**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, 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 was 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 or efficient.

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 interventions can 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 **(Woolhouse, Ward et al. 2015)**. 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 (Commission 2005, Food and Administration 2013).

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 (Aarestrup, Seyfarth et al. 2001, Commission 2005, Tang, Caffrey et al. 2017). 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 has also been identified in AMR literature (Casewell, Friis et al. 2003). 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 ((Aarestrup 2015, Schlundt and Aarestrup 2017)). However, the unforeseen nature of these potential consequences highlights the risks of introducing substantial interventions into highly complex and poorly understood systems as part of a “precautionary principle” based approach (Phillips, Casewell et al. 2004). 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 ((EUR‐Lex 2019)). However, the precise relationship between livestock antibiotic usage and antibiotic-resistant/sensitive human foodborne disease remains poorly understood (Tang, Caffrey et al. 2017).

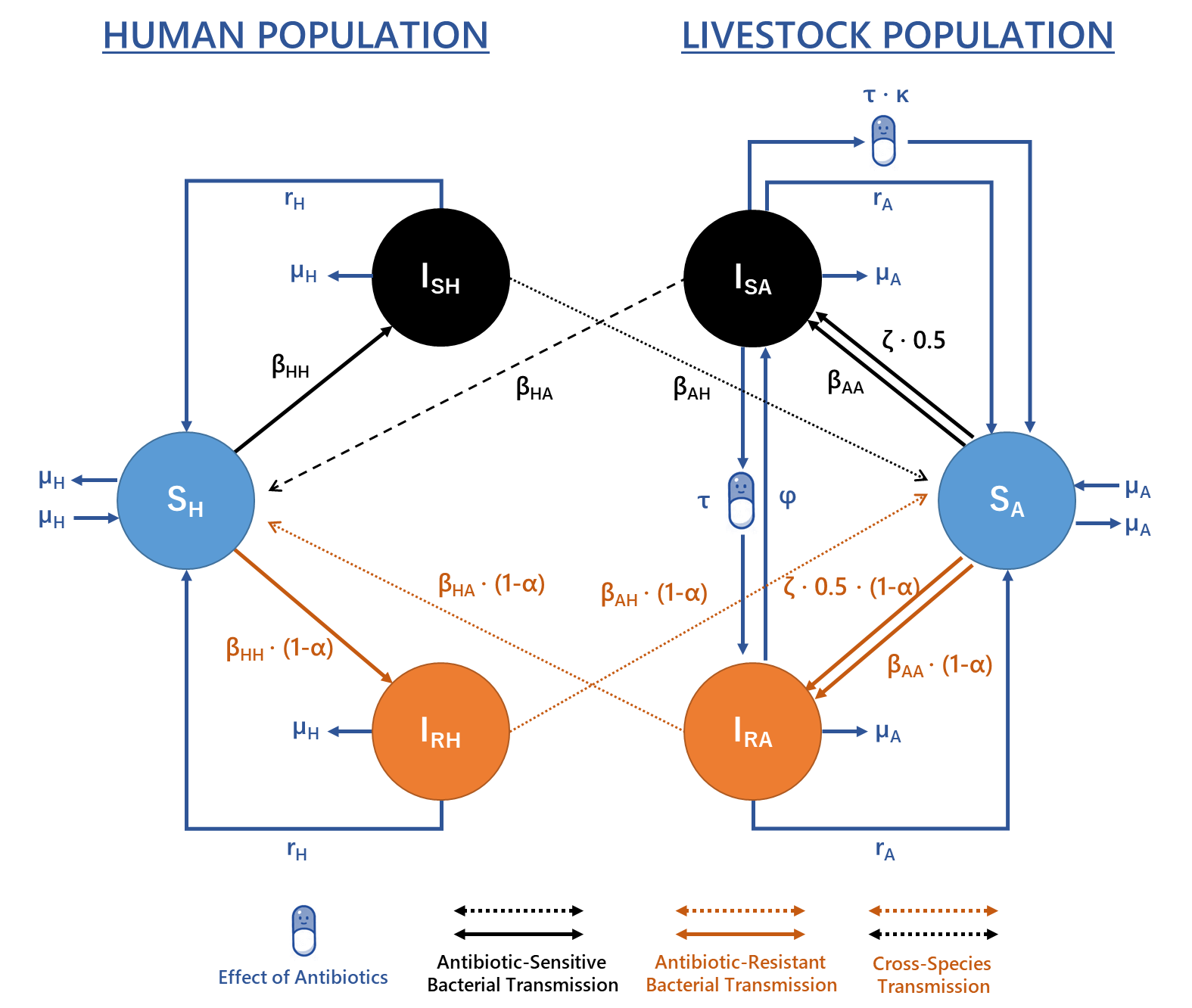
One approach to better understand the complexities of livestock antibiotic usage includes the use of mathematical models, which are simplified representations of complex real-world systems. These models can help by testing uncertainties, especially regarding the potential effects of livestock antibiotic 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 (Niewiadomska, Jayabalasingham et al. 2019). Existing frameworks include predictive risk assessment models and a small number of generalised deterministic models ((Anderson, Woo et al. 2001, Hurd, Doores et al. 2004, Cox 2005, Alban, Nielsen et al. 2008, Spicknall, Foxman et al. 2013, Caffrey, Invik et al. 2019)). Nevertheless, a significant number of 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.

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 will 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 will explore the effects and feasibility of introducing interventions to mitigate the potential negative consequences of livestock antibiotic curtailment.

**METHODOLOGY**

1. **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**) ((Kermack and McKendrick 1927)). 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 other livestock or humans. This generalised 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. 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 simplified 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) ((Spicknall, Foxman et al. 2013)). 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 ( **(Maisnier‐Patin, Berg et al. 2002)**).

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 were assumed to reduce the rate of transmission for antibiotic-resistant bacteria as a scaling factor (α).

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 incidence of antibiotic-sensitive and resistant infections at the long-term non-zero steady state. This required a scaling transformation to convert the model output daily prevalence/proportion infected to the daily incidence infected using EU population data (Supplementary Material). 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. This quantity was directly calculated from the ODE solver output.

The long-term non-zero steady state of the two previously defined quantities was calculated using the “rootSolve” package, which dynamically solves the ODEs numerically until the calculated derivatives are determined to be at steady state. Although we note that it is likely that the current dynamics of AMR are in flux due to the influence of ongoing interventions, studying it at equilbrium is a useful indication of the long-term dynamics of the AMR and where the system is heading. This is supported by temporal surveillance data which suggests that intervention-induced changes in the proportion of antibiotic resistance in populations tend to stabilise at a relatively constant levels in the absence of any further interventions (**cite**). 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 equilbrium.

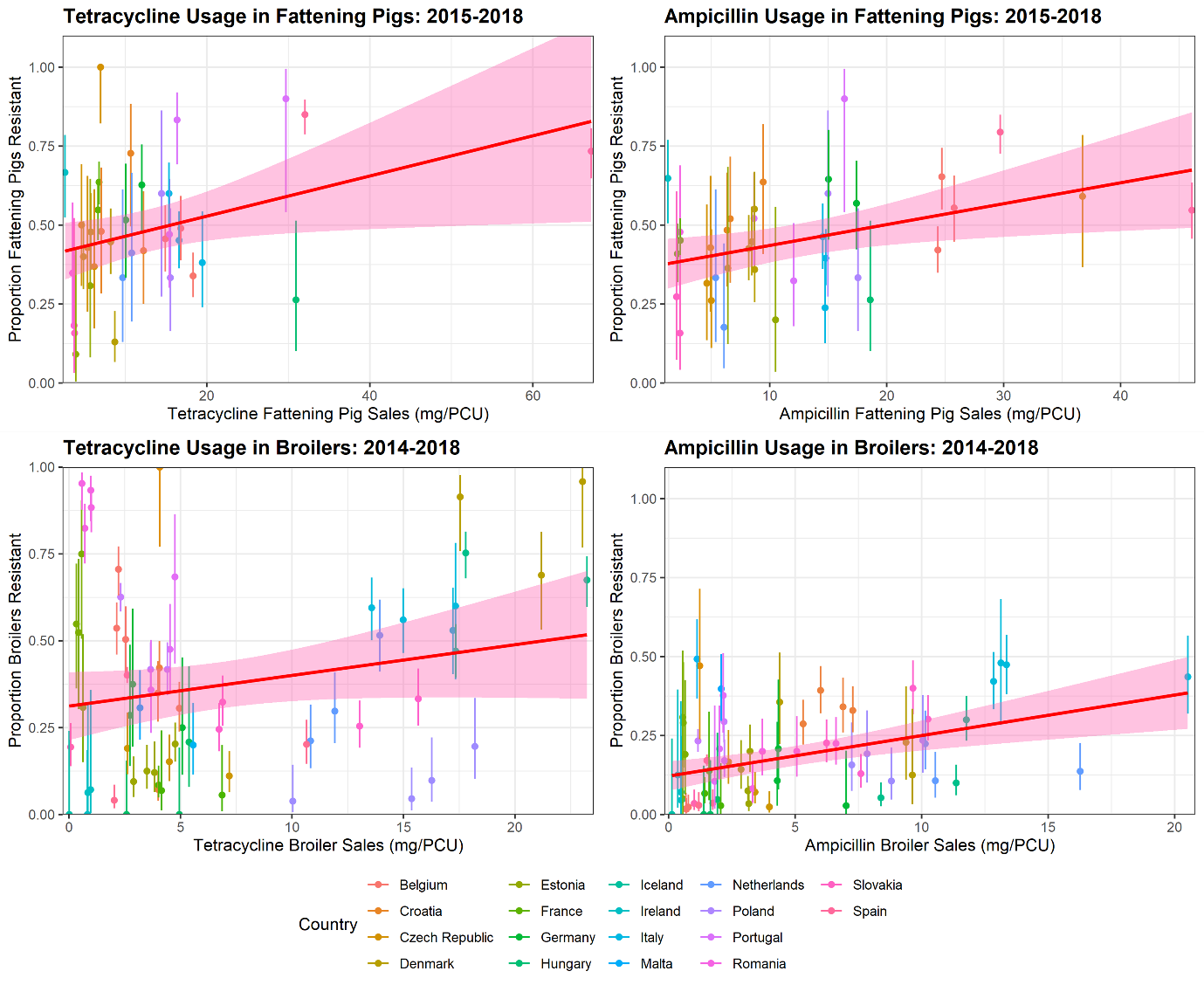
1. **Case Study and Model Parameterisation**

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 given the data, . Detailed methodology and pseudo-code of the ABC-SMC approach can be found in **Toni et al, (2009) (Toni, Welch et al. 2009)**.

**Livestock Distance Function**

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. We can fit this livestock portion of the model to surveillance data, to ensure that any modelled livestock interventions occur in a population with realistic dynamics. Four case studies were chosen to aid model parameterisation and to ground the model with EU epidemiological surveillance data.

These case studies were: 1) tetracycline-resistant non-typhoidal salmonella in fattening pigs to humans from 2015-2018, 2) ampicillin-resistant non-typhoidal salmonella in fattening pigs to humans from 2015-2018, 3) tetracycline-resistant non-typhoidal salmonella in broiler poultry to humans from 2014-2018 and 4) ampicillin-resistant non-typhoidal salmonella in broiler poultry to humans from 2014-2018 (**CITE**) (**Figure 2**).



**Figure 2 – Relationship between scaled antibiotic sales and the proportion of isolates resistant across different EU country/year pairs from 2014-2018. 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 line and ribbons represent the best fitting linear regression between sales and resistance with 95% CIs for model resistance predictions. We note that only the tetracycline usage in broilers case study was non-significant.

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. We justify exploring the relationship between sales/usage and resistance for these four case studies as the basis for the model fitting and parameterisation in this study due to 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).

Yearly ESVAC data for livestock antibiotic sales and EFSA data on the proportion of *Salmonella* spp. isolates obtained from livestock species resistant to the tetracycline/ampicillin were used to create usage/sales and livestock resistance pairs for each country in each respective case-study (**CITE**). These pairs spanned across multiple years for each country (**Figure S2-6**). 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 (cite), 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 S2-6**).

A simulated dataset for each case study was generated by modelling the simulated fraction of antibiotic resistant livestock infections for each country/year observation, given the observed level of antibiotic sales for each country/year included in the dataset. A sum of squared errors distance function was then used to minimise the distance between the simulated () and observed () fraction of antibiotic-resistant livestock infection for each country/year data point. The number of country/year data points in each case study is denoted by .

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. 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 an accurate proxy for usage. Mentions of “usage” are therefore in reference to the ESVAC sales data. In accordance with the EFSA guidelines, countries with <10 isolates in the respective EFSA dataset for a particular year were omitted from the model fit to preserve the integrity of the dataset when fitting.

**Human summary statistics**

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. Baseline antibiotic usage for each case study was considered the unweighted average tetracycline/ampicillin sales across each included antibiotic country/year data point. 1) tetracycline-resistance in fattening pigs (**0.00491 g/PCU**), 2) ampicillin-resistance in fattening pigs (**0.00686 g/PCU**), 3) tetracycline-resistance in broiler poultry (**0.0125 g/PCU**) and 4) ampicillin-resistance in broiler poultry (**0.0131 g/PCU**).

**Fitted Parameters and ABC-SMC details**

The ABC-SMC approach was used estimate the marginal posterior probability distribution for six model parameters (θ) given the data. 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). These latter parameters were instead held at static values. 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) can be found in thesupplementary material (Table S4). A multivariate normal distribution was chosen for the ABC-SMC perturbation kernel (**(Toni, Welch et al. 2009)**), with the randomly sampled mean and covariance matrix calculated from the previous generation of accepted particles.

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).

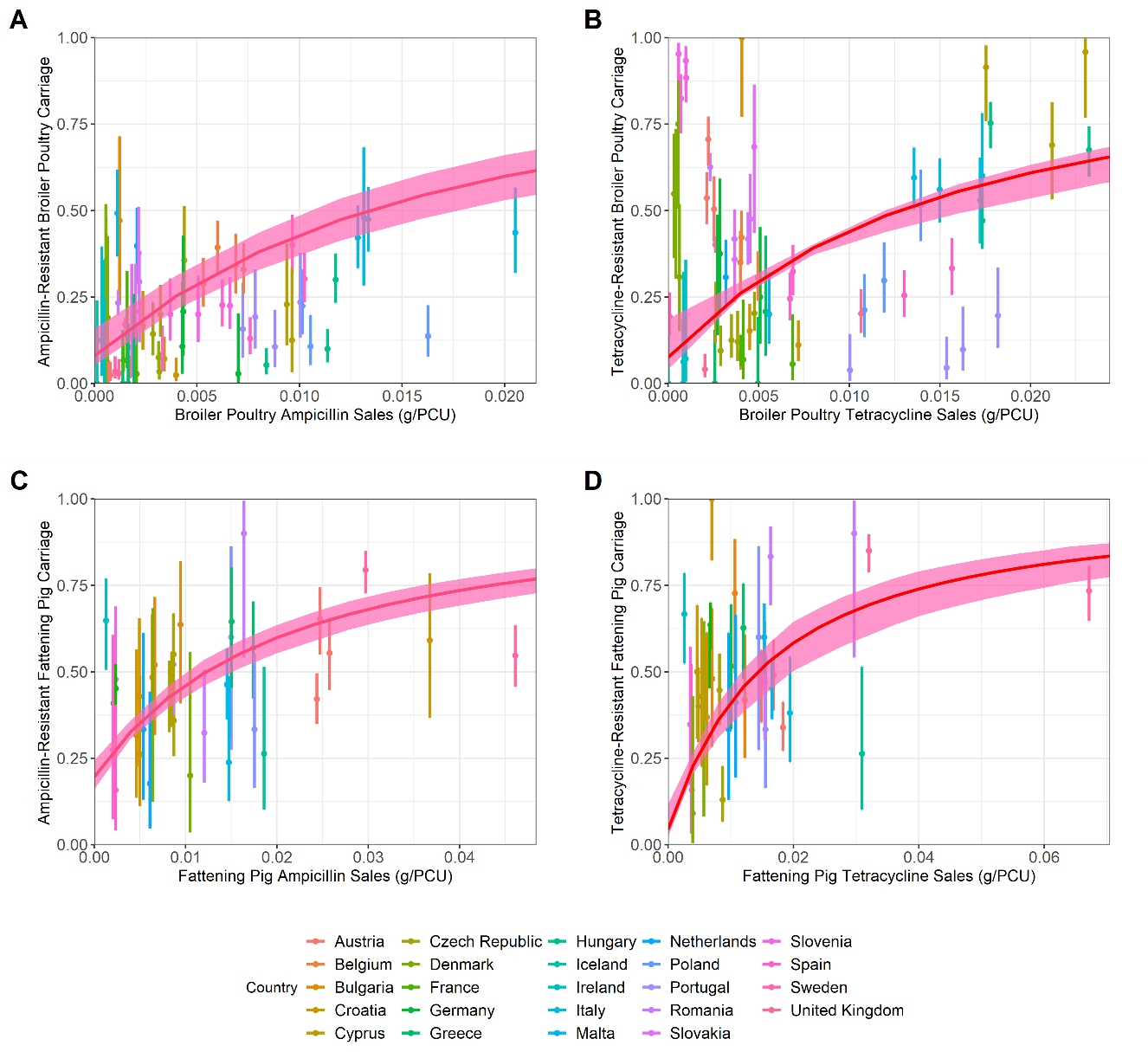
1. **Sensitivity Analysis**

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 (**(Saltelli and Bolado 1998)**): 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 mean of the fitted 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/population correction unit (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 what is currently observed 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**

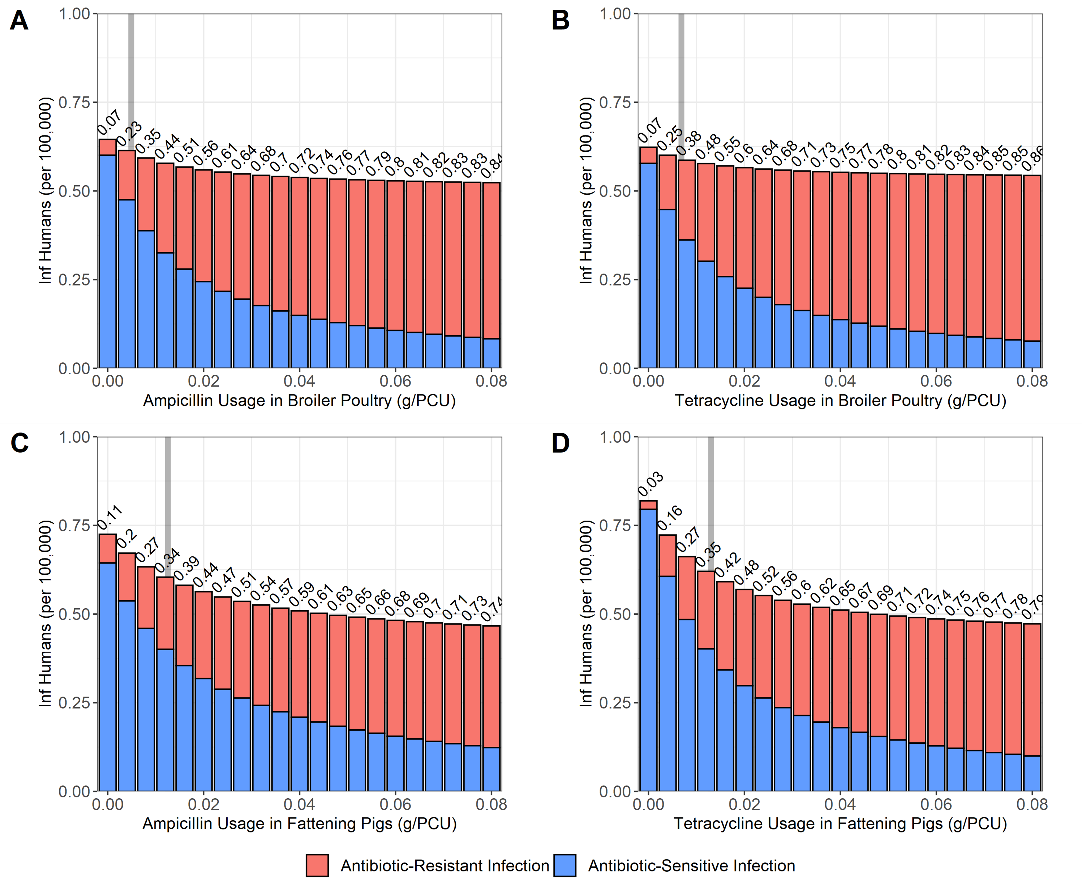
The relationship between observed country-level antibiotic usage data and livestock tetracycline/ampicillin-resistance surveillance data was plotted for all four case studies, with the model output overlaid, parameterised using ESVAC/EFSA data (Figure 3). It is important to note that the existence of the ζ parameter (ζ > 0) is necessary to prevent I\*RHProp decreasing to 0 upon livestock antibiotic curtailment. Inclusion of the ζ parameter was shown to provide a better fit to the model compared to a null model with ζ = 0(supplementary material; Figure S1). Approximated marginal posterior probability distributions for the fitted model parameters from the ABC-SMC approach can be found in the supplementary material (Figure S6).



**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% HDIs using the parameter point estimates from marginal posterior probability distribution. 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.

A Fourier amplitude sensitivity testing (FAST) approach was used to explore the sensitivity of the daily incidence of salmonellosis and I\*RHProp outcome measures to the model parameters. The most influential parameters for the daily incidence of salmonellosis were identified as the rate of animal-to-human transmission (βHA), with other parameters having a substantially reduced impact, and with I\*RHProp being most sensitive to transmission-related fitness costs (α), livestock antibiotic usage (τ), the efficacy of antibiotic-mediated recovery in livestock (κ) and antibiotic-resistant to antibiotic-sensitive reversion rate (φ) (Figure S7).

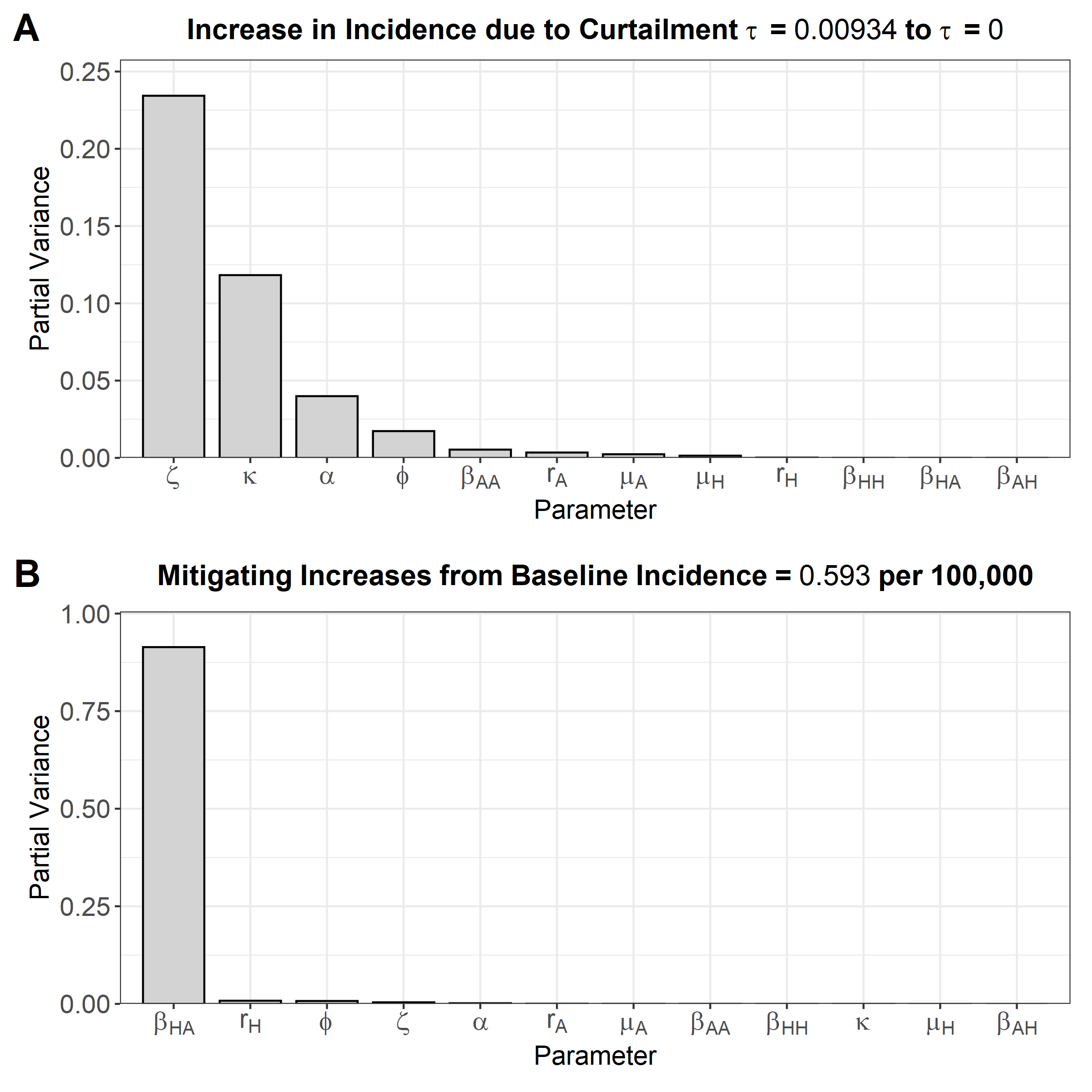
Using the fitted parameter values, the overall EU averaged daily incidence of human salmonellosis and the daily proportion of antibiotic-resistant human salmonellosis (I\*RHProp) was modelled at: 0.593 per 100,000 population and 0.35 for the ampicillin-resistant human salmonellosis from the broiler poultry case study at baseline ampicillin usage (τ = 0.0123 g/PCU). 0.593 per 100,000 population and 0.31 for the tetracycline-resistant human salmonellosis from the broiler poultry case study at baseline tetracycline usage (τ = 0.0116 g/PCU). 0.593 per 100,000 population and 0.31 for the ampicillin-resistant human salmonellosis from the fattening pigs case study at baseline ampicillin usage (τ = 0.0116 g/PCU). 0.593 per 100,000 population and 0.30 for the tetracycline-resistant human salmonellosis from the fattening pigs case study at baseline tetracycline usage (τ = 0.0067 g/PCU) (Figure 4).



**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.

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). Curtailment in the fattening pigs case studies resulted in the largest increase in the daily incidence with a X-fold (X per 100,000) increase relative to baseline levels, and an X-fold (X per 100,000) for the ampicillin and tetracycline case-studies respectively. Increases in the daily incidence for the broiler poultry case studies were relatively milder with an X-fold (X per 100,000) and an X-fold (X per 100,000) increase in the daily incidence for the ampicillin-usage tetracycline usage case studies respectively. 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.

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). Therefore, parameters that are identified as influential, are those that result in scenarios where curtailing livestock antibiotic usage has a greater relative increase in daily incidence. Daily incidence at mean baseline livestock antibiotic usage was allowed to vary and was not fixed across modelled parameter combination. 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 parameter values, and higher ζ parameter values resulted in lower relative increases in daily incidence when livestock antibiotics were curtailed (τ = 0 g/PCU) (Figure S8).

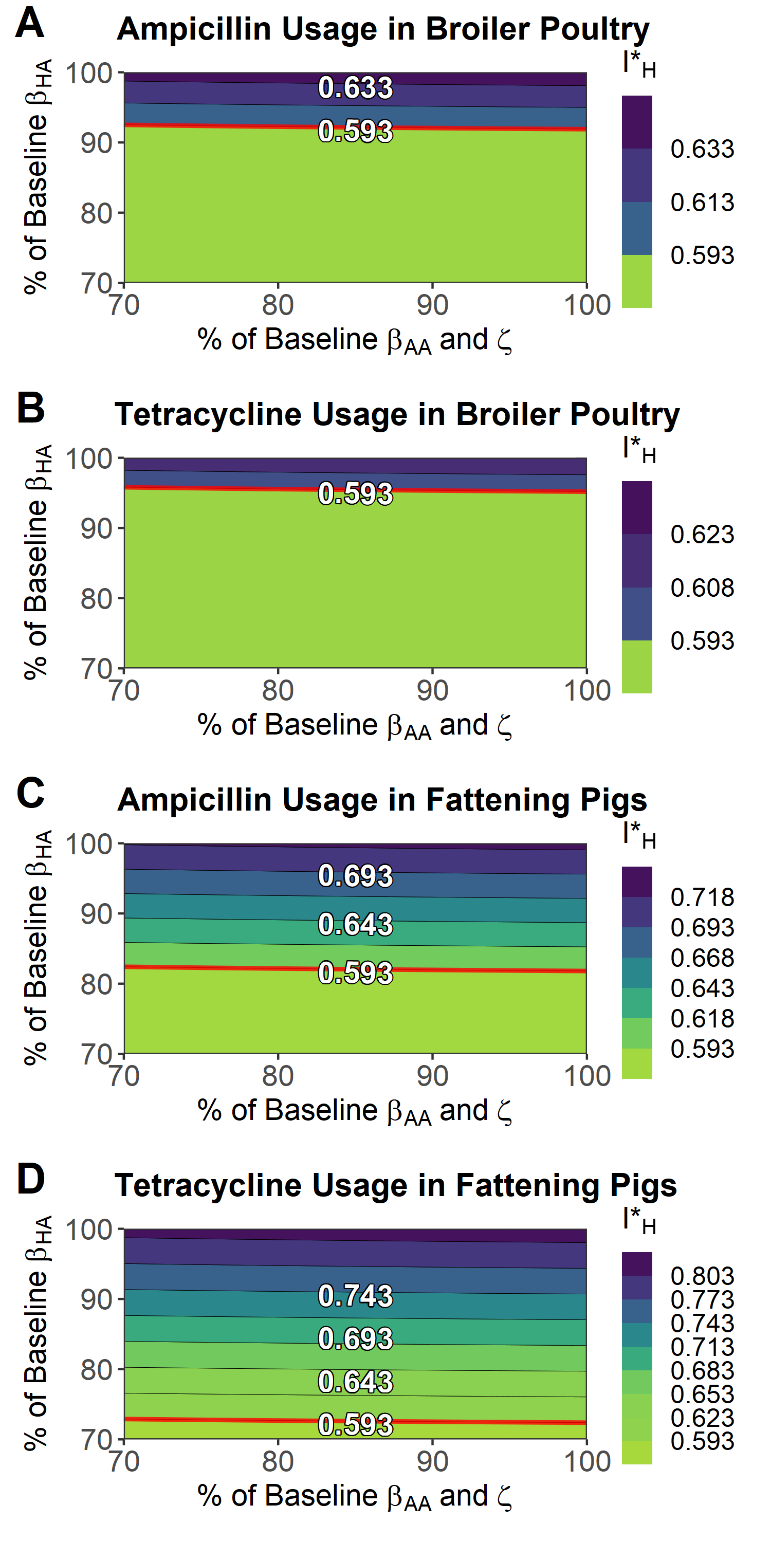


**Figure 5 – Fourier amplitude senstivity test (FAST) to identify the most influential model parameter for. Higher bars indicate greater sensitivity: A) Relative change in daily incidence under curtailment (0 g/PCU) compared to the averaged baseline antibiotic usage level (0.00934 g/PCU). B) Mitigating 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) (Figure 5B). This was identified by curtailing livestock antibiotic usage and identifying model parameters that cause the greatest relative change in daily incidence from the *fixed* baseline value of 0.593 per 100,000 (the level of salmonellosis currently observed). By extension, interventions targeting these identified parameters will be more capable of reducing levels of daily incidence back down to baseline levels.

We identified the per capita rate of animal-to-animal transmission (βHA) as the key parameter to mitigate increases in daily incidence. Intuitively, decreasing βHA resulted in lower relative changes in daily incidence under antibiotic curtailment compared to 0.593 per 100,000. This therefore represents the best parameter to target to mitigate potential increases in daily incidence due to livestock antibiotic curtailment (Figure S9).

Alterations to βHA, βAA and ζ parameters were explored to identify potential interventions 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). Both βAA and ζ parameters were also explored as potential intervention targets, due to their relevance in agricultural biosecurity strategies to promote livestock health and mitigate livestock disease/AMR (**CITE**). A limited range of transmission parameter reductions were explored for each intervention scenarios.(0% - 30%) (Figure 6)**.**



**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).

Only reductions to βHA were capable of mitigating increases to daily incidence below baseline levels across all considered case studies across the explored parameter space, with a reduction of X%, X % and X % required for each case study (Figure 6). Isolated or even combined reductions to βAA or ζ had a negligible effect on reducing daily incidence below baseline levels across any of the considered case studies. This corroborates the preceding sensitivity analysis suggesting that controlling animal-to-human transmission is vital to mitigate increases in daily incidence upon livestock antibiotic curtailment.

**DISCUSSION**

A deterministic compartmental model 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 case studies. Only interventions to target animal-to-human transmission routes were found to mitigate the potential increases in human salmonellosis following livestock antibiotic curtailment.

It is possible that ongoing efforts to ensure farm-level and post-harvest biosecurity have already had tangible impacts on reducing animal-to-human transmission (βHA). These efforts include increased awareness from workers in the farm-to-fork pathway to maintain good biosecurity, reduce microbial contamination on carcasses, as well as comprehensive public information campaigns to promote safe handling of food products (**CITE**). However, this should not be interpreted as a suggestion that interventions to ensure livestock health should be deprioritised to favour those targeting farm-to-fork transmission routes. As evidenced by the importance of the parameter describing background levels of infection in livestock (ζ), reducing ζ by ensuring clean livestock environs and good livestock health is important to prevent large increases in daily incidence occurring when livestock antibiotics are curtailed. Although the exact contribution of these interventions on transmission have yet to be quantified, current efforts to increase livestock wellbeing, agricultural biosecurity and farm-to-fork food safety are also likely to be having an ongoing impact on preventing increases in human foodborne disease resulting from current livestock antibiotic stewardship interventions.

The ability to completely mitigate the negative human consequences of livestock antibiotic curtailment in the scenario-specific examples implemented in this study (Figure 6), also suggests that in certain cases, there may be the potential for improved biosecurity practices to replace livestock antibiotics as an alternative to prevent diseases of a livestock origin (**CITE – 3Rs**). However, further research is required to quantify the efficacy of these interventions on the specified transmission routes (**CITE**).

We note that there is currently no consensus in AMR literature regarding the definitive impact of antibiotic withdrawal, with this increase in foodborne disease in humans recognised in AMR literature as a hypothetical “worst case scenario” following antibiotic stewardship (**CITE**). However, by identifying that moderate strength biosecurity interventions are sufficient to control any detrimental human health effects following curtailment, if this “worst case scenario” is a reality, it is likely that the effects of this scenario could be mitigated.

We note that the key determinant of the increases in human foodborne disease following livestock antibiotic curtailment is the extent of antibiotic-mediated livestock recovery and transmission-related fitness costs (κ and α). As an illustrative example, preventing livestock antibiotic usage from enhancing the rate of clearance (κ = 0) and removing fitness costs (α = 0) prevents increases in livestock or consequently human foodborne disease following livestock antibiotic curtailment (Figure S10). This is consistent with several assumptions in veterinary AMR literature, which suggest limited human health effects following livestock antibiotic curtailment (**CITE**). Further experimental and epidemiological studies must be conducted to confirm the impact of sub-therapeutic and therapeutic antibiotic usage on the period of livestock infectious shedding and the impact of fitness costs of resistance on transmission potential.

We note that the existence of the ζ parameter prevents the model from being considered a neutral-null model (cite) due to the presence of “immigration infections” not tractable to infections at t = 0. However, the exclusion of ζ was found to result in a poorer model fit compared to where the parameter is present in the model structure (Figure S1). Additionally, as the aim of the model was not to specifically characterise the evolutionary dynamics underlying coexistence, we can justify the exclusion of a neutral-null model by implicitly acknowledging 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. Future modelling into livestock antibiotic curtailment may benefit from model comparison and exploratory modelling to assess the effect of assumptions, model structure and explicit modelling of biological phenomena on the impact of modelled interventions.

We also note that the effort required to achieve specific reductions across different transmission parameters is likely to be asymmetrical and non-linear. Quantifying the impact of livestock interventions on transmission through future epidemiological studies would likely be necessary for further studies which aim to predict the impact of livestock interventions. Additionally, future predictive modelling is still limited by a lack of understanding of effect of farm-to-fork food processing on microbial loads and resistance (**CITE**).

We note that bans of livestock antibiotics such as avoparcin have been followed by sharp decreases in the prevalence of antibiotic resistance, therefore such trends would likely be observed if the “true” relationship between livestock antibiotic usage and livestock resistance was observed (**CITE**). However, this assumes that variation in livestock antibiotic usage is the sole driver of differences between country-level resistance in livestock. Hierarchical statistical models should be used to explore country-level effects on the prevalence of livestock antibiotic usage (**CITE**). We also note that in the absence of granular, country specific antibiotic usage data stratified by antibiotic and livestock, use of antibiotic sales data as a proxy is the only alternative. In the absence of higher quality surveillance data in the future, model fitting might benefit from model-based inference of livestock antibiotic usage data. There is also a dearth of high-quality livestock datasets regarding carriage of foodborne pathogens, especially when compared to availability and size of human datasets (**CITE)**.

Due to the uncertainties with the data used in this study, it is important to note that the resulting model fit was not intended to predict the definitive consequences following alterations in livestock antibiotic usage. Rather the ABC-SMC approach was used to explore roughly parameterised case studies with the best available data, used as an illustrative example to explore the hypotheses and model structure proposed in this study. It is more useful to consider the parameterisation in this study as a method to ground the model across diverse parameter values, rather than an exact reflection of each case study. 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 improvements to AMR surveillance will likely improve the accuracy of future parameterisation of livestock AMR models (**CITE**).

This results from this study corroborates epidemiological surveillance and modelling studies, with decreases in antibiotic resistance following livestock antibiotic curtailment. 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 an intensifying focus on improving livestock welfare to prevent human disease is critical when considering potential control strategies to tackle the AMR crisis.

Aarestrup, F. M. (2015). "The livestock reservoir for antimicrobial resistance: a personal view on changing patterns of risks, effects of interventions and the way forward." Philos Trans R Soc Lond B Biol Sci **370**(1670): 20140085.

The purpose of this review was to provide an updated overview on the use of antimicrobial agents in livestock, the associated problems for humans and current knowledge on the effects of reducing resistance in the livestock reservoir on both human health and animal production. There is still limiting data on both use of antimicrobial agents, occurrence and spread of resistance as well as impact on human health. However, in recent years, emerging issues related to methicillin-resistant Staphylococcus aureus, Clostridium difficile, Escherichia coli and horizontally transferred genes indicates that the livestock reservoir has a more significant impact on human health than was estimated 10 years ago, where the focus was mainly on resistance in Campylobacter and Salmonella. Studies have indicated that there might only be a marginal if any benefit from the regular use of antibiotics and have shown that it is possible to substantially reduce the use of antimicrobial agents in livestock production without compromising animal welfare or health or production. In some cases, this should be done in combination with other measures such as biosecurity and use of vaccines. To enable better studies on both the global burden and the effect of interventions, there is a need for global harmonized integrated and continuous surveillance of antimicrobial usage and antimicrobial resistance, preferably associated with data on production and animal diseases to determine the positive and negative impact of reducing antimicrobial use in livestock.

Aarestrup, F. M., et al. (2001). "Effect of abolishment of the use of antimicrobial agents for growth promotion on occurrence of antimicrobial resistance in fecal enterococci from food animals in Denmark." Antimicrobial Agents and Chemotherapy **45**(7): 2054-2059.

From 1995 to 2000, a total of 673 Enterococcus faecium and 1,088 Enterococcus faecalis isolates from pigs together with 856 E. faecium isolates from broilers were isolated and tested for susceptibility to four classes of antimicrobial agents used for growth promotion as part of the Danish program of monitoring for antimicrobial resistance. The four antimicrobials were avilamycin, erythromycin, vancomycin, and virginiamycin. Major changes in the use of antimicrobial agents for growth promotion have occurred during the last 6 years in Denmark. The government banned the use of avoparcin in 1995 and of virginiamycin in 1998, Furthermore, the producers have voluntarily stopped all use beginning in 1999. The avoparcin ban in 1995 was followed by a decrease in the occurrence of glycopeptide-resistant E. faecium (GRE) in broilers, from 72.7% in 1995 to 5.8% in 2000, The occurrence of glycopeptide resistance among isolates from pigs remained constant at around 20% from 1995 to 1997. It was shown that, in GRE from pigs, the genes encoding macrolide and glycopeptide resistance mere genetically linked and that, following the decrease in the use of tylosin during 1998 and 1999, the occurrence of GRE: in pigs decreased to 6.0% in 2000, From 1995 to 1997 the occurrence of erythromycin resistance among E. faecium and E. faecalis isolates from pigs was almost 90%. Use of tylosin decreased considerably during 1998 and 1999, and this decrease was followed by decreases in the occurrence of resistance to 46.7 and 28.1% among E. faecium and E. faecalis isolates from pigs, respectively. Erythromycin resistance among E. faecium isolates from broilers reached a maximum of 76.3% in 1997 but decreased to 12.7% in 2000 concomitantly with more limited use of virginiamycin. Use of virginiamycin increased from 1995 to 1997 and was followed by an increased occurrence of virginiamycin resistance among E. faecium isolates in broilers, from 27.3% in 1995 to 66.2% in 1997, In January 1998 the use of virginiamycin was banned in Denmark, and the occurrence of virginiamycin resistance decreased to 33.9% in 2000. Use of avilamycin increased from 1995 to 1996 and was followed by an increase in avilamycin resistance among E. faecium isolates from broilers, from 63.6% in 1995 to 77.4% in 1996. Since 1996 avilamycin usage has decreased, followed by a decrease in resistance to 4.8% in 2000, Our observations show that it is possible to reduce the occurrence of antimicrobial resistance in a national population of food animals when the selective pressure is removed. Cases in which resistance to vancomycin was linked to resistance to erythromycin were exceptions. In such cases resistance did not decrease until the use of both avoparcin and tylosin was limited.

Alban, L., et al. (2008). "A human health risk assessment for macrolide-resistant Campylobacter associated with the use of macrolides in Danish pig production." Preventive Veterinary Medicine **83**(2): 115-129.

In 2006, macrolides were withdrawn from the list of antibiotics recommended for veterinary treatment of diarrhoea in Danish pigs. The motive was to lower the antibiotic consumption in general and to mitigate the risk related to human infection with macrolide-resistant (Mres) Campylobacter. We subsequently conducted a risk assessment following international guidelines to address the risk for human health associated with usage of macrolides in Danish pigs. Data originated from surveillance programs, published papers, reports and statistics. Furthermore, an exposure model was built in @Risk. Mres Campylobacter is the hazard of interest. Data from different EU countries show that beef contains a very low prevalence (typically 0.1-1.1%) of Campylobacter; moreover, Mres is uncommon in Campylobacter isolates from cattle (between 0% and 6%). Beef was therefore left out of further analysis. For pork at retail, a high variation in the prevalence of Campylobacter has been reported within EU; but generally the prevalence is <10%, and the isolates are often Mres. EU data indicate that poultry meat harbor a high prevalence of Campylobacter (more more than 10%) with Mres at prevalence ranging from 0% to 8%. According to the exposure model - that included origin of meat as well as consumption patterns - most human cases of Mres campylobacteriosis (157 out of 186) was ascribed to imported meat. Only seven cases could be explained by veterinary usage of macrolides in Danish pigs. In general, human cases of campylobacteriosis are self-limiting, and it is questionable whether there is any excess risk related to infection with Mres Campylobacter compared to sensitive Campylobacter. In conclusion, the risk associated with veterinary use of macrolides in Danish pigs for the human health of Danes seemed to be low.

Anderson, S. A., et al. (2001). "Risk assessment of the impact on human health of resistant Campylobacter jejuni from fluoroquinolone use in beef cattle." Food Control **12**(1): 13-25.

Use of antimicrobials in livestock is controversial and may lead to the emergence of resistant organisms that could be transmitted to humans through the food supply. Our quantitative risk assessment employs Monte Carlo methodology to analyze the potential public health risk from Campylobacter jejuni and fluoroquinolone (FQ)-resistant C. jejuni because of fresh beef and ground beef consumption. The quantitative study begins with beef products in the retail display case. Data from a variety of sources have been assembled into the model as predictors of the prevalence and quantity of C. jejuni in specific types of beef. Consumer behaviors handling, cooking and consumption - are modeled in our study to predict exposure. The consequences of exposure in some individuals are infection, illness, hospitalization, or even death. We estimated that approximately 16,000 individuals in the US might be infected by C. jejuni derived from both ground beef and fresh beef sources. Furthermore, we predicted the probability of adverse consequences arising from both C. jejuni and FQ-resistant C. jejuni Results from our quantitative risk assessment model are lower when compared to similar public health outcomes for beef products estimated by the Centers for Disease Control (CDC) and the US Department of Agriculture's Economic Research Service (USDA-ERS). However, incorporation of uncertainty and variability in estimates from our model and the CDC and USDA-ERS suggest that the disparity among the estimates is small. (C) 2000 Elsevier Science Ltd. All rights reserved.

Caffrey, N., et al. (2019). "Risk assessments evaluating foodborne antimicrobial resistance in humans: a scoping review." Microbial Risk Analysis **11**: 31-46.

Casewell, M., et al. (2003). "The European ban on growth-promoting antibiotics and emerging consequences for human and animal health." Journal of Antimicrobial Chemotherapy **52**(2): 159-161.

Following the ban of all food animal growth-promoting antibiotics by Sweden in 1986, the European Union banned avoparcin in 1997 and bacitracin, spiramycin, tylosin and virginiamycin in 1999. Three years later, the only attributable effect in humans has been a diminution in acquired resistance in enterococci isolated from human faecal carriers. There has been an increase in human infection from vancomycin-resistant enterococci in Europe, probably related to the increased in usage of vancomycin for the treatment of methicillin-resistant staphylococci. The ban of growth promoters has, however, revealed that these agents had important prophylactic activity and their withdrawal is now associated with a deterioration in animal health, including increased diarrhoea, weight loss and mortality due to Escherichia coli and Lawsonia intracellularis in early post-weaning pigs, and clostridial necrotic enteritis in broilers. A directly attributable effect of these infections is the increase in usage of therapeutic antibiotics in food animals, including that of tetracycline, aminoglycosides, trimethoprim/sulphonamide, macrolides and lincosamides, all of which are of direct importance in human medicine. The theoretical and political benefit of the widespread ban of growth promoters needs to be more carefully weighed against the increasingly apparent adverse consequences.

Commission, E. (2005). IP/05/1687 - Ban on antibiotics as growth promoters in animal feed enters into effect. Brussels, European Commission.

Cox, L. A., Jr. (2005). "Potential human health benefits of antibiotics used in food animals: a case study of virginiamycin." Environ Int **31**(4): 549-563.

Risk management of food-animal antibiotics has reached a crucial juncture for public health officials worldwide. While withdrawals of animal antibiotics previously used to control animal bacterial illnesses are being encouraged in many countries, the human health impacts of such withdrawals are only starting to be understood. Increases in animal and human bacterial illness rates and antibiotic resistance levels in humans in Europe despite bans on animal antibiotics there have raised questions about how animal antibiotic use affects human health. This paper presents a quantitative human health risk and benefits assessment for virginiamycin (VM), a streptogramin antibiotic recommended for withdrawal from use in food animals in several countries. It applies a new quantitative Rapid Risk Rating Technique (RRRT) that estimates and multiplies data-driven exposure, dose-response, and consequence factors, as suggested by WHO (2003) to estimate human health impacts from withdrawing virginiamycin. Increased human health risks from more pathogens reaching consumers if VM use is terminated (6660 estimated excess campylobacteriosis cases per year in the base case) are predicted to far outweigh benefits from reduced streptogramin-resistant vancomycin-resistant Enterococcus faecium (VREF) infections in human patients (0.27 estimated excess cases per year in the base case). While lack of information about impacts of VM withdrawal on average human illnesses-per-serving of food animal meat precludes a deterministic conclusion, it appears very probable that such a withdrawal would cause many times more human illnesses than it would prevent. This qualitative conclusion appears to be robust to several scientific and modeling uncertainties.

EUR‐Lex (2019). "Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC."

Food, U. and D. Administration (2013). "Guidance for Industry# 213: new animal drugs and new animal drug combination products administered in or on medicated feed or drinking water of food-producing animals: recommendations for drug sponsors for voluntarily aligning product use conditions with GFI# 209." Center for Veterinary Medicine.

Hurd, H. S., et al. (2004). "Public health consequences of macrolide use in food animals: a deterministic risk assessment." J Food Prot **67**(5): 980-992.

The potential impact on human health from antibiotic-resistant bacteria selected by use of antibiotics in food animals has resulted in many reports and recommended actions. The U.S. Food and Drug Administration Center for Veterinary Medicine has issued Guidance Document 152, which advises veterinary drug sponsors of one potential process for conducting a qualitative risk assessment of drug use in food animals. Using this guideline, we developed a deterministic model to assess the risk from two macrolide antibiotics, tylosin and tilmicosin. The scope of modeling included all label claim uses of both macrolides in poultry, swine, and beef cattle. The Guidance Document was followed to define the hazard, which is illness (i) caused by foodborne bacteria with a resistance determinant, (ii) attributed to a specified animal-derived meat commodity, and (iii) treated with a human use drug of the same class. Risk was defined as the probability of this hazard combined with the consequence of treatment failure due to resistant Campylobacter spp. or Enterococcus faecium. A binomial event model was applied to estimate the annual risk for the U.S. general population. Parameters were derived from industry drug use surveys, scientific literature, medical guidelines, and government documents. This unique farm-to-patient risk assessment demonstrated that use of tylosin and tilmicosin in food animals presents a very low risk of human treatment failure, with an approximate annual probability of less than 1 in 10 million Campylobacter-derived and approximately 1 in 3 billion E. faecium-derived risk.

Kermack, W. O. and A. G. McKendrick (1927). "A contribution to the mathematical theory of epidemics." Proceedings of the royal society of london. Series A, Containing papers of a mathematical and physical character **115**(772): 700-721.

Maisnier‐Patin, S., et al. (2002). "Compensatory adaptation to the deleterious effect of antibiotic resistance in Salmonella typhimurium." Molecular Microbiology **46**(2): 355-366.

Niewiadomska, A. M., et al. (2019). "Population-level mathematical modeling of antimicrobial resistance: a systematic review." BMC Med **17**(1): 81.

BACKGROUND: Mathematical transmission models are increasingly used to guide public health interventions for infectious diseases, particularly in the context of emerging pathogens; however, the contribution of modeling to the growing issue of antimicrobial resistance (AMR) remains unclear. Here, we systematically evaluate publications on population-level transmission models of AMR over a recent period (2006-2016) to gauge the state of research and identify gaps warranting further work. METHODS: We performed a systematic literature search of relevant databases to identify transmission studies of AMR in viral, bacterial, and parasitic disease systems. We analyzed the temporal, geographic, and subject matter trends, described the predominant medical and behavioral interventions studied, and identified central findings relating to key pathogens. RESULTS: We identified 273 modeling studies; the majority of which (> 70%) focused on 5 infectious diseases (human immunodeficiency virus (HIV), influenza virus, Plasmodium falciparum (malaria), Mycobacterium tuberculosis (TB), and methicillin-resistant Staphylococcus aureus (MRSA)). AMR studies of influenza and nosocomial pathogens were mainly set in industrialized nations, while HIV, TB, and malaria studies were heavily skewed towards developing countries. The majority of articles focused on AMR exclusively in humans (89%), either in community (58%) or healthcare (27%) settings. Model systems were largely compartmental (76%) and deterministic (66%). Only 43% of models were calibrated against epidemiological data, and few were validated against out-of-sample datasets (14%). The interventions considered were primarily the impact of different drug regimens, hygiene and infection control measures, screening, and diagnostics, while few studies addressed de novo resistance, vaccination strategies, economic, or behavioral changes to reduce antibiotic use in humans and animals. CONCLUSIONS: The AMR modeling literature concentrates on disease systems where resistance has been long-established, while few studies pro-actively address recent rise in resistance in new pathogens or explore upstream strategies to reduce overall antibiotic consumption. Notable gaps include research on emerging resistance in Enterobacteriaceae and Neisseria gonorrhoeae; AMR transmission at the animal-human interface, particularly in agricultural and veterinary settings; transmission between hospitals and the community; the role of environmental factors in AMR transmission; and the potential of vaccines to combat AMR.

Phillips, I., et al. (2004). "Does the use of antibiotics in food animals pose a risk to human health? A critical review of published data." Journal of Antimicrobial Chemotherapy **53**(1): 28-52.

Saltelli, A. and R. Bolado (1998). "An alternative way to compute Fourier amplitude sensitivity test (FAST)." Computational Statistics & Data Analysis **26**(4): 445-460.

Schlundt, J. and F. M. Aarestrup (2017). "Commentary: Benefits and risks of antimicrobial use in food-producing animals." Frontiers in microbiology **8**: 181.

Spicknall, I. H., et al. (2013). "A modeling framework for the evolution and spread of antibiotic resistance: literature review and model categorization." American journal of epidemiology **178**(4): 508-520.

Tang, K. L., et al. (2017). "Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis." The Lancet Planetary Health **1**(8): e316-e327.

Toni, T., et al. (2009). "Approximate Bayesian computation scheme for parameter inference and model selection in dynamical systems." J R Soc Interface **6**(31): 187-202.

Approximate Bayesian computation (ABC) methods can be used to evaluate posterior distributions without having to calculate likelihoods. In this paper, we discuss and apply an ABC method based on sequential Monte Carlo (SMC) to estimate parameters of dynamical models. We show that ABC SMC provides information about the inferability of parameters and model sensitivity to changes in parameters, and tends to perform better than other ABC approaches. The algorithm is applied to several well-known biological systems, for which parameters and their credible intervals are inferred. Moreover, we develop ABC SMC as a tool for model selection; given a range of different mathematical descriptions, ABC SMC is able to choose the best model using the standard Bayesian model selection apparatus.

Woolhouse, M., et al. (2015). "Antimicrobial resistance in humans, livestock and the wider environment." Philos Trans R Soc Lond B Biol Sci **370**(1670): 20140083.

Antimicrobial resistance (AMR) in humans is inter-linked with AMR in other populations, especially farm animals, and in the wider environment. The relatively few bacterial species that cause disease in humans, and are the targets of antibiotic treatment, constitute a tiny subset of the overall diversity of bacteria that includes the gut microbiota and vast numbers in the soil. However, resistance can pass between these different populations; and homologous resistance genes have been found in pathogens, normal flora and soil bacteria. Farm animals are an important component of this complex system: they are exposed to enormous quantities of antibiotics (despite attempts at reduction) and act as another reservoir of resistance genes. Whole genome sequencing is revealing and beginning to quantify the two-way traffic of AMR bacteria between the farm and the clinic. Surveillance of bacterial disease, drug usage and resistance in livestock is still relatively poor, though improving, but achieving better antimicrobial stewardship on the farm is challenging: antibiotics are an integral part of industrial agriculture and there are very few alternatives. Human production and use of antibiotics either on the farm or in the clinic is but a recent addition to the natural and ancient process of antibiotic production and resistance evolution that occurs on a global scale in the soil. Viewed in this way, AMR is somewhat analogous to climate change, and that suggests that an intergovernmental panel, akin to the Intergovernmental Panel on Climate Change, could be an appropriate vehicle to actively address the problem.