**Understanding the role of global food trade on the transmission dynamics of antibiotic-resistant foodborne bacteria**

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**ABSTRACT**

**INTRODUCTION**

1. Resistance is a big issue – specifically the resistance that might occur from livestock.
2. This is part of this one health issue – with studies often exploring the impact of transmission from livestock
3. However transmission from livestock is a multifaceted issue – transmission can come in the form of direct contact with domestic livestock, food products from domestic sources, but also from imported sources
4. Note some studies which have done this – the Ludden et al study as an example – which sampled food products from local supermarkets which obviously have food products from imported sources
5. But also mentioned that this often is not done – there needs to be more of an emphasis to explore the heterogeneity in terms of AMR transmission from livestock populations – to stratify the livestock population into both imported and domestic
6. This is important considering the implications of having heterogeneity in terms of transmission pressure – for example – give examples of other mathematical models showing that heterogeneity in terms of transmission pressure
7. This is therefore also the case in terms of AMR in a one health context – many reviews have stated that to understand AMR mechanistically from a modelling POV – we need to understand how the different sources of AMR might also contribute to AMR transmission
8. One such example is understanding how import of AMR on food products from different sources may also impact AMR transmission to humans – especially from livestock
9. This is an important aspect to consider considering a slow increase in food products over the next few years – the increase in the population requiring food to be imported
10. A likely reliance on imported food – and Brexit signing deals with countries with less than stellar food safety records
11. Means it makes sense to explore the impact of imported food products on the overall dynamics
12. We seek to explore the effect of heterogeneity in transmission pressure from livestock populations through the use of a compartmental metapopulation type model where we try to understand the impact of stratifying livestock antibiotic usage
13. We try to understand the impact on the impact of interventions such as the effect of curtailing livestock antibiotic usage when there is an import fraction.

**METHODS**

**Homogenous Import Model**

A compartmental model was developed to describe the transmission of antibiotic-resistant and antibiotic-sensitive *Salmonella* spp. from domestic and imported livestock food products to humans (**Figure 1**). *Salmonella* spp. transmission dynamics were modelled explicitly for domestic livestock and human populations, with each modelled population stratified based on their 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 (**SUPPLEMENTARY**).

The influence of imported food products was modelled as a constant transmission pressure to human populations. The proportion of imported food products contaminated with either antibiotic-sensitive/resistant *Salmonella* spp. was modelled as a function of the proportion of contaminated food products that are antibiotic-resistant (PropResImp) and the proportion of contaminated food imports with *Salmonella* spp. (FracImp). The proportion of food imports contaminated with antibiotic-sensitive bacteria follows the same calculation, is defined as the complement of the former parameter (1-PropResImp). We term this model, the “homogenous” import model.

Two transmission routes of antibiotic-sensitive/resistant *Salmonella* spp. were modelled. Domestic animal-to-animal transmission (βAA) and transmission from contaminated domestic/imported livestock animal carcasses/food products to humans (βHA). This βHA parameter represents either direct transmission from the carcasses or through food-borne transmission following further processing in the farm-to-fork pathway. Human-to-human and human-to-animal transmission routes were not modelled due to the focus of the study on the transmission dynamics of foodborne transmission of *Salmonella* spp. and the negligible role of both pathways on the foodborne transmission ([Infection with Salmonella (cdc.gov)](https://www.cdc.gov/training/SIC_CaseStudy/Infection_Salmonella_ptversion.pdf)). A relative scaling parameter was also used to model the relative reduction in *Salmonella* spp. prevalence from domestic livestock carriage to contamination on domestic livestock carcasses (η).

A background rate of transmission in the livestock population was also modelled to represent infection of livestock hosts from non-livestock sources (ζ). This 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.

A parameter (τ) was used to describe the selective pressure and therapeutic effect of antibiotic usage in domestic livestock. The selective pressure of livestock antibiotics was modelled as a single transition rate, encompassing a range of evolutionary and biological phenomena that convert livestock between antibiotic-sensitive to resistant states. Similarly, a single reversion parameter (φ) was used to encompass a range of different biologically plausible phenomena that may cause reversion of antibiotic-resistant (IRA) to sensitive strains (ISA). **A description of these biologically plausible phenomena can be found in the methodology for Chapter 2.**

The relative proportion of domestic food consumption from domestic livestock sources was modelled as ψ, with 1-ψ representing the extent of human food products sources from imported non-domestic sources. References to “increases in importation” (ψ → 0) or “decreases in importation” (ψ → 1) refer to alterations to this parameter.

**Heterogenous Import Model**

To explore the effects of import heterogeneity on antibiotic-sensitive/resistant *Salmonella* spp. transmission dynamics, the import pressure (FracImp, PropResImp) was stratified into multiple parameters. This represents the different countries that would constitute the food trade network for the domestic country (**Figure 2**), with each importing countries requiring individual parameterisation regarding the proportion of contaminated food imports with *Salmonella* spp and the proportion of contaminated food products that are antibiotic-resistant. As an example, if we have n = 10 importing countries, FracImp and PropResImp can be defined as: FracImp ϵ [FracImp1, …, FracImpn] and PropResImp ϵ [PropResImp1, …, PropResImpn].



Figure 2. **Model structure describing the transmission of foodborne pathogens between/within livestock and human populations in the model with increased import heterogeneity.** Model equations and parameters can be found described in the supplementary material ().

The increased heterogeneity in import also requires the addition of another set of parameters describing the relative share that each importing country contributes to the overall importation in the domestic country of interest, Share ϵ [Share1, …, Sharen]. Note that , due to the role of the parameter as a scaling factor.

**Model Case Study**

The United Kingdom was chosen as the “domestic” country of interest for the model. Therefore, the compartmental model, including dynamic livestock and human populations was parameterised with regard to UK livestock/human outcome measures.

The bug/drug/livestock population of interest was modelled as ampicillin usage/resistance in fattening pigs. This case study was chosen due to the high level of usage (both historical and current) of ampicillin in fattening pigs, and the availability of resistance data for this livestock species. We note that the model was not meant to imply that fattening pigs are the sole source of ampicillin-resistant Salmonella to humans. Rather it was intended to act as a case study to parameterise the data due to the difficulty in choosing a representative population to represent all possible drug/livestock combinations.

**Efficacy of Curtailment Outcome measure**

The primary outcome of interest for this study was the relative change in the proportion of contaminated food products that are antibiotic-resistant upon domestic livestock antibiotic curtailment (τ = 0.0009 g/PCU → 0 g/pCU). We term this relative reduction in the proportion of antibiotic-resistant human salmonellosis as the efficacy of curtailment (EoC) (eqn 1.1).

Eqn 1.1

This outcome measure is calculated at the long-term model non-zero steady state. Studying the system at an equilibrium state is a useful indication of the long-term dynamics of antibiotic-resistant salmonella infection and the long-term trajectory of the system. However, we recognise that the “real-world” dynamics of AMR are not temporally stable and in flux.

**Data Sources and Model Fitting**

An approximate Bayesian computation sequential Monte Carlo (ABC-SMC) approach was used to fit the model to the ampicillin usage/resistance in fattening pigs case study, using the United Kingdom as the domestic country of interest. This required the curation of three different datasets.

The first dataset was a usage/resistance dataset, curated to parameterise the relationship between livestock ampicillin usage and the proportion of contaminated food products that are antibiotic-resistant (**SUPPLEMENTARY**). The proportion of ampicillin-resistant isolates fattening pig carcasses was extracted from the respective European Food Safety Authority (EFSA) summary reports (**cite**). Ampicillin sales data was obtained from European surveillance of veterinary consumption (ESVAC) reports. A scaling calculation was required to convert the generic ampicillin sales for livestock to a value specific to fattening pigs with sales described as grams per population correction unit (g/PCU). **Details of this scaling calculation and proof of the temporal stability of the data can be found in the supplementary information for chapter 2**. Note that due to a lack of accurate country-level antibiotic usage data, sales were assumed to be a proxy for usage.

The second dataset was curated to import-relevant PropResImp, FracImp and Share parameters. Data from the UK Department for Environment & Rural Affairs (DEFRA) was used to identify the UKs major livestock food product trade partners. The EU was stratified into nine distinct import sources/countries: Netherlands, Irish Republic, Germany, France, Spain, Italy, Belgium, Poland, Denmark, and a single non-EU import source. Scaling calculations were required to determine the relative contribution of these ten contributors to the UKs food supply for general livestock food products (ψ = 0.656) and swine-specific food products (ψ = 0.4455). **Details of these scaling calculations can be found in the supplementary material**. Note that data on the contribution of domestic, EU and nEU countries/regions for general livestock food products (ψ = 0.656) was used for baseline model parameterisation. Data on the proportion of *Salmonella* spp. contaminated food imports (FracImp) was obtained from ECDC surveillance reports, with contamination data obtained from 400cm2 swabs and competent authority (CA) surveillance prioritised. Data on the proportion of isolates obtained from contaminated swine carcasses that are antibiotic-resistant was obtained from EFSA surveillance reports. This was used as a proxy for the proportion of contaminated food products that are antibiotic-resistant (PropResImp).

The third dataset focused on data regarding UK-specific livestock/human outcome measures to act as targets for model fitting. Baseline UK ampicillin usage/sales for the ampicillin-resistance in fattening pigs case study was considered the unweighted average ampicillin usage observed across 2015-2018 for the UK (τ = 0.0009 g/PCU). The observed ECDC daily EU incidence of human salmonellosis was used as a proxy for the baseline incidence of UK salmonellosis (0.593 per 100,000). This proxy was chosen due to the lack of multiplication factors available to scale UK-specific reported incidence of salmonellosis to community levels (**cite BCoDE**). The proportion of ampicillin-resistant UK human salmonellosis was obtained from 2015-2018 ECDC AMR summary reports (0.207). The proportion of ampicillin-resistant UK livestock Salmonella spp. carriage was parameterised from 2015-2018 EFSA surveillance reports (0.417). The extent of contamination in UK swine carcasses was calculated from 2015-2018 ECDC one health surveillance reports (0.0628). **Details of the calculations to determine these UK-specific outcome measures can be found in the supplementary material** (**SUPPLEMENTARY**)**.**

The η scaling parameter was also parameterised using UK specific epidemiological data, with a caecum carriage of Salmonella spp. in UK fattening pigs of 32.2% ([Abattoir-based study of Salmonella prevalence in pigs at slaughter in Great Britain | Epidemiology & Infection | Cambridge Core](https://www.cambridge.org/core/journals/epidemiology-and-infection/article/abattoirbased-study-of-salmonella-prevalence-in-pigs-at-slaughter-in-great-britain/3FDEA88F8CF084908FC34C7A6A57052E)). This information was combined with data on the extent of UK Salmonella spp. contamination on fattening pig carcasses (2.87%), to parameterise a 88.98% reduction from carriage to contamination in UK livestock (η = 0.1102).

**ABC-SMC Model Fitting**

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

Four additional summary statistics were used in the fitting approach: 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 ampicillin-resistant human salmonellosis at baseline antibiotic usage and the UK-specific proportion of resistant human salmonellosis (0.207), 3) minimise the difference between the model estimated prevalence of *Salmonella* spp. contamination on swine carcasses and the value observed for surveillance data (0.0628) and 4) minimise the difference between the model estimated proportion of contaminated food products that are antibiotic-resistant and the proportion observed in EFSA averaged data (0.417).

An ABC-SMC approach was used for both homogenous and heterogenous import models (Figure 1-2) to fit the model to available datasets. For the first model, the ABC-SMC approach was used to estimate the marginal posterior probability distribution for six model parameters (θHOM) given the data, . The heterogenous import model required the estimation of eight model parameters (θHET). Non-EU parameters were fitted due to the heterogeneity in the values across UK non-EU trading partners. Other model parameters were not fitted as estimates with high levels of certainty were available (rH, rA, μA and μH). Prior distributions for each fitted parameter can be found in the supplementary material (**Table S4**).

The ABC-SMC approach was run for eight generations, with each generation running until the acceptance of 1000 particles. Acceptance thresholds for each distance measure and summary statistic (ε) can be found in thesupplementary material (Table S5). A multivariate normal distribution was chosen for the ABC-SMC perturbation kernel. The randomly sampled mean and covariance matrix was calculated from the previously accepted generation of accepted particles. An intersection metric was used to ensure that accepted particles satisfied tolerance values set for the distance measure for each calculated for each summary statistic per generation.

Mean point estimates from the approximated marginal posterior probability distributions of the 8th 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 S3).

**Sensitivity Analysis**

Latin-hypercube sampling partial rank correlation coefficient (LHS-PRCC) and extended Fourier amplitude sensitivity test (eFAST) approaches were used to conduct sensitivity analyses on both study models (Figure 1, 2) with regard to the efficacy of curtailment outcome measure. Supplementary sensitivity analyses were also conducted to identify important parameters regarding the incidence of human Salmonellosis and the proportion of ampicillin-resistant human salmonellosis outcome measures. Monotonicity analyses were performed for model parameters to identify potential non-monotonicities before conducting LHS-PRCC analyses. The parameter range chosen for the sensitivity analysis was limited to an order of magnitude above and below the fitted mean point estimate for each model parameter.

**RESULTS**

The homogenous import model was fitted to the UK case study for ampicillin-resistance/usage in fattening pigs (**Figure 4A**). Approximated marginal posterior probability distributions for the fitted model parameters from the ABC-SMC approach and respective model diagnostics can be found in the supplementary material (**SUPPLEMENTARY**). An **X** fold increase in the incidence of human salmonellosis was observed, with an increase from **X** per 100,000 population under baseline antibiotic usage (τ = 0.0009 g/PCU) to **X** per 100,000 population when antibiotics are curtailed (τ = 0 g/PCU) (**Figure 4B**). The proportion of ampicillin-resistant human salmonellosis decreased from **X** to **X** when antibiotics were curtailed. This represents an efficacy of curtailment of **X**% (supplementary material).

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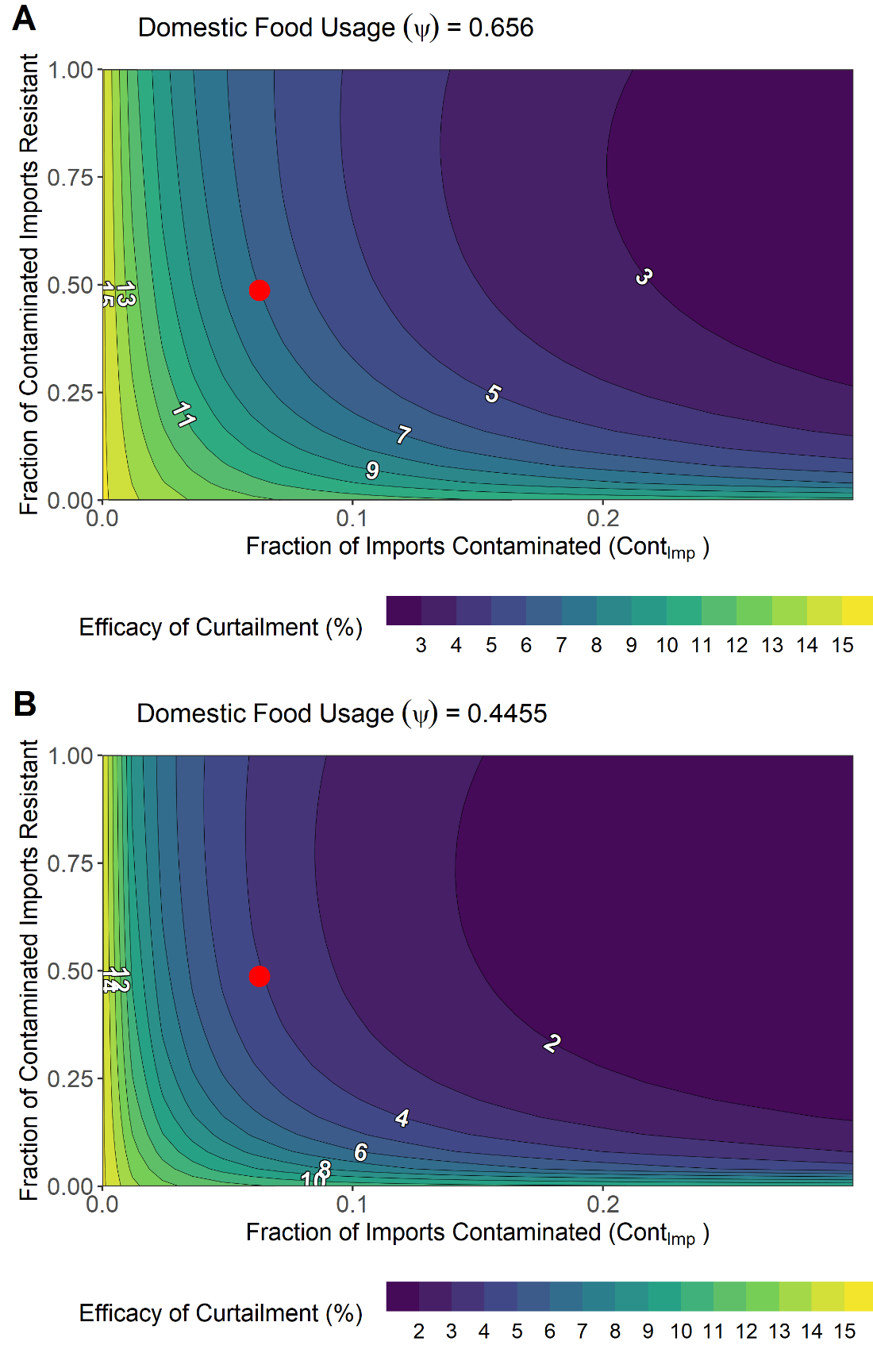
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**Figure 4. A) Observed/estimated relationship between livestock ampicillin usage and ampicillin-resistant salmonellosis in humans using the homogenous model. B) Impact of alterations in livestock ampicillin usage on the daily incidence of salmonellosis and the proportion of ampicillin-resistant salmonellosis.** Solid purple lines/ribbons represent model fit resulting from the approximated posterior distribution and the corresponding 95% HDI. 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. Red square and denotes the target level of ampicillin-resistance (0.4167) for baseline levels of UK ampicillin usage (τ = 0.0009 g/PCU), the latter also being represented by the dotted red line.

Increasing the relative proportion of UK food consumption from domestic livestock sources from a value consistent with general livestock produce (ψ = 0.656), to a value more consistent with swine livestock produce (ψ = 0.4455), resulted in an overall increase in the incidence of salmonellosis (X -> X per 100,000) and the proportion of ampicillin-resistant human salmonellosis (X% -> X%) at baseline antibiotic usage (τ = 0.0009 g/PCU) (**SUPPLEMENTARY**). Note that the proportion of contaminated food products that are antibiotic-resistant and the proportion of contaminated food products was higher in imported sources (FracImp = ; PropResImp = ) than in domestic sources (0.00; 0.04). Fitting the model without importation, results in qualitative curtailment dynamics similar to the homogenous import model (**SUPPLEMENTARY**). However, note that due to the lack of import pressure, the efficacy of curtailment will be higher, with a less ampicillin-resistant human salmonellosis attributable to imports and therefore more controllable through domestic interventions.

A sensitivity analysis using LHS-PRCC and eFAST approaches identified the proportion of ampicillin-resistant contaminated imports (PropResImp) and the transmission-related antibiotic resistance fitness cost (α), as the most important parameters for determining the proportion of ampicillin-resistant human salmonellosis (**SUPPLEMENTARY**). The animal-to-human transmission rate (βHA), the proportion of imports contaminated (FracImp) and the proportion of UK food supply from domestic sources (ψ) were important for determining the incidence of human salmonellosis (**SUPPLEMENTARY**).

We next identified the effect of import-relevant parameters in a scenario analysis by altering the proportion of imports contaminated (FracImp) and the proportion of ampicillin-resistant contaminated imports (PropResImp) and observing the effect on the efficacy of curtailment outcome measure (**Figure 5**). Explored parameter ranges were limited to ground the analysis (FracImp ϵ [0, 0.3], PropResImp ϵ [0, 1]), with these ranges observed in ECDC datasets (**cite**).



**Figure 5. Impact of altering FracImp and PropResImp import parameters on the efficacy of curtailment for two values of the proportion of UK food supply from domestic sources (ψ). A) General livestock import case study (ψ = 0.656). B) Swine food product import case study (ψ = 0.4455).** Red dot represents the baseline parameterisation for FracImp and PropResImp parameters from ECDC data (FracImp = 0.0628; PropResImp = 0.487).

Increasing proportion of imports contaminated and the proportion of ampicillin-resistant contaminated imports to the maximum explored values (FracImp = 0.3; PropResImp = 1) decreased the efficacy of curtailment relative to baseline parameterisation, with EoC being reduced from ~7% to ~2% (**Figure 5A**). Eliminating ampicillin-sensitive/resistant contamination on imports (FracImp = 0; PropResImp = 0) had the opposite effect, with an EoC of X%. A related phenomenom was also observed with decreases to the proportion of UK food supply from domestic sources (importing more) (ψ = 0.4455), with maximal reductions to FracImp and PropResImp compared to baseline (ψ = 0.656) resulting in greater reductions to EoC (X% vs X%) (**Figure 5B**).

Increases to the relative reduction in *Salmonella* spp. prevalence from domestic livestock carriage to contamination on domestic livestock carcasses parameter (η = 0.20; poorer clearance) resulted in increases to the efficacy of curtailment (**SUPPLEMENTARY**). Decreases (η = 0.05; better clearance) resulted in the opposite effect when compared to equivalent reductions to FracImp and PropResImp in the baseline scenario (η = 0.1102).

An LHS-PRCC and eFAST sensitivity analysis was next conducted to assess the importance of model parameters on the efficacy of curtailment (**Figure 6**). Monotonicity plots were used to identify any potential non-monotonic behaviour (**SUPPLEMENTARY**). Among import parameters, the proportion of UK food supply from domestic sources (ψ) had a strong effect of increasing the efficacy of curtailment (coef) (**Figure 6A**). The proportion of ampicillin-resistant contaminated imports had a strong effect of reducing the efficacy of curtailment, with the extent of contamination on imported food products (coef) having a small effect of reducing the efficacy of curtailment (coef). The importance of these import parameters is corroborated by the relative height of the sensitivity indices for the first order effects in the eFAST analysis (**Figure 6B**). Second order effects comprised the majority of the variation explained by the PropResImp parameter, suggesting that interactions with other model parameters are necessary for PropResImp to affect efficacy of curtailment.



**Figure 6. Sensitivity analyses for the efficacy of curtailment (EoC) outcome measure. A) Latin hypercube sampling partial rank correlation coefficient test (LHS-PRCC). B) Extended Fourier amplitude sensitivity test (eFAST).** Note that 95% confidence intervals for each correlation coefficient was generated through generating n = 100 bootstrap replicates. The remaining proportion of the total order effects after accounting for first order effects in the eFAST can be considered the second order effects for each explored model parameter.

Among non-import related parameters, the rate of livestock recovery from *Salmonella* spp. carriage (rA) had a strong effect of reducing the efficacy of curtailment when increased (coef) (**Figure 6A**). The efficacy of antibiotic-mediated livestock recovery (κ), transmission related fitness costs associated with antibiotic-resistance (α), the per capita rate of background transmission to livestock populations (ζ) and the relative reduction in *Salmonella* spp. prevalence from domestic livestock carriage to contamination on carcasses (η) had moderate effects on increasing the efficacy of curtailment (coef).

**Section 2**

To assess the effect of heterogeneity in importation on AMR dynamics, we fit the model with heterogenous import to the study datasets (**Figure 7A**). Import was stratified into ten distinct importing countries based on the UKs major trading partners for livestock food products: Netherlands, Irish Republic, Germany, France, Spain, Italy, Belgium, Poland, Denmark, and general non-EU import. Approximated marginal posterior probability distributions for the fitted model parameters from the ABC-SMC approach and the respective diagnostics can be found in the supplementary material (**SUPPLEMENTARY**).

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**Figure 7. A) Observed and estimated relationship between livestock ampicillin usage and ampicillin-resistant salmonellosis in humans using the complex model. B) Impact of alterations in domestic livestock ampicillin usage (τ) on the daily incidence of human salmonellosis. C) Impact of alterations in domestic livestock ampicillin usage (τ) on the proportion of ampicillin-resistant human infection.** Solid red lines and ribbons represent model fit resulting from the approximated posterior distribution using ABC-SMC and the corresponding 95% HDI. 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. Red square denotes the target level of ampicillin-resistance (0.4167) for baseline levels of UK ampicillin usage (τ = 0.0009 g/PCU).

We note similar X-fold increases in the overall incidence of salmonellosis (X per 100.000) and X-fold decreases proportion of ampicillin-resistant human salmonellosis (.00%) compared to the previously described model (**Figure 7B-C**). Under baseline livestock ampicillin usage (τ = 0.0009 g/PCU), the majority of overall and ampicillin-resistant human salmonellosis was attributed to domestic livestock (X%), with X% attributed to EU countries and X% attributed to non-EU sources. The extent attributable to domestic livestock to domestic livestock decreased in both outcome measures (X%; X%) when domestic ampicillin usage was curtailed (X%; X%) (**SUPPLEMENTARY**).

Alterations to the proportion of UK food from domestic livestock (ψ) were next explored in relation to the efficacy of curtailment (EoC) outcome measure (**Figure 8**). Efficacy of curtailment under baseline levels of import (ψ = 0.656) was 7% and reached a minimum/maximum value of X% and X% when under full import (ψ = 0) and no import respectively (ψ = 1). The shape of the EoC/ψ relationship under baseline parameterisation resembled an exponential-type curve, with a low efficacy of curtailment at high-moderate values of import and only increasing to the maximum EoC value at high levels of domestic usage (ψ).

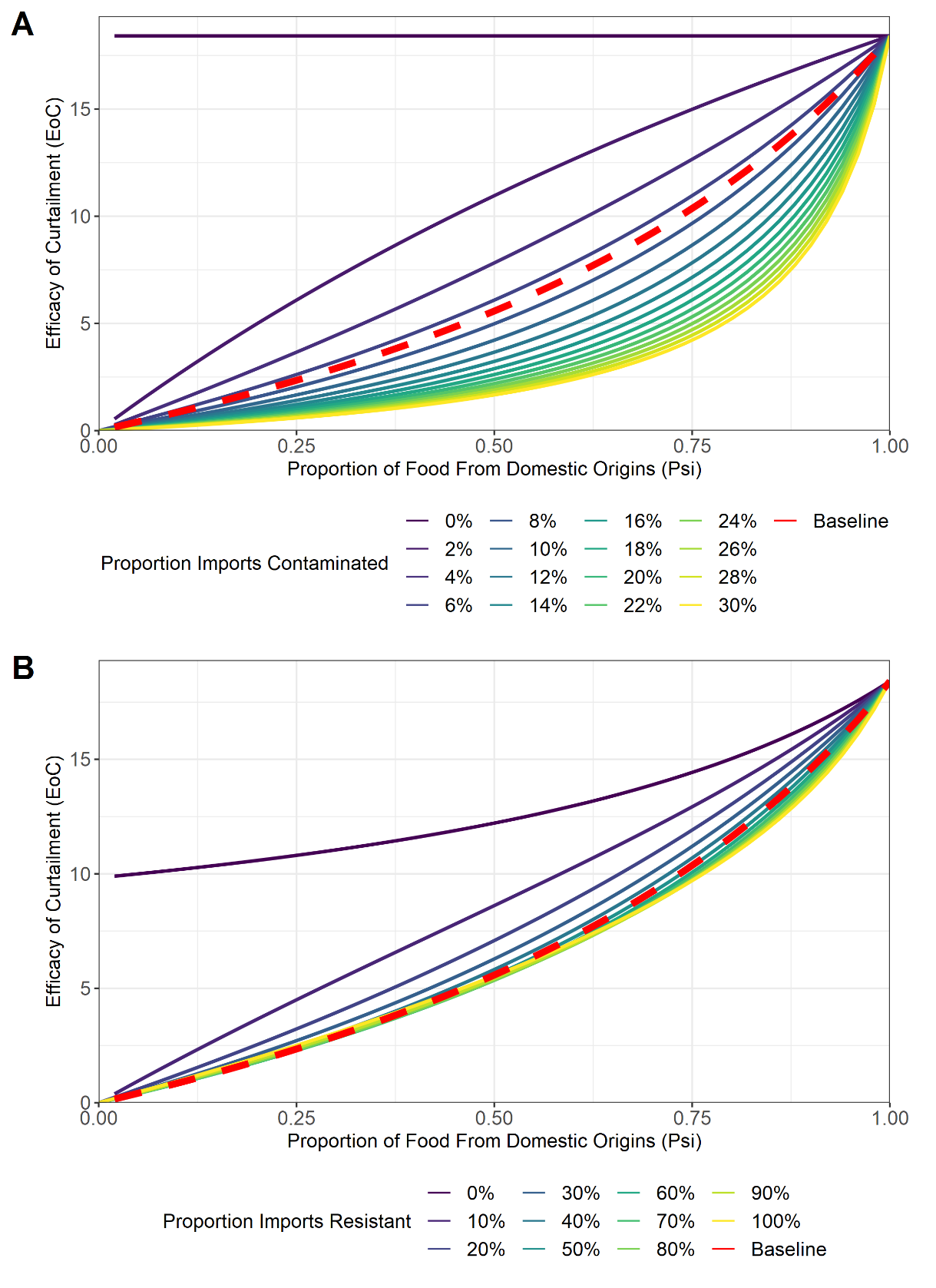
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**Figure 8. Relationship between the proportion of UK food products (ψ) and the efficacy of curtailment (EoC) for baseline parameterisation.** Using the values of EoC for the maximum and minimum values of ψ, we can split the figure into two sections: an area where import has a greater negative impact on lowering EoC (red area) and an area where import has a lower negative impact on lowering the EoC (green area).

We can define two areas on the EoC/ψ plot, defined by the minimum and maximum value of EoC obtained under full and no importation () **Figure 8**). The first area contains EoC/ψ curves similar to the baseline relationship (bottom-right of plot), where EoC is low for a large range of import values, and increasing rapidly when import is at low levels. This has a EoC/ψ curve with a shape similar to an exponential growth curve and we can denote this area as “greater impact of import”. The second area contains EoC/ψ curves where EoC is high at relatively high levels of import (top-left of plot), but which plateaus as import is increased. This results in the EoC/ψ relationship having a shape akin to logarithmic growth and we can denote this area as “lower impact of import”. We note that the latter EoC/ψ curve shape is qualitatively better area for increasing importation, as high values of EoC can still be obtained despite the saturating effect of import on local interventions.

We next explored the effect of changing import characteristics across the ten importing sources on the relationship between the proportion of UK food from domestic sources (ψ) and the effiacy of curtailment (**Figure 9**). Explored parameters included the proportion of contaminated food products that are antibiotic-resistant (PropResImp) and the proportion of contaminated food imports with *Salmonella* spp. (FracImp). Note that when PropResImp/FracImp were altered, they were altered across all ten importing sources. Therefore, this represents an average change in PropResImp/FracImp across all importing sources.

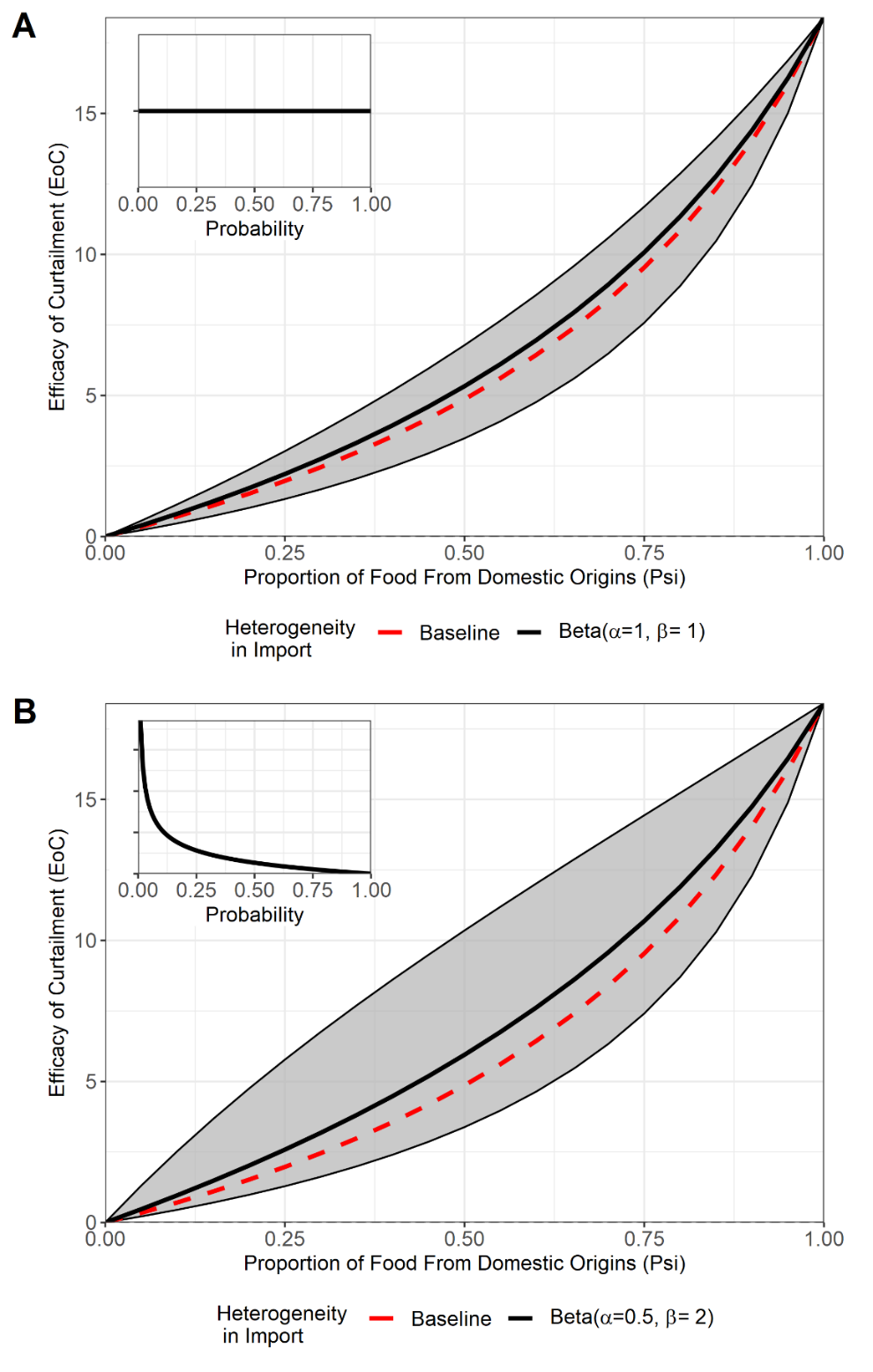


**Figure 9. Relationship between the proportion of UK food products (ψ) and the efficacy of curtailment (EoC) under different average parameterisation for FracImp and PropResImp across importing countries. A) Changes to the proportion of Salmonella spp. contaminated food imports across importing countries (FracImp). B) Changes to the proportion of ampicillin-resistant Salmonella spp. contaminated food imports across importing countries (PropResImp).** Baseline relationship between EoC/ψ is denoted by the red and dotted line. FracImp was ranged from, FracImp ϵ [0, 0.3], in accordance with the range of values observed in ECDC reports.

Decreasing the proportion of contaminated food imports (FracImp) across all importing sources to 0-4% resulted in a large shift in relationship between EoC/ψ curve to the “lower impact of import” area, where increases to import have less effect on reducing EoC (**Figure 9A**). The opposite phenomenon was observed with increases to the average FracImp above 8% with the relationship between EoC/ψ rapidly reaching a state where EoC was low across a large range of ψ values. A “saturation” type effect was also observed at higher values of FracImp, with the EoC/ψ relationship rapidly stabilising in a region where EoC remains low for a large range of ψ values. Intuitively, changes to ψ where the proportion of contaminated food imports was 0% had no impact on the EoC.

Altering the proportion of contaminated food products that are antibiotic-resistant (PropResImp) had less effect on the EoC/ψ relationship curve than alterations to FracImp (**Figure 9B**). However, decreasing PropResImp to relatively low levels (PropResImp > 20%) shifted the EoC/ψ curve into an area more favourable for import, with higher values of EoC for explored values of ψ. Interestingly, removing ampicillin-resistant contamination on imports (PropResImp = 0) resulted in changes ψ still having an impact on EoC. A “saturation” type effect was also observed with increases to PropResImp above ~40%, with minor effects on the shape of the relationship between EoC/ψ. Increases to the relative reduction in prevalence from domestic livestock carriage to contamination on carcasses (η) (lower levels of contamination) resulted in EoC/ψ relationship where EoC was low across a large range of values of ψ (**Supplementary**). Note that alterations to η result in a linear effect on changing the extent of *Salmonella* spp. on domestic livestock carcasses (**Supplementary**).

We next explored the effect of heterogeneity in the relative contribution to import across importing countries (Share) on the relationship between the proportion of UK food from domestic sources (ψ) and the effiacy of curtailment (**Figure 10**). The Share parameter was sampled ten times, corresponding to the ten modelled importing countries/regions in the heterogeneous import model, from two different beta distributions, Beta(α = 1, β = 1) and Beta(α = 0.5, β = 2). These distributions represent two hypotheses about importation, with the relative share of import being distributed equally across importing countries or import being prioritised from a select few countries. Note that the total sum of ShareX must sum to 1, therefore each group of ten samples was scaled by the sum of the samples, . Sampling was performed n = 1000 for each Beta distribution, and the average, minimum and maximum value of EoC for each explored value of ψ was identified.



**Figure 10.** **Relationship between the proportion of UK food products (ψ) and the efficacy of curtailment (EoC) under different assumptions regarding the heterogeneity of import from importing countries. A) Share samples from a uniform sampling distribution, Beta(α = 1, β = 1). B) Share samples from a “skewed” sampling distribution, Beta(α = 0.5, β = 2).** Note that the average, minimum and maximum value of EoC for each value of ψ, is denoted by the middle-black line, lower bound, and upper bound of the grey shaded area respectively.Baseline relationship between EoC/ψ is denoted by the red and dotted line.

Sampling from either Beta distribution resulted in minor changes to the average EoC/ψ relationship, with minor increases in EoC across explored ψ values to baseline parameterisation. However, sampling from the Beta distribution promoting more heterogeneity, Beta(α = 0.5, β = 2), resulted in a greater heterogeneity in the minimum and maximum EoC values observed for each value of ψ compared to the distribution promoting a more uniform share of import, Beta(α = 1, β = 1) (**Figure 10**). This suggests that a more heterogeneous distribution of import across importing countries may result in greater uncertainty with the outcome of changing the extent of importation on the efficacy of local curtailment interventions. As an example, the minimum and maximum EoC values for baseline values of ψ (ψ = 0.656) were X% and X% with Beta(α = 0.5, β = 2), compared to X% and X% for Beta(α = 0.5, β = 2).

**DISCUSSION**

**Recap the model results**

Mathematical models of importation were used to identify that increasing the extent of food importation from non-domestic sources may decrease the efficacy of domestic livestock antibiotic stewardship interventions in the context of resistant human foodborne infections. This was explored across a realistic UK-specific case study for ampicillin-resistant Salmonella spp. in fattening pigs. Import parameters such as the … and … are important for reducing the efficacy of local livestock antibiotic curtailment in reducing the extent of antibiotic-resistant human infections. Increasing the level of heterogeneity in import parameters had little effect on the average relationship between import and the efficacy of curtailment, with the average level of … and to a lesser extent … driving the majority of changes in the relationship between the efficacy of curtailment and import. Specifically, the average prevalence of Salmonella contamination on imports must be driven to near elimination for importation to have a negligible effect on the efficacy of domestic antibiotic curtailment. Heterogeneity in the relative distribution of imports across importing countries has an effect of increasing the potential uncertainty with the relationship between import and the efficacy of curtailment

**Talk about import and how it affects out results** – but place in the relevance of other studies in AMR which show something similar – how robust are out study results

A key result of our study was identifying that external transmission pressures of AMR may affect AMR dynamics such as the withdrawl of antibiotic resistance on resistant human foodborne disease in our country of interest. This is not a new phenonomenom in disease modelling or in AMR literature with the influence of external sources of transmission affecting local patches and with the influence of other sources of AMR also affecting AMR interventions such as withdrawal of antibiotics in a local patch. The novel aspect of this work is to provide another study with similar aims but contextualised within a realistic case study such as foodborne disease.

We also identify why this phenomenom occurs with foodborne disease, which is an intuitive result. Increasing import results in an increase in the amount of foodborne disease both sensitive and resistant attributable to imported sources, which is not affecting by local livestock interventions. Therefore, interventions that increase this import attributable FBD, such as increases in the extent of contamination of imports, increasing the proportion of food from imported sources, and unintuitively, increasing the amount of biosecurity to reduce the prevalence on contamianted domestic food products all serve to increase the amount of foodborne disease attributable to imports.

* Relate this result to previous understanding in disease modelling literature – of changes in attributable infections and how this affects local interventions (maybe something with the Krieger study?)
* Maybe I can relate the other non-import model parameters in contributing to the efficacy of curtailment by relating it to decreases and changes in the attributable resistance etc.
  + i.e – this also extends to non-import related parameters. As an example rA has been found import – this is because ….

**Talk about the saturation effect**

* We identify two types of shapes for the relatiuonship between eoc/psi (and what do they mean)
* Why this shape is important – i.e – Understanding this shape is important due to the

It is interesting to note that the baseline relationship between the proportion of UK/domestic food attrituable to domestic sources and the efficacy of curtailment outcome measure resulted in a shape that makes import detrminetal to EoC.

This can likely be attributable to the balance between the average level of imported contamination and the level of contamiantion found on domestic carcasses. This can be observed with changes to the eta parameter pushing the contamiantion levels to the average level observed in the data – resulting in a lmore lienar relationship and a further reduction pushing the relationship more into he green area.s

Therefore understanding the baseline level of contamination is important – as an example for the UK this presents a problem. As the UK level of contamination is already excessively low – this means that the average level of import must also be pushed to an excessively low level to be able to increase the level of import and not result in an even worse relationship between psi/eoc. There is also an issue of a type of saturation effect occuring with increases in contamination – where beyond a certain amount it doesn’t matter naymore.

This presents a problem as it suggests that beyond keeping it near baseline levels of domestic cocntmainatioin -increasing level so f contamiantion will lead to the worst possible result. This is an incentive for public health policy for increased monitoring of contamiantion and a reassurance of policy to only accept imported food products which are as good or better contamination wise than doemstiuc product (cite oolicy like this)

**Talk about the lack of the effect of heterogeneity**

As identified in the results it is the average effect of fracimp and propresimp that affects the average relationshio

* The relative share of countries doesn’t really matter that much
* Why is this the case
* Maybe need to relate to mathemtical phenomenom

Talk about the public health implications of the results

* Either reduce contamination and resistance from importing countries or only import from low contamination countries

Why we used the case stuidy

* Would it look different with another resistabnce
* Would it look different with another foodborne disease or other pathogen
* Would it look different with another livestock species
* Would it look different with another case study – like with a country with high levels of domestic contamination and resistance – refer to the uncertainty analysis in the first part – which shows that as the import decreases or the level of contamination is worse – then the efficacy of curtailment will actually increase – but this would also result in a higher level of resistance and foodborene disease (more attribable to domestic sources – double edged sword).

Study limitations

* Inability to validate the atribale fraction from different countries – talk about source attribution studies – but mention why we cant use these
* Definitely need to talk about how there’s a balance between the four outcome measures and the overall relationship between usage and resistance – maybe another rmodel structure would be able to allow for a btter model fit
* Data limitations with the case studies – why ampicillin, fattenings pigs and the UK might not be presentative enough

Overall Conclusion Paragraph