantially reduced impact. Furthermore, I\*RHProp was most sensitive to transmission-related fitness costs (α), livestock antibiotic usage (τ), the antibiotic-resistant to antibiotic-sensitive reversion rate (φ) and efficacy of antibiotic-mediated recovery in livestock (κ) (Figure S12).

Curtailment of livestock antibiotic usage (τ → 0 g/PCU) resulted in small increases in the daily incidence relative to at baseline antibiotic usage levels across all case studies (Figure 4). The fitted daily incidence and I\*RHProp for each case study can be found in the supplementary material (**Table S5**). Curtailment in the fattening pigs case studies resulted in the largest increase in the daily incidence with a 1.11-fold (0.668 per 100,000) increase relative to baseline levels, and a 1.20-fold (0.72 per 100,000) for the ampicillin and tetracycline case studies respectively. Increases in the daily incidence for the broiler poultry case studies were almost non-existent, with no fold change below 3 significant figures (0.598 per 100,000) being identified for the ampicillin case study and a 1.02-fold (0.617 per 100,000) increase in the daily incidence for the tetracycline usage case study. Increases in livestock antibiotic usage above baseline usage levels in the four case studies resulted in the opposite phenomenon being observed, with small decreases in overall human foodborne disease and increases in the proportion of resistant infection.

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**Figure 4. Impact of alterations in livestock antibiotic usage (τ) on the daily incidence of salmonellosis and the proportion of resistant human infection (I\*RHProp).** A) Ampicillin-resistant human salmonellosis from broiler poultry. B) Tetracycline-resistant human salmonellosis from broiler poultry. C) Ampicillin-resistant human salmonellosis from fattening pigs. D) Tetracycline-resistant human salmonellosis from fattening pigs. Grey bar denotes the case study specific baseline livestock antibiotic usage. Numbers above the bars denote I\*RHProp.

We next identified the parameters which had the greatest influence on relative increases in the daily incidence when livestock antibiotics were curtailed, compared to daily incidence at mean baseline livestock antibiotic usage across the four case studies (τ = 0.00934 g/PCU) (Figure 5A). Daily incidence at mean baseline livestock antibiotic usage was allowed to vary and was not fixed across modelled parameter combinations. This corresponds to relative differences in the daily incidence at τ = 0.00934 g/PCU that would be observed with case studies other than the specific drug/livestock/pathogen combinations used in this study. Influential model parameters can therefore be interpreted as parameters that lead to case studies with large relative increases in daily incidence compared to baseline antibiotic usage.

Transmission related fitness costs associated with antibiotic-resistance (α), the per capita rate of background transmission to livestock populations (ζ) and efficacy of antibiotic-mediated livestock recovery (κ) were found to be the most influential parameters in determining the relative increase in daily incidence from baseline livestock antibiotic usage when antibiotics where curtailed. (Figure 5A). Lower κ and α, and higher ζ parameter values resulted in lower relative increases in daily incidence when livestock antibiotics were curtailed (τ = 0 g/PCU) (Figure S13).

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**Figure 5. Fourier amplitude senstivity test (FAST) to identify the most influential model parameter for. Higher bars indicate greater sensitivity: A) Relative change in daily incidence under curtailment (0 g/PCU) compared to the averaged baseline antibiotic usage level (0.00934 g/PCU). B) Mitigating changes in daily incidence under curtailment compared to the level of foodborne disease experienced under current levels of livestock antibiotic usage (0.593 per 100,000 population).**

A sensitivity analysis was next performed to identify parameters that could best mitigate increases in daily incidence under antibiotic curtailment (0 g/PCU) for the particular ampicillin/tetracycline in broiler poultry/fattening pigs case studies used in this study (Figure 5B). This was identified by fixing the daily incidence at baseline antibiotic usage at 0.593 per 100,000 population, as this is the baseline daily incidence of salmonellosis relevant to our case studies. Influential model parameters are therefore those that cause the greatest relative change in daily incidence from the *fixed* baseline value of 0.593 per 100,000. By extension, interventions targeting these identified parameters will be more capable of reducing levels of daily incidence back down to the baseline levels currently observed for the modelled case studies.

We identified the per capita rate of animal-to-human transmission (βHA) as the key parameter to mitigate increases in daily incidence. Intuitively, decreasing βHA leads to a non-linear decrease in the daily incidence observed (Figure S14). This therefore represents the best parameter to target to mitigate potential increases in daily incidence due to livestock antibiotic curtailment.

Due to the importance of targeting the animal-to-human transmission route to control increases in daily incidence, we next attempted to quantify the alterations in βHA required to mitigate increases in daily incidence under antibiotic curtailment (0 g/PCU), below a threshold of 0.593 per 100,000 population. This threshold represents a removal of livestock antibiotic selection pressure (0 g/pCU) and a prevention of increases in daily incidence above what is currently observed for human salmonellosis (0.593 per 100,000). Alterations to βAA and ζ parameters were also chosen as potential intervention targets, due to their relevance in agricultural biosecurity strategies to promote livestock health and mitigate livestock disease/AMR (37, 38). Limited transmission parameter reductions were explored for βHA (0% - 25%), but with alterations to βAA and ζ parameters allowed to vary from 0-100% (Figure 6)**.**

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**Figure 6. Reductions to key model parameters, animal-to-human transmission (βHA), animal-to-animal transmission (βAA) and the background transmission rate to animal populations (ζ) to mitigate increases in the daily incidence of salmonellosis under livestock antibiotic curtailment (τ = 0 g/PCU). A) Ampicillin-resistance in broiler poultry, B) tetracycline-resistance in broiler poultry, C) ampicillin-resistance in fattening pigs and D) tetracycline-resistance in fattening pigs.** Axes represent interventions that reduce the labelled transmission rate(s) to % of their original values. Note that the top right corner of each contour plot represents a scenario with curtailment of antibiotics and no further alterations to any model parameter. The red line represents the threshold at which daily incidence is below current levels (0.593 per 100,000). Note the asymmetrical % reduction for both x and y-axis.

Only reductions to βHA were capable of mitigating increases to daily incidence below baseline levels across all considered case studies in the explored parameter space, with a reduction of 1%, 4%, 12% and 18% required for each case study (Figure 6). Isolated or even combined reductions to βAA or ζ were only capable of reducing daily incidence below baseline levels with strong reductions below ~50%, or if the initial increase in daily incidence is negligible upon antibiotic curtailment, as seen with the ampicillin usage in broiler poultry case study (Figure 6A).

**DISCUSSION**

A mathematical modelling approach was used to identify increases in the daily incidence of non-typhoidal human salmonellosis as well as decreases in the proportion of resistant human salmonellosis following livestock antibiotic curtailment. This was explored across four relevant antibiotic/livestock specific case studies. We identified that scenarios with high transmission-related fitness costs of resistance (α), high efficacies of antibiotic-mediated livestock recovery (κ) and low background transmission rates of *Salmonella* spp. in livestock (ζ) resulted in large increases in the daily incidence of human salmonellosis upon antibiotic curtailment. However, for the particular case study used in this study, interventions targeting the farm-to-fork or animal-to-human transmission route (βHA) was found to effectively mitigate increases in the daily incidence of human salmonellosis following livestock antibiotic-curtailment.

**First Section – why are there differences between species and what do the negligible increases mean**

Curtailment of livestock antibiotic usage was found to have varying effects across the modelled livestock host species, with almost negligible changes in the daily incidence of human salmonellosis observed in the broiler poultry case studies **(Figure X**). Negligible-to-minor changes in the overall prevalence of infection following antibiotic stewardship can be found corroborated in related epidemiological surveillance and modelling analysis (7) (DAVIES ET AL). However, these negligible changes have profound implications when placed in the context of the *Salmonella* spp. case study. *Salmonella* spp. is a pathogen with a well-understood, direct transmission pathway to humans from livestock and a major contributor to foodborne infection in humans. Therefore, if the loss of antibiotic pressure in livestock has negligible effects on salmonellosis in humans, then this represents a large proportion of common foodborne infections that will remain unchanged after future livestock antibiotic stewardship interventions.

It is important to recognise that *Salmonella* spp. do not represent the complete range of foodborne pathogens, with *Campylobacter* spp. another major source of livestock-origin human illness. However, we note that due to similarities in the … period of livestock carriage, … etc, there are unlikely to be major differences in the relative increase in campylobacteriosis compared to salmonellosis when livestock antibiotics are curtailed. However, it is important to note that due to the higher baseline incidence of campylobacteriosis compared to salmonellosis, comparable relative changes in incidence in *Campylobacter* spp. will result in greater absolute increases in daily incidence for campylobacteriosis. This may have implications for the public health burden in humans after antibiotic stewardship interventions. Work should be performed to adapt the study model to other case studies such as for *Campylobacter* spp. to fully assess the impact from other important human pathogens.

As suggested by Figure 5A, differences in the relative increase in daily incidence of salmonellosis between modelled case studies and livestock hosts can be attributed to ζ, κ and α parameters. The implications of these parameters on the impact of curtailment are twofold: Firstly, treatments which have a greater therapeutic impact on carriage, , will intuitively result in a larger increases in prevalence when withdrawn (high κ). Secondly, as antibiotic-sensitive strains are the only *Salmonella* spp. strains impacted by treatment, if the proportion of antibiotic-sensitive relative to antibiotic-resistant strains is higher, then we will observe a greater increase in overall disease when treatment is withdrawn. This tendency for antibiotic-sensitive strains to dominate occurs when there are greater transmission-related fitness costs associated with antibiotic-resistance (high α) and when constant background levels of transmission do not “interfere” with the natural relationship between strains towards a ratio that is more favourable for antibiotic-resistance (high ζ). As an illustrative example, increases in daily incidence upon curtailment are prevented when livestock antibiotic usage does not enhance the rate of clearance (κ = 0) and fitness costs are removed (α = 0) (Figure S15).

However, the main differences between modelled livestock hosts in this study can likely be attributed to large differences in transmission-related fitness costs associated with antibiotic resistance, with the mean fitted parameter value for α, 0.084 and 0.416 for the broiler poultry and fattening pig case studies respectively. This may reflect differences in the distribution of *Salmonella* spp. serotypes colonising poultry and pig hosts, with different serotypes possessing varying transmission-related fitness costs. Further experimental analyses must be performed to assess if these differences in α are a real phenomenon observed between livestock species or simply an artefact of the data/model fitting procedure performed in this study.

**Second section – we can easily mitigate increases in foodborne infections**

The greatest relative increase in daily incidence upon livestock antibiotic curtailment was observed in the tetracycline-resistance in fattening pigs case study, with this representing the “worst-case” scenario out of the four explored case studies. Interestingly, even in this worst-case scenario, these increases in incidence could be effectively mitigated by interventions targeting the animal-to-human transmission route (βHA). Although the exact contribution of these interventions have yet to be quantified, this may provide promising indications that increases in salmonellosis may be entirely controlled by ongoing efforts to ensure farm-level and post-harvest biosecurity. These efforts include increased awareness from workers in the farm-to-fork pathway to maintain good biosecurity, reducing microbial contamination on carcasses, as well as comprehensive public information campaigns to promote safe handling of food products (37, 41).

The ability to completely mitigate the negative human consequences of livestock antibiotic curtailment (Figure 6), may also suggest that in certain cases, there is the potential for improved biosecurity practices to replace livestock antibiotics as an alternative to prevent diseases of a livestock origin (18, 39, 40). However, further research is required to quantify the efficacy of these interventions on the specified transmission routes. A crucial initial step would be to improve understanding on the effect of farm-to-fork food processing on microbial loads and contamination on food products (18). Cost-efficiency assessments could also be performed to assess the costs required to achieve x% reductions in transmission – to see if betaHA interventions are feasible.

**Third Paragraph - Null Neutrality and other model considerations**

It is important to note that the aim of this study was not to specifically explore the evolutionary dynamics underlying coexistence. Instead we implicitly acknowledge that this phenomenon exists, simplifying the mechanisms underlying coexistence and instead concentrating on the impact of host heterogeneity and zoonotic transmission on livestock AMR interventions. Additionally the primary result of this study, increases in the prevalence of disease following antibiotic curtailment, is robust across models that explicitly incorporate population and within-host level mechanisms that drive coexistence (cite - Davies). However, we note that the existence of the ζ parameter prevents the model from being considered a neutral-null model due to the presence of “immigration infections” not tractable to infections at t = 0 (cite), but with the exclusion of ζ resulting in a poorer model fit compared to where the parameter is present (Figure S1). Further exploration into the dynamics of livestock antibiotic curtailment may benefit from explicitly modelling this general background transmission rate as an environmental reservoir of infection. This would have the additional benefit of removing “immigration infections” from the model system.

**Fourth paragraph – Issues with quality of data – NEEDS WORK can collapse I thinkl**

Large variability exists in both literature and the explored case studies regarding the relationship between livestock/human antibiotic usage and resistance, with three out of the four explored case studies exhibiting a statistically significant relationship between antibiotic usage and resistance, and with similar variance also observed in epidemiological literature (**cite**). Additionally, due to the historical lack of high quality AMR surveillance and presence of confounding factors, it is also difficult to disentangle whether observed significant relationships are due to an **actual relationship** between usage and resistance or just do due to “**noise**” (type 2 error) in the data. This is important to recognise, as the extent of increases in the daily incidence of salmonellosis upon livestock antibiotic curtailment is determined through fitting modelled livestock dynamics to a presumed “observed” relationship between usage and resistance.

However, through exploring a range of different case studies, each possessing different parameter combinations and varying increases in daily incidence following curtailment, we can explore a large gamut of potential future scenarios and make our results robust to data uncertainty. Specifically, we note that across the four explored case studies, increases in daily incidence were identified as manageable, even in worst-case scenarios (Figure 6D). It is also interesting to note the ability of alterations to the βHA parameter in controlling increases in daily incidence many orders of magnitude above what we observed in the modelled cases studies. Despite the limitations of this data-driven modelling approach, we note that this is a significant improvement compared to an arbitrary parameterisation of the model system. Future modelling would benefit from better/more representative data than what we have available currently – key of which is better usage and country level resistance data at different levels of the farm to fork pathway to better understand the relationship between usage and resistance.

**Conclusion Paragraph**

The results from this study corroborates epidemiological surveillance and modelling studies with decreases in antibiotic resistance following livestock antibiotic curtailment (**cite**). However, we identify a potential increase in human foodborne disease following curtailment that may be completely mitigated through effective agricultural biosecurity interventions. The efficacy of these interventions suggests that a “one-health” attitude and a focus on improving farm-to-fork biosecurity and livestock welfare to prevent human disease is critical when considering potential control strategies to tackle the AMR crisis.

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