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Modelling the effects of antibiotic usage in livestock on human salmonellosis

Alex L.K Morgan[12], Mark E.J Woolhouse[13], Jaap A Wagenaar[456] and Bram A.D van Bunnik[7]

[1]Centre for Immunity, Infection & Evolution and School of Biological Sciences, University of Edinburgh, Edinburgh, United Kingdom

[2]Department of Environmental Systems Science, ETH Zürich, Zürich, Switzerland

[3]Usher Institute, University of Edinburgh, Edinburgh, United Kingdom

[4]Division of Infectious Diseases and Immunology, Faculty of Veterinary Medicine, Utrecht University, Utrecht, Netherlands

[5]Wageningen Bioveterinary Research, Lelystad, Netherlands

[6]WHO Collaborating Center for Reference and Research on Campylobacter and Antimicrobial Resistance from a One Health Perspective/WOAH Reference Laboratory for Campylobacteriosis, Utrecht, Netherlands,

[7]Roslin Institute, University of Edinburgh, Midlothian, United Kingdom

Keywords: antimicrobial resistance, foodborne disease, mathematical model, antibiotic reduction, one health

ABSTRACT

Antibiotic usage in livestock has been suggested as a driver of antimicrobial resistance in human and livestock populations. This has contributed to the implementation of stewardship programs to curtail usage of antibiotics in livestock. However, the consequences of antibiotic curtailment in livestock on human health are poorly understood. In particular, there is the potential for increases in the carriage of pathogens such as *Salmonella* spp. in livestock, and subsequent increases in human foodborne disease. We use a mathematical model fitted to four case studies, ampicillin and tetracycline usage in fattening pig and broiler poultry populations, to explore the impact of curtailing antibiotic usage in livestock on salmonellosis in humans.

Increases in the daily incidence of salmonellosis and a decrease in the proportion of resistant salmonellosis were identified following curtailment of antibiotic usage in livestock. The extent of these increases in foodborne disease ranged from negligible, to controllable through interventions to target the farm-to-fork pathway. This study provides a motivating example of one plausible scenario following curtailment of antibiotic usage in livestock and suggests that a focus on ensuring good farm-to-fork hygiene and livestock biosecurity is sufficient to mitigate the negative human health consequences of antibiotic stewardship in livestock populations.

INTRODUCTION

Antimicrobial resistance (AMR) is one of the largest threats to human health, with a growing number of key antibiotic therapeutics being rendered ineffective by resistant bacterial pathogens. Antibiotic usage in livestock has been identified as a potentially important driver of AMR in human populations, with transmission of resistant bacteria and resistance determinants potentially occurring at the livestock/human interface [1]. This has led to efforts to curtail the usage of antibiotics in livestock. Examples include bans on usage of antibiotics for both growth promotion and for prophylaxis of livestock diseases [2-4]. The aims of these curtailment strategies are to safeguard the efficacy of clinical antibiotics and reduce the potential for transmission of resistant pathogens to human populations.

Curtailment of antibiotic usage in livestock has resulted in desired reductions to AMR, with an example being reductions to faecal *Enterococci* resistance rates in Denmark and Germany resulting from the 2006 growth promotion ban [5-7]. These reductions in usage have also been associated with transient increases in the carriage of other resistant pathogens, increases in livestock carriage of foodborne pathogens and increases in therapeutic antibiotic usage in livestock [8-10]. However, arguments have been made that these negative consequences can be largely attributed to increases in livestock productivity [11-13].

The uncertainty surrounding the consequences of curtailing antibiotic usage in livestock highlights the risks of introducing interventions into highly complex and poorly understood population/microbial level systems that have been built up through decades of antibiotic use as part of a “precautionary principle” based approach [10]. The need to better understand

the potential long-term impacts of future AMR policy is also likely to increase, with EU legislation strictly controlling the use of antibiotics in livestock for metaphylaxis or prophylaxis in 2022 [4]. Therefore, there is a need for an increased understanding into the potential human health consequences following curtailment of antibiotics in livestock, especially when placed into a "one health" context.

One approach to better understand the complexities of antibiotic usage in livestock includes the use of mathematical models. These models can help by testing uncertainties, especially regarding the potential effects of antibiotic usage in livestock on human health and the extent of AMR transmission at the livestock/human interface. However, there is a dearth of models which quantitatively explore these uncertainties [14]. Existing frameworks include predictive risk assessment models and a small number of generalised deterministic models [15-21]. Nevertheless, significant knowledge gaps still exist, including a lack of understanding of the potential outcomes resulting from curtailment of antibiotic usage in livestock and the impact of different mitigating scenarios on altering these outcomes [22].

To address gaps in AMR modelling literature, a deterministic mathematical model was developed to explore the effects of antibiotic curtailment in livestock on *Salmonella* spp. infections in humans. Salmonellosis was explicitly chosen as a case study due to the clear zoonotic link between livestock carriage of *Salmonella* spp. and human infections. By explicitly modelling both livestock/human populations and various assumptions regarding the effects of antibiotic usage in livestock, we explore the potential long-term consequences of antibiotic curtailment in livestock, including alterations to the overall incidence of human salmonellosis and the antibiotic-resistant fraction of infections. Additionally, we explore the effects and

93 feasibility of introducing interventions to mitigate the potential negative consequences of
94 antibiotic curtailment in livestock.
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METHODOLOGY

Model Structure and Description

A compartmental model was developed to describe the transmission of antibiotic-resistant and antibiotic-sensitive *Salmonella* spp. within and between livestock and human populations (Figure 1) [23]. Each host population can be stratified based on their respective infection status: susceptible humans (S_H), humans infected with antibiotic-sensitive bacteria (I_{SH}) or antibiotic-resistant bacteria (I_{RH}), susceptible livestock food-animals (S_A) and livestock food-animals infected with antibiotic-sensitive bacteria (I_{SA}) or antibiotic-resistant bacteria (I_{RA}). For simplicity, we considered "infected" states in livestock to also include asymptomatic carriage.

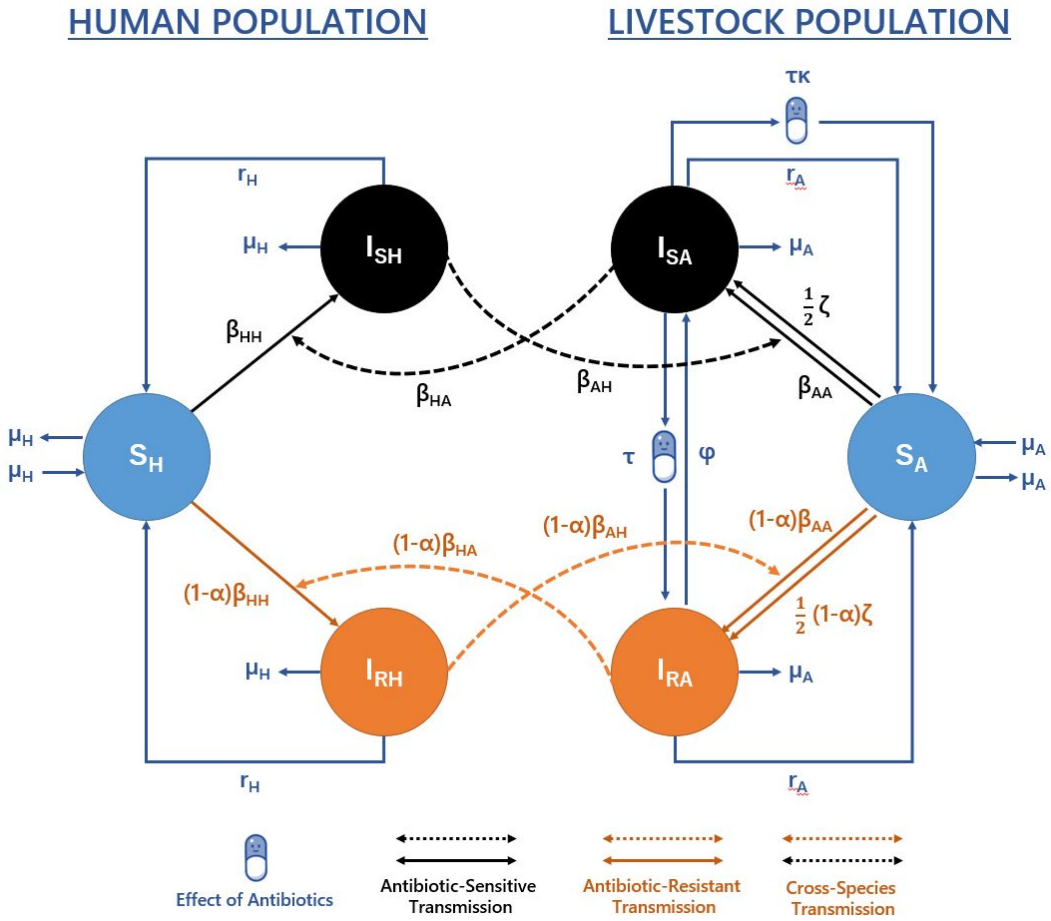

Figure 1. Model structure describing the transmission of foodborne pathogens between/within livestock and human populations. Model equations and parameters can be found described in the supplementary material (eqn S1.1, Table S5).

Transmission is simplified into four transmission routes: animal-to-animal (β_{AA}), human-to-human (β_{HH}), animal-to-human (β_{HA}) and human-to-animal (β_{AH}) transmission, with each β parameter describing both indirect and direct transmission between compartments for model tractability.

A background rate of transmission in the livestock population was also modelled (ζ). This represents infection/contamination of livestock hosts from sources other than livestock or humans, including the environment or new introductions from other (non) considered populations. This background transmission rate was scaled by a factor of 0.5 to ensure an

144 equal influence of ζ on both antibiotic-sensitive and resistant transmission routes. This value
145 was chosen due to a lack of *a priori* information on potential differences in background
146 livestock contamination rate for antibiotic-sensitive/resistant strains. Natural recovery from
147 antibiotic-sensitive/resistant infection/carriage occurs in both human/livestock populations
148 at rate r_H and r_A respectively. Per capita birth/death rates are represented by μ_A in livestock
149 and μ_H in human populations.
150
151 Antibiotic usage was modelled as a rate (τ) and was assumed to have a combined therapeutic
152 and selective pressure effect on antibiotic-sensitive *Salmonella* spp infection/carriage. This
153 therapeutic effect was assumed to both shorten the duration of carriage and clear carriage of
154 antibiotic-sensitive bacteria. However, as there is currently an unclear relationship between
155 antibiotic usage and clearance of *Salmonella* spp. in livestock species, a scaling parameter was
156 also included to describe the efficacy of antibiotic mediated recovery in livestock (κ). As an
157 illustrative example, lower values of κ correspond to a lower ability of antibiotic usage in
158 livestock to shorten the duration of carriage or clear *Salmonella* spp. in livestock. Antibiotic
159 usage was also modelled to have a selective pressure converting livestock between antibiotic-
160 sensitive to resistant states. This could be interpreted as an implicit majority-minority
161 relationship in each infected state, with livestock in each infected compartment possessing a
162 small proportion of bacteria belonging to the other susceptibility class. Subsequent antibiotic
163 usage may therefore clear antibiotic-sensitive bacteria (I_{SA}) and allow the minority antibiotic-
164 resistant (I_{RA}) strain to proliferate and dominate, leading to “conversion” [15].
165
166 A reversion rate (ϕ) was also used to encompass a range of different biologically plausible
167 phenomena that may cause reversion of antibiotic-resistant (I_{RA}) to sensitive (I_{SA})

carriage/infection. For example, this rate may describe growth-mediated competition within-host, where antibiotic-sensitive strains may outcompete antibiotic-resistant strains in the absence of antibiotics. This is assumption is captured through the antibiotic treatment rate (τ), with this rate implicitly assuming that while some livestock are treated and exposed to antibiotics, others may not be.

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). This parameter can be interpreted as a decrease in capacity for resistant strains (relative to sensitive strains) to establish infectious carriage in new hosts due to changes in important cellular machinery to facilitate resistance to antibiotics [24-26].

Primary outcome measures

Two primary outcome measures were considered in this study: 1) the daily incidence of human non-typhoidal human 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 of 446.8 million and then scaled by 100,000 [27]. 2) The fraction of antibiotic-resistant human non-typhoidal salmonellosis (I^*_{RHProp}) (defined as $I_{RH} / (I_{SH}+I_{RH})$ 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”

192 dynamics of AMR are in flux due to the influence of interventions, population dynamics etc.,
193 studying it at equilibrium is a useful indication of the long-term dynamics of the AMR and
194 where the system is heading. This is especially the case for resistant *Salmonella* spp.
195 infections, with a short duration of infectious human carriage ($1/r_H$), facilitating a rapid
196 approach to equilibrium. This approach is also justified with temporal surveillance data
197 suggesting the proportion of antibiotic resistance in livestock populations has stabilised at
198 roughly constant levels in recent years (Figure S1-4).
199
200 **Case Studies and Datasets**
201
202 As a key part of our model is to assess dynamics following a withdrawal of antibiotic usage in
203 livestock, it is critical that the model is able to reproduce the relationship between antibiotic
204 usage in livestock and fraction of antibiotic-resistant livestock infection. Therefore, this
205 livestock portion of the model was fitted using an approximate Bayesian computation
206 sequential Monte-Carlo (ABC-SMC) to the relationship between antibiotic usage and the
207 resistance using resistance/treatment surveillance data. Detailed methodology for the ABC-
208 SMC approach can be found in Toni et al, (2009) [28].
209
210 Phenotypic resistance data was obtained from the European Food Safety Authority (EFSA)
211 summary reports. The proportion of isolates resistant to the specific antibiotic class from
212 carcasses of broiler poultry/fattening pigs was extracted from the respective EFSA datasets
213 [29-34]. Antibiotic sales data was obtained from European surveillance of veterinary
214 consumption (ESVAC) reports [35-39]. ESVAC antibiotic sales data are averaged for all
215 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 (Table S1). 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. Details of the raw datasets and data manipulation of the ESVAC and EFSA datasets can be found in the supplementary information.

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 from 2014-2018, 2) tetracycline-resistant non-typhoidal salmonella in broiler poultry from 2014-2018, 3) ampicillin-resistant non-typhoidal salmonella in fattening pigs from 2015-2018 and 4) tetracycline-resistant non-typhoidal salmonella in fattening pigs from 2015-2018.

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 [35-40]. However, it is acknowledged that more relevant case studies regarding direct clinical relevance and drug/bug combination may exist in literature but cannot be modelled to lack of adequate surveillance data. As a preliminary test for a relationship between usage and resistance before simulating the dynamics of this relationship, we identified an observed statistically significant relationship between usage and resistance for three out of four included case studies (Figure S5, Table S2).

ABC-SMC Model Fitting Procedure

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 for use in the ABC-SMC inference process. In accordance with the EFSA methodology, countries with <10 isolates in the respective EFSA dataset for a particular year were omitted from the dataset [29, 30, 33, 34].

Two additional summary statistics were also used for ABC-SMC model fitting: 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-resistant *Salmonella* spp. in broiler poultry (0.314 at 0.0049 g/PCU), 2) tetracycline-resistant *Salmonella* spp. in broiler poultry (0.316 at 0.0069 g/PCU), 3) ampicillin-resistant *Salmonella* spp. in fattening pigs (0.345 at 0.0125 g/PCU) and 4) tetracycline-resistant *Salmonella* spp. in fattening pigs (0.340 at 0.01305 g/PCU).

Fitted Parameters

The ABC-SMC approach was used to estimate the marginal posterior probability distribution for six model parameters (θ) given the data, $\theta = [\beta_{AA}, \kappa, \varphi, \alpha, \beta_{HA}, \zeta]$ [28, 41]. Other model parameters were not fitted as estimates with high levels of certainty were available (r_H, r_A, μ_A and μ_H), or due to the relative nature of other transmission parameters with respect to β_{AA}, β_{HA} and ζ (β_{HH} and β_{AH}). β_{HH} and β_{AH} 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 [42]. Prior distributions and fitted model values can be found in the supplementary material (Table S3).

Sensitivity Analyses

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 [43]: 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.

The FAST approach was also used to identify the sensitivity of the model system to two additional intervention related outcome measures: 1) Relative changes in daily incidence when antibiotic usage in livestock were curtailed (τ = 0 g/PCU), compared to daily incidence at mean baseline 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

288 observed daily incidence with current levels of antibiotic usage (0.593 per 100,000). An in-
289 depth description of this sensitivity analysis can be found in the supplementary material.
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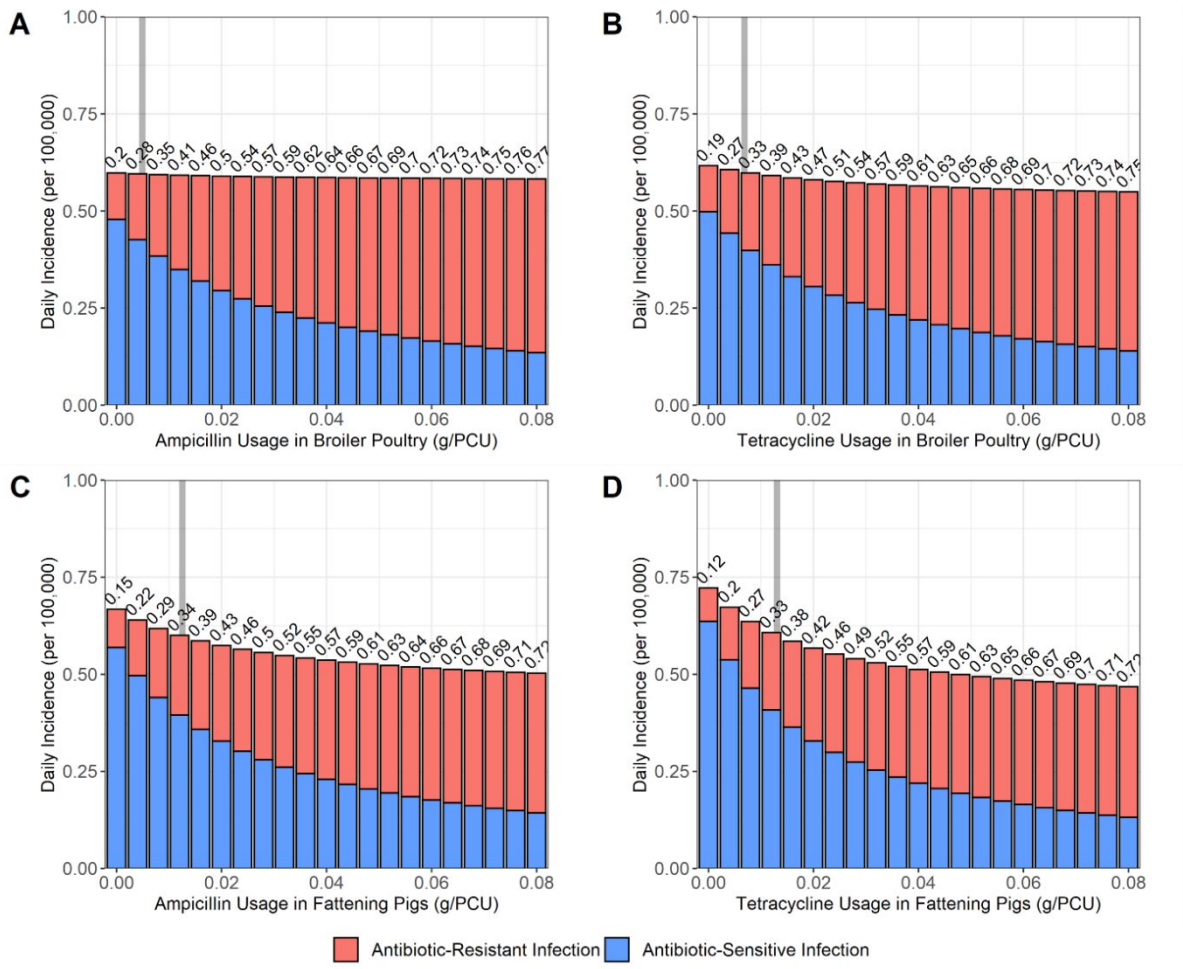
RESULTS

Curtailment of antibiotic usage ($\tau \rightarrow 0$ g/PCU) 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 (Figure 2). In contrast, increases in daily incidence for the broiler poultry case studies ranged from a zero-fold change below 3 significant figures (0.598 per 100,000) 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.



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331 **Figure 2. Impact of alterations in antibiotic usage in livestock (τ) on the daily incidence of**
332 **salmonellosis and the proportion of resistant human infection (I^*_{RHProp}).** A) Ampicillin-
333 resistant human salmonellosis from broiler poultry. B) Tetracycline-resistant human
334 salmonellosis from broiler poultry. C) Ampicillin-resistant human salmonellosis from fattening
335 pigs. D) Tetracycline-resistant human salmonellosis from fattening pigs. Grey bar denotes the
336 case study specific baseline antibiotic usage in livestock (α = 0.0035/0.0049/0.0081/0.0109).
337 Numbers above the bars denote I^*_{RHProp}. Information on the model fitting procedure and the
338 fitted daily incidence and I^*_{RHProp} for each case study can be found in the supplementary
339 material (Table S6).
340

341 Increases in antibiotic usage in livestock above baseline usage levels in the four case studies
342 resulted in the opposite phenomenon, with decreases in overall human foodborne disease
343 and increases in the proportion of resistant infection (Figure 2).
344

345 A Fourier amplitude sensitivity test (FAST) was next performed to identify the parameters
346 which had the greatest influence on the relative increase in the daily incidence when
347 antibiotic usage in livestock was curtailed ($\tau \rightarrow 0$ g/PCU) (Figure 3). Briefly, FAST analyses are
348 a type of global sensitivity test using periodic sampling and Fourier transformations to
349 decompose variance in a model outcome measure to individual model parameters.
350 Therefore, influential model parameters in this specific FAST analysis can be interpreted as
351 parameters that lead to case studies with large relative changes in daily incidence compared
352 to baseline antibiotic usage under antibiotic curtailment.
353
354 The model outcome measure used to explore relative increases in daily incidence under
355 curtailment was defined as the relative change in the daily incidence at mean baseline
356 antibiotic usage in livestock ($\tau = 0.00934$ g/PCU) when compared to incidence under antibiotic
357 curtailment ($\tau = 0$ g/PCU) across the four case studies (Figure 3A). As each parameter
358 combination explored by the FAST search curve will result in a different daily incidence at
359 baseline antibiotic usage ($\tau = 0.00934$ g/PCU), this can be interpreted as exploring case studies
360 and scenarios other than the specific drug/livestock/pathogen combinations used as baseline
361 scenarios in this study.
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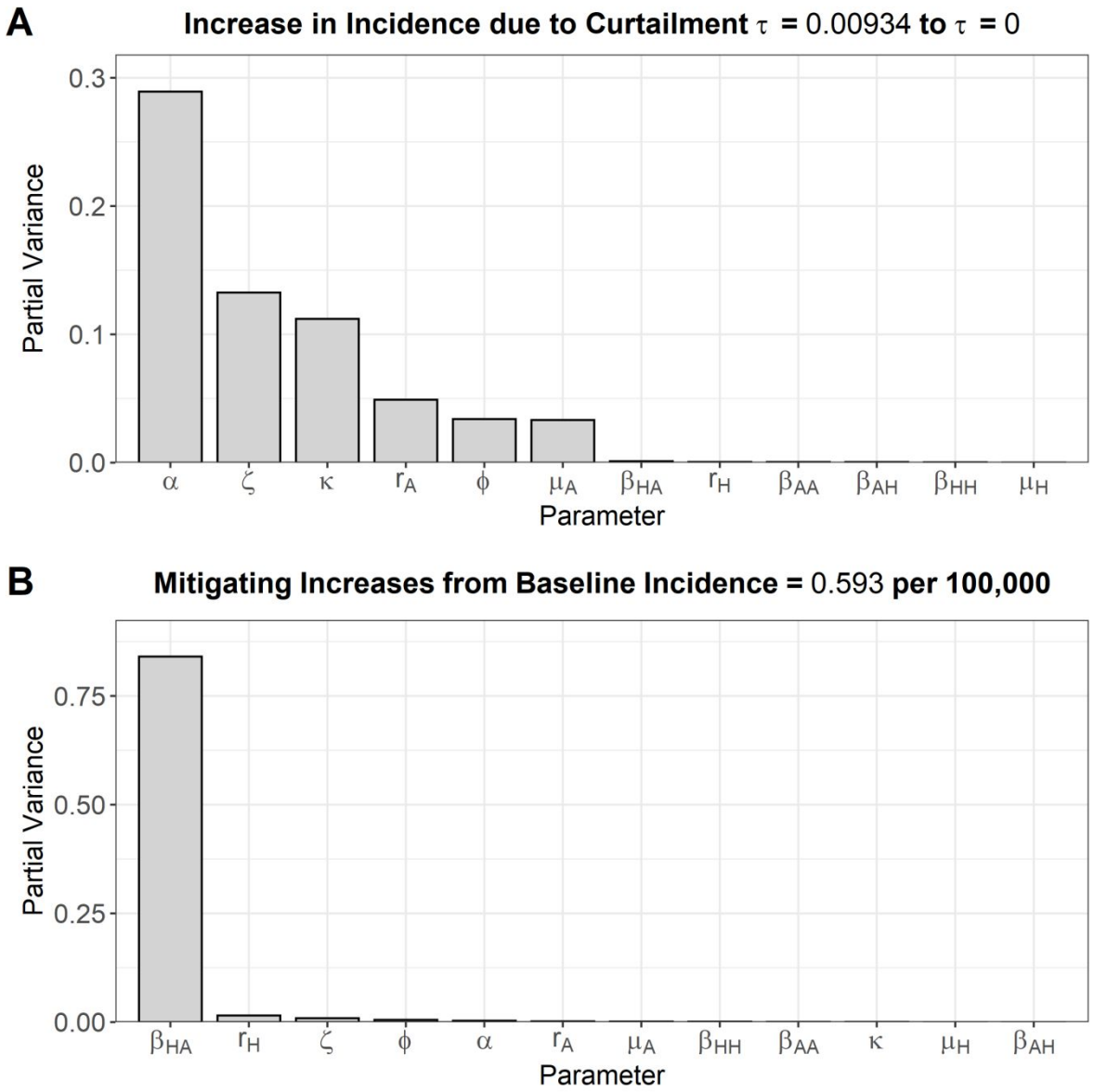

Figure 3. Fourier amplitude sensitivity test (FAST) to identify the most influential model parameter for: A) Relative change in daily incidence under curtailment (0 g/PCU) compared to the averaged baseline antibiotic usage level (0.00934 g/PCU). B) Mitigating changes in daily incidence under curtailment compared to the level of foodborne disease experienced under current levels of antibiotic usage in livestock (0.593 per 100,000 population). Higher bars indicate greater sensitivity. A FAST analysis of baseline model outcome measure, daily incidence and I^*_{RHProp} was also performed (Figure S14).

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 antibiotic usage in livestock when antibiotics where curtailed. (Figure 3A). Specifically, lower κ and α, and higher ζ parameter values resulted in lower relative increases in daily incidence when antibiotic usage in livestock was curtailed (τ = 0 g/PCU) (Figure S16).

A follow up sensitivity analysis was performed to identify parameters that could best *mitigate* increases in daily incidence under antibiotic curtailment for the particular ampicillin/tetracycline in broiler poultry/fattening pigs case studies used in this study (Figure 3B). This was identified by comparing increases in daily incidence under antibiotic curtailment ($\tau \rightarrow$ 0 g/PCU) to a fixed daily incidence at baseline antibiotic usage of 0.593 per 100,000 population (average τ = 0.00934 g/PCU), as this is the baseline daily incidence of salmonellosis relevant for 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 these baseline levels currently observed for the modelled case studies.

The per capita rate of animal-to-human transmission (β_{HA}) was identified as the key parameter to mitigate increases in daily incidence (Figure 3B). Intuitively, decreasing β_{HA} leads to a non-linear decrease in the daily incidence observed (Figure S16). This therefore represents the best parameter to target to mitigate potential increases in daily incidence due to curtailment of antibiotic usage in livestock.

Due to the importance of targeting the animal-to-human transmission route to control increases in daily incidence, we next quantified the alterations in β_{HA} required to mitigate increases in daily incidence under antibiotic usage curtailment (0 g/PCU), below a threshold of 0.593 per 100,000 population (Figure 4). This threshold represents a removal of antibiotic selection pressure in livestock (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 β_{AA} 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 [44, 45]. Limited transmission parameter reductions were explored for β_{HA} (0% - 25%), but with alterations to β_{AA} and ζ parameters allowed to vary from 0-100%.

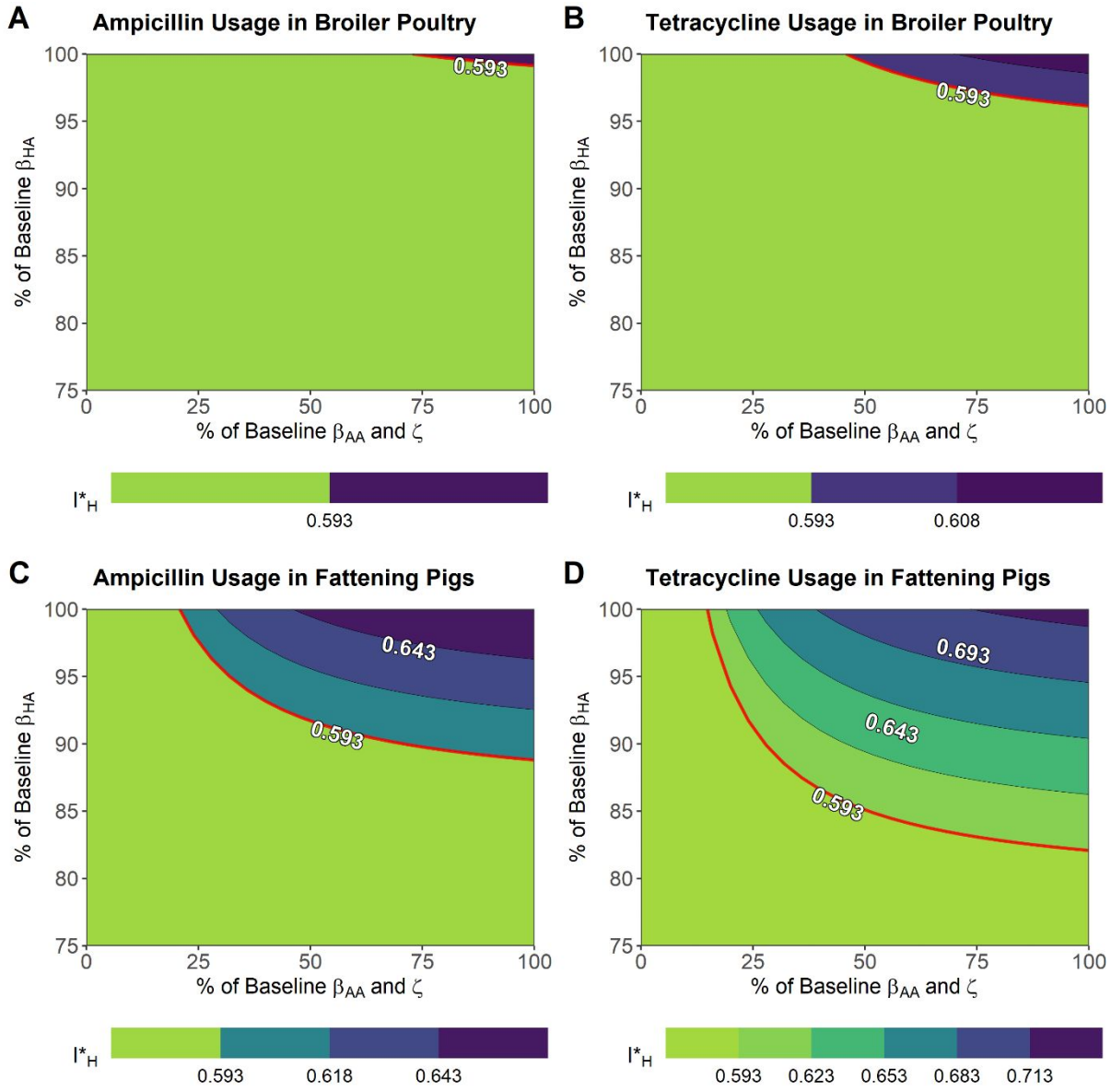

Figure 4. Reductions to key model parameters, animal-to-human transmission (β_{HA}), animal-to-animal transmission (β_{AA}) and the background transmission rate to animal populations (ζ) to mitigate increases in the daily incidence of salmonellosis under curtailment of antibiotic usage in livestock (τ = 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 β_{HA} 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 4). Isolated or even combined reductions to β_{AA} 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 4A).

446 **DISCUSSION**

447

448 A mathematical modelling approach was used to identify changes in the daily incidence of
449 non-typhoidal human salmonellosis, as well as changes in the proportion of resistant human
450 salmonellosis following curtailment of antibiotic usage in livestock. This was explored across
451 four relevant antibiotic/livestock specific case studies. Scenarios with high transmission-
452 related fitness costs of resistance (α), high efficacies of antibiotic-mediated livestock recovery
453 (κ) and low background transmission rates of *Salmonella* spp. in livestock (ζ) were found to
454 result in large increases in the daily incidence of human salmonellosis upon antibiotic
455 curtailment. However, interventions to decrease animal-to-human transmission (β_{HA}) were
456 found to effectively mitigate increases in the daily incidence of human salmonellosis following
457 curtailment of antibiotic usage in livestock.

458

459 These reductions to β_{HA} could take the form of interventions to increase awareness from
460 workers in the farm-to-fork pathway to maintain good hygiene, reducing microbial
461 contamination on carcasses, as well as comprehensive public information campaigns to
462 promote safe handling of food products [44, 46]. Many of these interventions have already
463 been implemented, with legislation requiring businesses to comply with stringent hygiene
464 standards [47]. This could be a promising signal that current business-as-usual approaches or
465 small improvements to the current situation, could be sufficient to control increases in
466 foodborne disease following future antibiotic usage stewardship interventions [22, 48, 49].

467

468 However, despite these improvements to farm-to-fork hygiene and farm-level biosecurity, it
469 is important to note that *Salmonella* incidence/prevalence has plateaued in certain regions

[50, 51]. This may be an indication that further reductions to incidence, if not already reduced by current interventions to reduce transmission, may be difficult to achieve. It is also worth noting there will also likely be large heterogeneity in the impact of different interventions to improve hygiene at the farm-to-fork pathway to reduce β_{HA} [52]. Further work must be done to quantify the exact contribution of these individual interventions on the animal-to-human transmission route to improve future predictions [53]. This could include the integration of dynamic epidemiological models with explicit microbial risk-assessment models detailing the farm-to-fork pathway [22, 54, 55]. Additionally, incorporating economic models into future dynamic modelling could also assess the economic feasibility of introducing hypothetical interventions in the food production chain [56].

Curtailment of antibiotic usage in livestock was found to have varying impacts across the modelled livestock host species, with negligible changes in the daily incidence in the broiler poultry case studies and with the largest increases in incidence observed with the fattening pig case studies (Figure 2). These differences across broilers and pigs can be attributed to the large differences in transmission-related fitness costs associated with antibiotic resistance between species (α = 0.084 and 0.416 for broiler poultry and fattening pigs respectively). Difference in fitness cost between species may reflect heterogeneity in the distribution of *Salmonella* spp. serotypes colonising poultry and pig hosts [57]. Heterogeneity in fitness cost across hosts could also be attributable to distinct plasmid types in chickens and pigs, with studies in *E.coli* identifying differences in fitness cost across these resistance-encoding plasmids [58].

493 In addition to α, differences in the relative increase in daily incidence of salmonellosis
494 between modelled case studies can also be attributed to ζ and κ parameters (Figure 3A). The
495 effects of changes in these parameters on the impact of curtailment are twofold: Firstly,
496 treatments which have a greater therapeutic impact on the duration of antibiotic-sensitive
497 carriage, $\left(\frac{1}{\tau\kappa + r_A}\right)$, will intuitively result in larger increases in prevalence when withdrawn
498 (high κ) (Figure S17). Secondly, as antibiotic-sensitive strains are the only *Salmonella* spp.
499 strains impacted by treatment, if the proportion of antibiotic-sensitive relative to antibiotic-
500 resistant strains is higher, then we will observe a greater increase in overall disease when
501 treatment is withdrawn. This tendency for antibiotic-sensitive strains to dominate occurs
502 when there are greater transmission-related fitness costs associated with antibiotic-
503 resistance (high α), as sensitive strains will have an even greater relative fitness advantage
504 over resistant strains. Additionally, a constant source of antibiotic-resistant bacteria from
505 external sources such as the environment (high ζ) may also reduce the proportion of
506 antibiotic-sensitive to resistant strains (Figure S18).
507
508 The importance of the therapeutic effect of antibiotic usage (τκ) in determining the relative
509 increase in incidence of salmonellosis also has important implications when considering the
510 assumptions used in this study. Antibiotic usage in livestock was modelled to be a proxy for
511 all modes of application (meta-phylaxis, prophylaxis etc.) and therefore by extension, our
512 model implicitly assumes that all types of antibiotic usage have a therapeutic effect in
513 livestock. This assumption can be considered an edge-case, highly positive interpretation of
514 antibiotic usage in livestock, considering that the impact of antibiotic exposure to *Salmonella*
515 carriage in livestock is likely highly variable and dependent on the antibiotics used [59, 60].

516 However, the fact that increases in human incidence are still relatively minor under an
517 assumption that curtailment is occurring to antibiotic usage with a highly therapeutic effect
518 in livestock, further reinforces the message that the real-life impact of antibiotic curtailment
519 on human salmonellosis will likely be minimal.
520
521 It is worth highlighting that bacteria species such as *Listeria* spp. and *E.coli* (i.e. VTEC) will
522 likely have different dynamics upon curtailment of antibiotic usage in livestock, with both
523 being commonly found in the intestinal flora of immunocompetent individuals and only
524 causing disease as opportunistic infection [61, 62]. Therefore, it is likely that there will be a
525 less clear link between improvements in farm-to-fork hygiene and the incidence of
526 opportunistic infections of *Listeria* spp. and *E.coli*.
527
528 It is important to note that the aim of this study was not to specifically explore the
529 evolutionary dynamics underlying the coexistence of sensitive and resistant strains. Instead,
530 we implicitly acknowledge that this phenomenon exists, simplifying the mechanisms
531 underlying coexistence and instead concentrating on the impact of host heterogeneity and
532 zoonotic transmission on livestock AMR interventions. Additionally, the primary result of this
533 study, increases in the prevalence of disease following antibiotic curtailment, is robust across
534 models that explicitly incorporate population and within-host level mechanisms that drive
535 coexistence [63]. However, we note that the existence of the ζ parameter prevents the model
536 from being considered a neutral-null model due to the presence of “immigration infections”,
537 that is infections that cannot be traced back through a chain of infection events back to initial
538 infectives [64]. However, it is worth noting that the exclusion of ζ resulted in a poorer model
539 fit compared to where the parameter is present (Figure S8). Further exploration into the

dynamics of curtailment of antibiotic usage in livestock may benefit from explicitly modelling this general background transmission rate as an environmental reservoir of infection.

Large variability exists in both literature and the explored case studies regarding the relationship between livestock/human antibiotic usage and resistance, ranging from non-significant to significant across the four explored case studies (Figure S5, Table S2). Due to the historical lack of high-quality AMR surveillance and presence of confounding factors, it is difficult to disentangle whether observed significant relationships are due to a genuine relationship between usage and resistance or due to the inherent noise associated with AMR surveillance data [65]. This is important to recognise, as the extent of increases in the daily incidence of salmonellosis upon curtailment of antibiotic usage in livestock is determined through fitting modelled livestock dynamics to a presumed direct relationship between usage and resistance.

However, our key message, specifically that potential increases in the daily incidence are likely to be low and potentially controllable through interventions targeting the farm-to-fork pathway, is robust to these uncertainties and variations in the data. To highlight the robustness of our results to uncertainty in the surveillance data, we describe two hypothetical scenarios concerning the "real" relationship between antibiotic usage and resistance. Firstly, if the true relationship between usage and resistance is not real, then we would expect to see negligible increases in the daily incidence of foodborne disease in humans. This is due to the effects of transmission-related fitness costs (α) being an important parameter in driving both relative changes in resistance and increases in the daily incidence of foodborne disease upon curtailment (Figure 4A, S17). Therefore, if there is a weak/no association between antibiotic

564 usage and resistance due to negligible fitness costs, then increases in incidence will also be
565 unimportant and of limited public health concern. Secondly, if a significant relationship
566 between usage and resistance was observed, then we have also demonstrated in this study
567 that the associated increases in daily incidence of salmonellosis following antibiotic
568 curtailment can be controlled through ensuring good biosecurity at the farm-to-fork-pathway
569 (Figure 4).
570
571 The results from this study suggest that curtailment of antibiotic usage in livestock may have
572 unforeseen effects, with a reduction in both livestock and human antibiotic resistance, but
573 with increases in the livestock carriage and onwards transmission of foodborne pathogens
574 such as *Salmonella* spp. to humans. However, potential increases in the daily incidence of
575 salmonellosis range from negligible to preventable through interventions that target animal-
576 to-human transmission routes. The efficacy of these interventions suggests that a one-health
577 approach with a focus on improving farm-to-fork hygiene to minimise human disease is
578 essential when considering potential strategies to tackle the AMR crisis.
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Authors' Contributions

A.L.K.M. participated in the study design, carried out model analysis and drafted the manuscript. B.A.D.v.B. participated in the study design and provided feedback on manuscript drafts. M.E.J.W. participated in the study design and provided feedback on manuscript drafts. J.A.W. provided feedback on manuscript drafts.

Data Availability

Datasets and reproducible code can be found available from https://github.com/alexmorgan1995/FoodborneDisease.

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Conflict of Interest Statement

All authors declare that they have no conflicts of interest.

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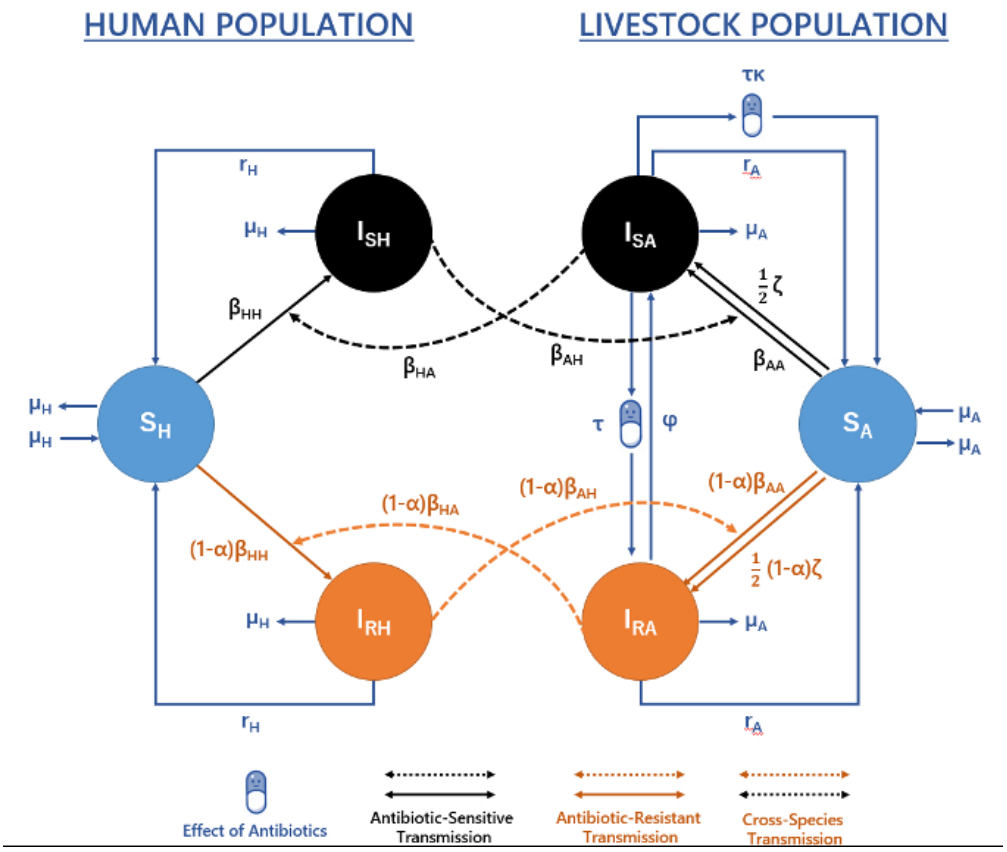

Figure 1. Model structure describing the transmission of foodborne pathogens between/within livestock and human populations. Model equations and parameters can be found described in the supplementary material (eqn S1.1, Table S5).

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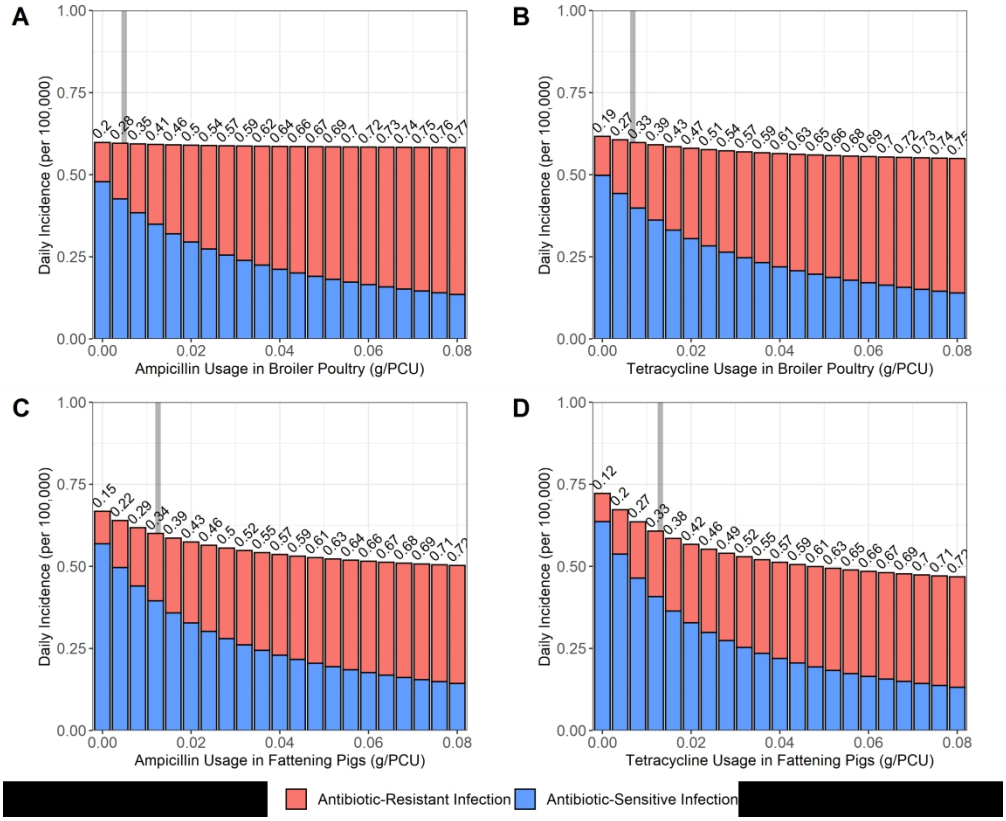

Figure 2. Impact of alterations in antibiotic usage in livestock (τ) on the daily incidence of salmonellosis and the proportion of resistant human infection (I*RHProp). A) Ampicillin-resistant human salmonellosis from broiler poultry. B) Tetracycline-resistant human salmonellosis from broiler poultry. C) Ampicillin-resistant human salmonellosis from fattening pigs. D) Tetracycline-resistant human salmonellosis from fattening pigs. Grey bar denotes the case study specific baseline antibiotic usage in livestock (□ = 0.0035/0.0049/0.0081/0.0109). Numbers above the bars denote I*RHProp. Information on the model fitting procedure and the fitted daily incidence and I*RHProp for each case study can be found in the supplementary material (Table S6).

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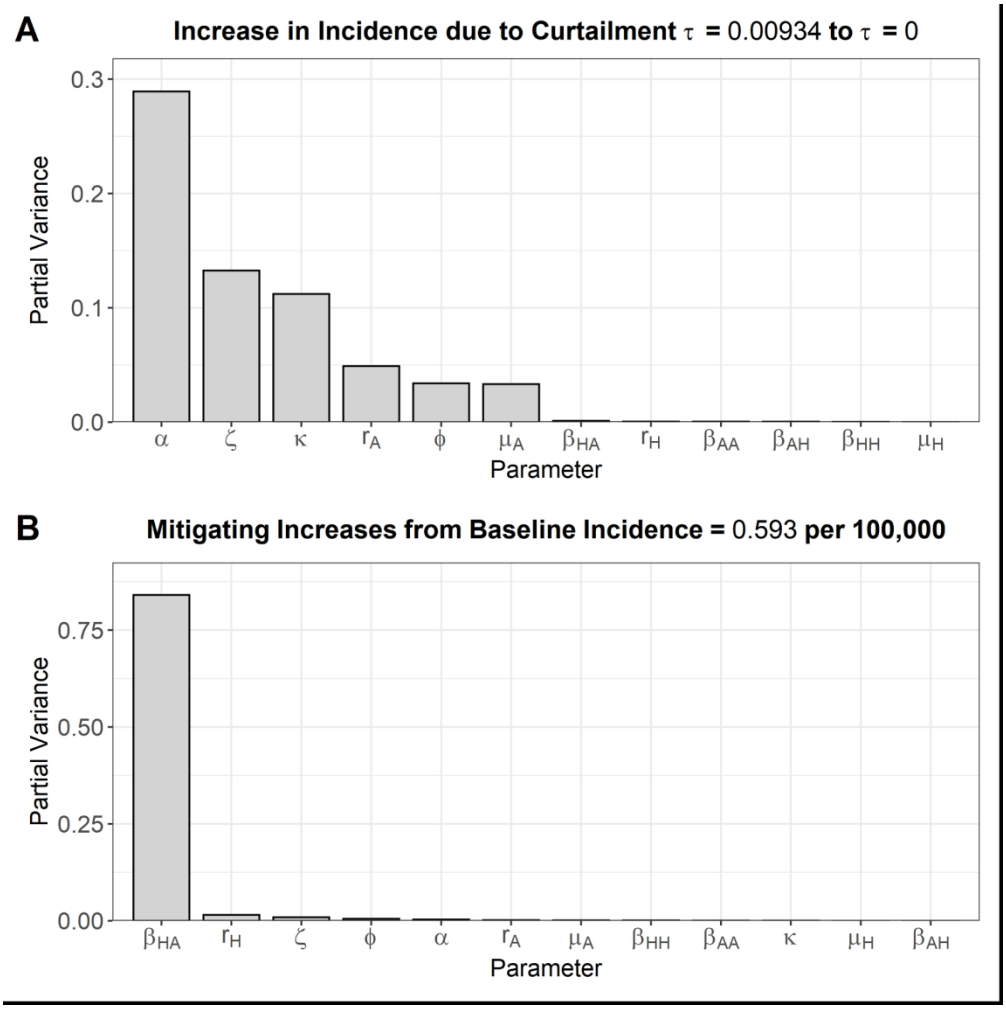

Figure 3. Fourier amplitude sensitivity test (FAST) to identify the most influential model parameter for: A) Relative change in daily incidence under curtailment (0 g/PCU) compared to the averaged baseline antibiotic usage level (0.00934 g/PCU). B) Mitigating changes in daily incidence under curtailment compared to the level of foodborne disease experienced under current levels of antibiotic usage in livestock (0.593 per 100,000 population). Higher bars indicate greater sensitivity. A FAST analysis of baseline model outcome measure, daily incidence and I*¬RHProp was also performed (Figure S14).

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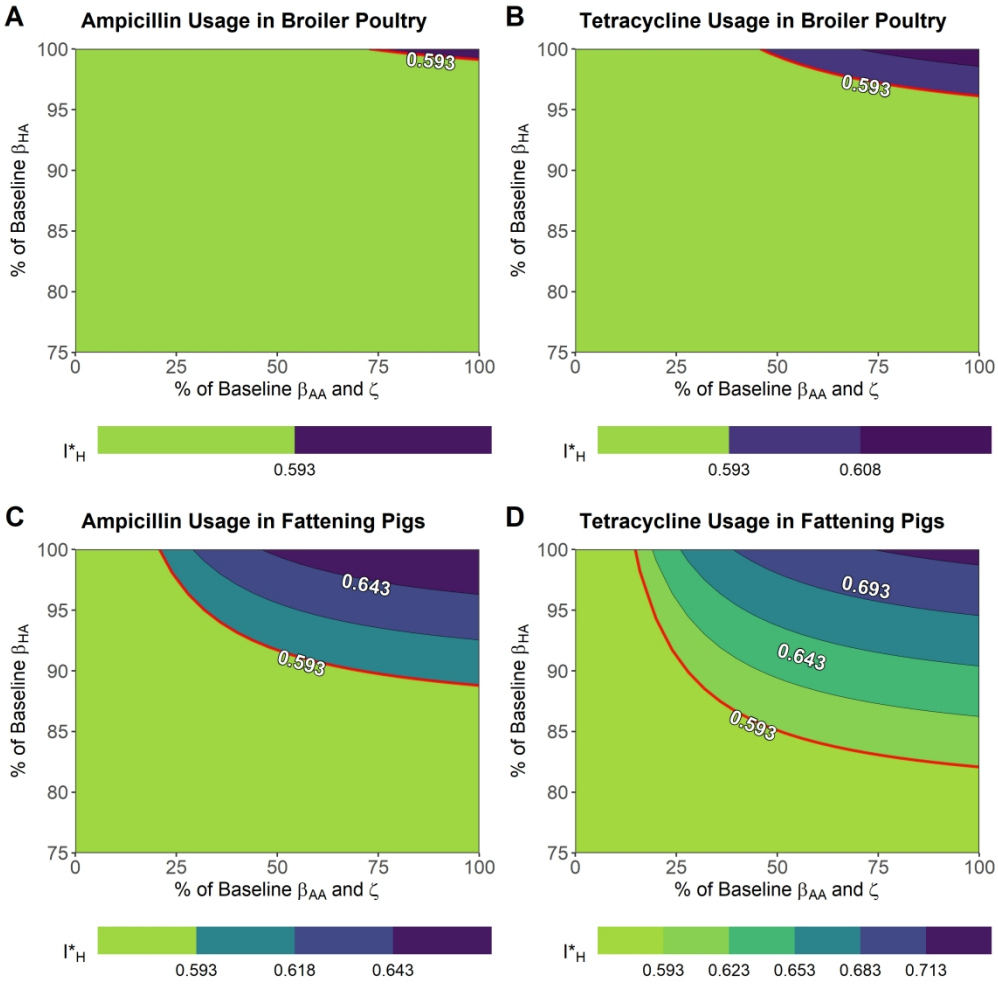

Figure 4. Reductions to key model parameters, animal-to-human transmission (βHA), animal-to-animal transmission (βAA) and the background transmission rate to animal populations (ζ) to mitigate increases in the daily incidence of salmonellosis under curtailment of antibiotic usage in livestock (τ = 0 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.

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