**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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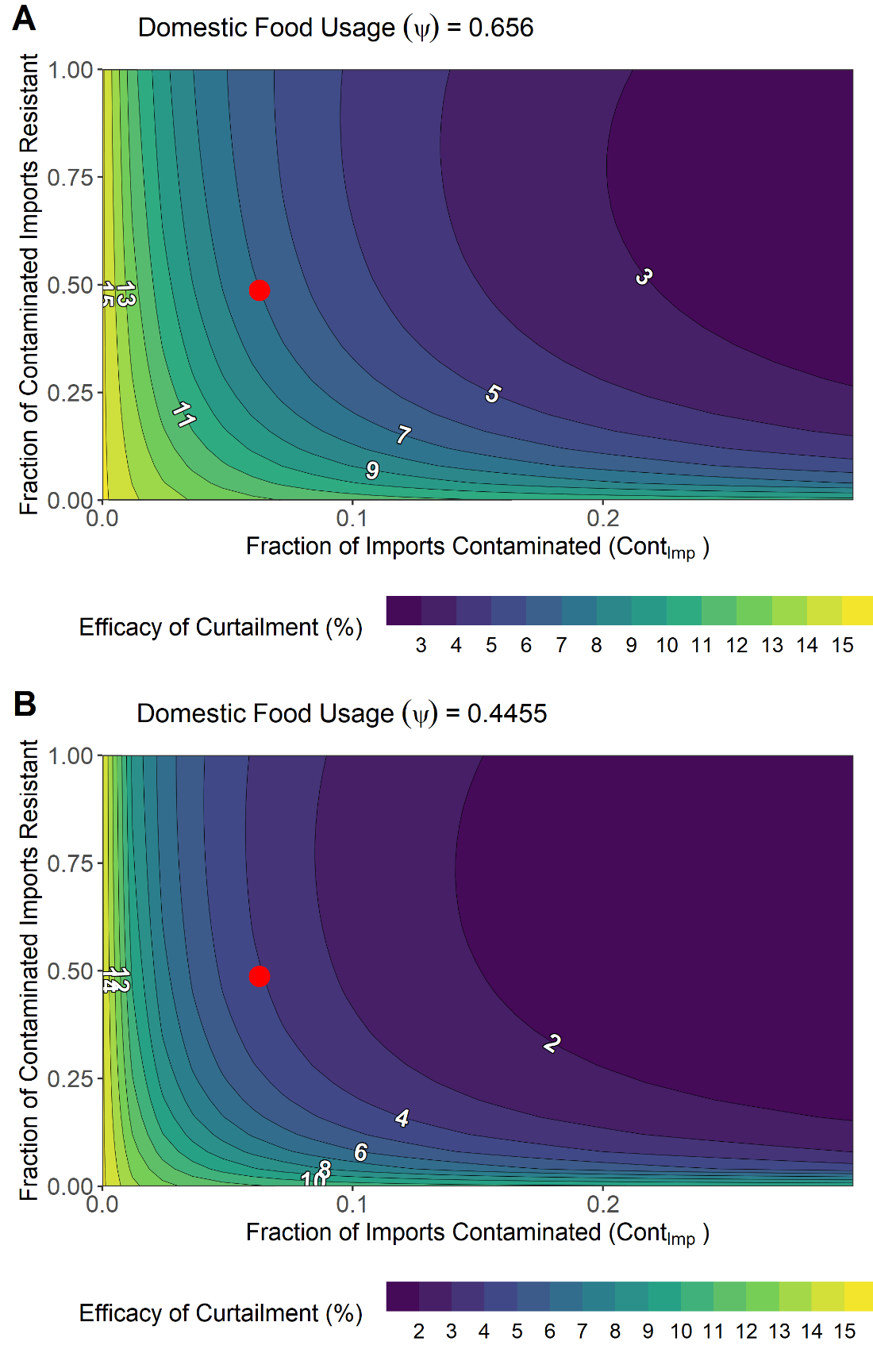
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**Figure 4. A) Observed/estimated relationship between livestock ampicillin usage and ampicillin-resistant salmonellosis in humans using the homogenous model. B) Impact of alterations in livestock ampicillin usage on the daily incidence of salmonellosis 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).

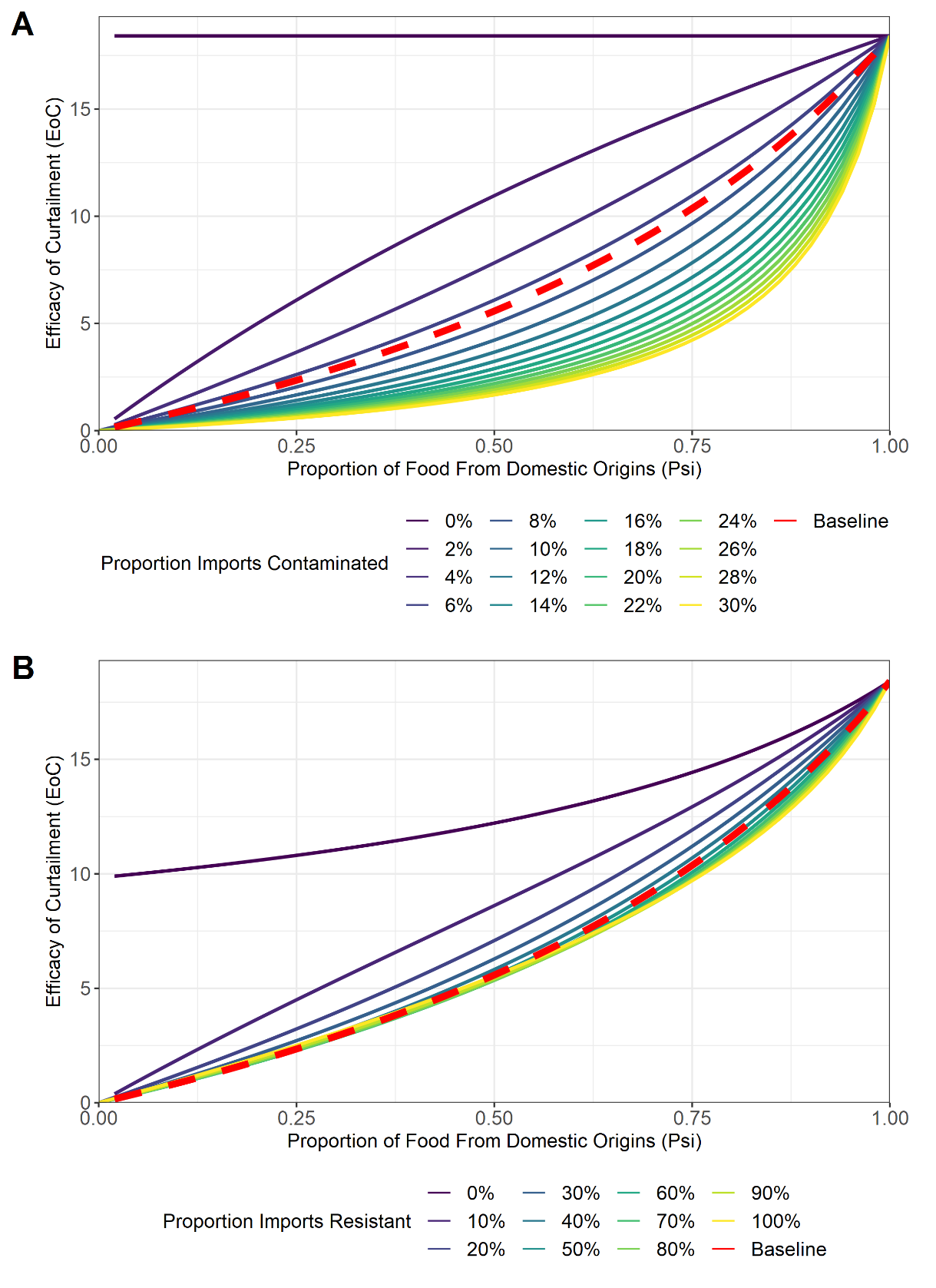
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**Figure 8. Relationship between the proportion of UK food products (ψ) and the efficacy of curtailment (EoC) for baseline parameterisation.** Using the values of EoC for the maximum and minimum values of ψ, we can split the figure into two sections: 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 relationships similar to baseline (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 relationship 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.

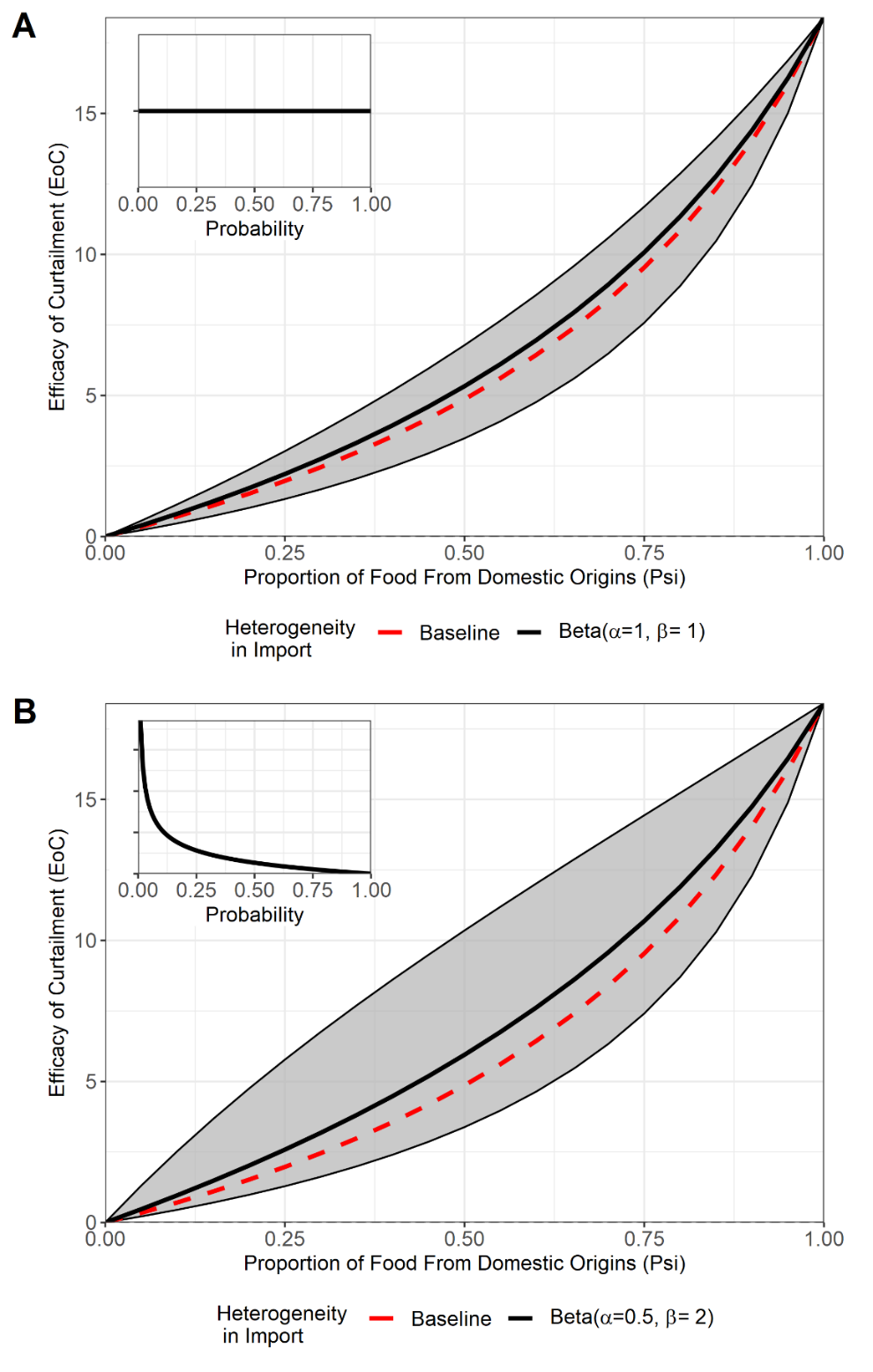


**Figure 9. Relationship between the proportion of UK food products (ψ) and the efficacy of curtailment (EoC) under different average parameterisation for FracImp and PropResImp across importing countries. A) Changes to the proportion of Salmonella spp. contaminated food imports across importing countries (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. 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**

**Talk about the public health implications of the results – can mention throughout**

**Recap the model results**

Two mathematical models of food importation were used to identify that increasing the amount of food importation from non-domestic sources may decrease the efficacy of domestic livestock antibiotic curtailment in the context of reducing antibiotic-resistance in livestock/humans. This was explored across a UK-specific case study for ampicillin-resistant *Salmonella* spp. in fattening pigs. Import parameters such as the proportion of UK food supply from domestic sources (ψ) and the extent of *Salmonella* spp. contamination on imports (FracImp) were important for reducing the efficacy of local livestock antibiotic curtailment. Expanding the homogenous import model to describe heterogeneity in import identified that under a UK-specific case study, increasing the extent of non-domestic food product usage (import) resulted in sharp decreases in the efficacy of local livestock antibiotic curtailment. Increases to the average extent of *Salmonella* spp. contamination on imports had a major impact on further reducing the efficacy of curtailment when importation was increased. However, increasing the heterogeneity in how import was divided across importing countries increased the level of uncertainty in the efficacy of curtailment following changes to the extent of food product importation.

**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 this study was identifying that external AMR transmission pressure due to food imports may disrupt domestic interventions targeting local AMR such as antibiotic curtailment. Increases in this external transmission pressure promotes antibiotic-sensitive/resistant foodborne disease attributable to imported sources, which is unaffected by domestic livestock interventions. By extension, parameters, which increase the extent of foodborne disease attributable to imported sources, will have a greater influence on disrupting the efficacy of local antibiotic curtailment. This includes intuitively important parameters such as the decreasing the extent of UK food usage from domestic sources (ψ) and increasing the extent of overall or ampicillin-resistant *Salmonella* spp. contamination on imports (FracImp and PropResImp). Interestingly, this also applied to more efficacious reductions in *Salmonella* spp. prevalence from livestock carriage to carcass contamination (ψ) and increases in the rate of *Salmonella* spp. clearance in fattening pigs (rA), which reduces foodborne disease attributable to domestic livestock and similarly disrupts the efficacy of local livestock curtailment.

The interruption of local disease dynamics through external transmission pressures is a known phenomenon in dynamic modelling literature (**cite**). For example, studies have identified that interaction between sub-populations and spill over of AMR may drastically reduce the efficacy of local curtailment interventions, and with meta-population models also predicting strain coexistence due to the interaction and maintenance of AMR due to subpopulation interaction (**cite**). However, this study places these interactions in the context of antibiotic-resistance in imported foodborne pathogens and the potential interruption of one-health interventions.

**Talk about the saturation effect**

The relationship between the proportion of UK food products from domestic sources (ψ) and the efficacy of curtailment outcome measure (EoC) was a key result for this study. If a greater amount of importation is desired, then it is objectively better to shift the EoC/ψ relationship to an area where EoC remains high for a large range of import values (Figure 5; green area). Interestingly, the baseline UK case study occupies the opposing area, with increases in import (ψ < 0.656), quickly resulting in large decreases to EoC. This suggests that increasing the extent of UK food products from imported sources may result in a disruption in the efficacy of local livestock curtailment strategies.

* Place this in the context of increasing reliance of UK interventions and just general an increase in import
* Not much attention has been placed on how food imports may affect resistant foodborne disease – cite studies which say this

The balance between the average level of contamination on imported food products and the extent of contamination on domestic food products/carcasses drives the shape of the relationship between EoC/ψ. High levels of domestic food contamination relative to contamination on imports results in a more positive EoC/ψ relationship (Figure X; green area). Conversely, as with the UK case study, EoC/ψ relationship sits in a less advantageous area for increasing import (), due to the average level of non-domestic contamination exceeding that of domestic livestock food product contamination (). As an illustrative example, changes to η = … % result in import/domestic contamination being roughly equal resulting in a near linear relationship between EoC/ψ. Further increases to η result in greater levels of domestic contamination relative to import and therefore the EoC remains high for a large range of import values due to the high levels of attributable foodborne disease to domestic sources.

Interestingly, there is also the existence of a saturation effect with the relationship between EoC/ψ. For example, increases in the average level of overall/ampicillin contamination on imports () above baseline values () quickly reaches stabilises at an EoC/ψ relationship where the efficacy of curtailment is at its worst possible relationship with increases to import ().

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

It is important to note that we define two phenomneom here, heterogeneity in the relative share of importing countries and the average level of contamiantion and reisstance. This is because heterogeneity in the latter two terms affetcs the eocpsi relationship simply by shifting the average across these countries. Therefore it is not heterogeneity rather the average level that is impact the eoc/psi relationship.

Therefore we limit analysis into heterogeneity into the Share parameter, that because of the inherent need to sum to 1, we can actually explore heterogeneity here. Although it is recognised that this may siomply work to shift the average

It is important to note that heterogeneity in the outcome measures alter the relationship between EoC/Psi primarily through changes to the average level of contamiantion or resistance. The clearest example of this is the contamiantion and frac imp analyses where the average effect has a strong effect.

A more subtle example is the changes int eh relative share of import – which likely affects the average contamination and resistance through more indirect means – i.e a skewed import distribution might skew towards countries with high levels of contamiantion or resistance.

This is the case due to the star network aspect of the heterogenous model,w ith the only things affecting the importation transmission pressure the relatiknship between cont and share and psi parameters.

* Here emntion the need to reduce the average level of import

However, we note that heterogeneity does increase the level of uncertainty with the relationship – primarily due to more cvariation in which countries you might sample a lot from.

* This is a known phenomneom with 80/20 rule situations
* It also means that the effect of interventions may be more uncertain – with a more skewed distribution.
  + What are the policy implications of this uncertainty??

**Policy implications**

The results of this study have a clear policy implication – that the extent of average overall/ampicillin-resistant *Salmonella* spp. contamination should be decreased as low as possible if changes to the extent of importation are desired. Or at the very least, reducing contamination to an equal level seen on domestic food products to preserve the efficacy of curtailment of local livestock antibiotic stewardship on human health. This is particularly relevant in countries such as the UK case study, where the level of *Salmonella* spp. carcass contamination is already low relative to imports (). The need to understand the balance of contamination/resistance between imports and domestic food products highlights the critical need for foodborne pathogen/AMR surveillance at the origin of import, the point of entry and also within domestic livestock (**cite**).

Examples of surveillance at the point of origin include EU requirements for so-called “third-country” importing organisations not within the EU framework to meet EU food safety requirements and submit to inspection by FVO officers ([Third country approval guidelines (europa.eu)](https://ec.europa.eu/food/system/files/2016-10/ia_ic_guidance_thirdcountries2009_en.pdf)). Stringent inspection at border control posts at the point of import has also been widely recognised as a standardised method to reduce consumer exposure to contamination on imports (**cite**). Harmonised systems such as the RASFF has also been shown as effective as spreading the burden of BCP checks across multiple countries, with identification of contaminants and sources of single/multi-country foodborne pathogen outbreaks in one country, rapidly sent as an alert to all RASFF-participants. Policy to reduce import contamination can also be introduced at a macro-scale, controlling which countries to form import based trade connections with based on the extent of contamination on food products. The clearest example of this includes EU differentiation of food product “trade” between member states and “imports/introductions” from non-member state “third countries” with a higher amount of regulation and inspection placed on trade from the latter (**cite**). Adherence to these measures can ensure that contamination can be kept at low levels to avoid potential decreases to the efficacy of curtailment following changes in food importation.

However, there are obvious limitations to current surveillance and inspection infrastructure.

* However, BCP checks are often limited to occasional physical checks, with a compromise existing between ensuring rapid transit into the importing country and the use labour intensive/costly sampling and testing to thoroughly identify microbial contaminants
* The COVID-19 has proven that rapid sequencing and identification can be undertaken, however it is still yet to be seen if this rapid sequencing trechnology can be utilised. However, if sequencing caould be introduced, this would provide unrivalled information on the ability to attribute contamiantion and AMR to points of origin (mention where the source attribution studies get their data from).
* However, while the surveillance ofsalmonella and other contaminants on imports has been stadnardsised, livestock AMR is critically lacking – as suggested in a number of studies we note that this puts the emphasis to develop better surveillance to identify the impact of AMR – as suggested in this study – AMR in contaminants is also as important. Howver, use of modelling based approaches could also be used. Use of sampling and sequencing at border control posts of AMR contaminants – with public release of anonmyised data could be used to great effect for future

However, physical examinations are often performed more commonly preferred compared to sampling and testing, let alone sequencing of strains. There is an obvious compromise between the latter being obviously labour intensive and costly and still enabling rapid transit of goods into a country ([FDA Strategy for the Safety of Imported Food](https://www.fda.gov/media/120585/download)).

Point of Origin

* For example, EU legislation to ensure EU-stadnradised accreditation in terms of food safety for agriculture in third countries importing into the EU, and the use of EU inspectors travellingoutside of the EU can help import meet contamination standrads.

Border Control Posts

* Additionally, it is recognised that control at borders is exceptionally important to reduce the exposure of high contamiant food products. Use of common border control posts to check good sa are commonly used to check goods. However, there is often a comproiimise to ensure the free and fair access to imports while still ensuring good biosecurtity. Integrated systems such as the EU RASFF system may also provide an exceptionally good boost to border control posts – by recognisising contamination at borders and also reporting foodborne disease outbreaks (multicountry and single country) and alerting all EU countries within the RASFF framework of the causatory food product.

General Policies

* It is also important to note that policies can also be introduced at a higher level to redfuce the risk of contamination. However, it is remarkedly much more difficult to change the fundamental way in which you trade. This can be region wide – such as the EU differentiation of “trade” within EU partners and imports/introduction from third countries. Each with differing requriements due to the harmonisation system of intra EU trade () and third country trade (), which is primarily driven by EU-wide policies on food safety.

Need to ultimately relate all this back to the efficacy of curtailment argument – if more import is required – then we need to make sure that contamination is puished down as low as possible

include policies to ensure strict border control mixed with surveillance to ensure that countries which exceed certain levels of contamination are not accepted (any policy to puish down contaminatiion) (). Additionally, policy to only import from countries

The importance of the average level of overall/ampicillin-resistant Salmonella spp. contamination across imports has important implications for public health policy. This is particularly the case in countries where the level of domestic contamination is already low and therefore imports must similarly have low levels of contamination to prevent

This reinforces a message that if greater levels of import are wanted then surveillance at both the border control, in domestic farms and in the vcuntry of irigin is vital. This will ensure that the efficacy of any local antibiotic curtailment strategies will be maintained.

* This is in line with many of the UK and EU policies of ensuring adequate surveilalnmce (cite)
* HJowever, thjis also requires an exampsnion of livestock surveillance which is notoriously poor.
* We can imagine regions outside of the EU, where surveillance is not so good and changes in import are wanted – whioch might have disstorous effects.

This also suggests that for countris like the UK, where contamindation is alsready sort of low – then contamination must also be pushed extremely low

* This is in line with many UK centric and EU centric incentives to reduce the level of contamination
* It is interesting to note that the policy implications of this suggest that eetihrte pushing the average level low or pushing

This reinforces a message that surveillance of food imports or any phenomenon, which may import disease into a sink country of interest is vital. As an example, the extent of contamination for domestic food products is relatively low relative to importing countries in the model. Meaning that the average level of import must be pushed to a low level to start safely thinking about changing the level of import.

* Combine together

This presents a problem as it suggests that beyond keeping it near baseline levels of domestic contamination - increasing levels of contamination 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 domestic product (cite policy like this)

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

**Why we used the case study?**

* Would it look different with another resistabnce
* Would it look different with another foodborne disease or other pathogen – extrapolate to less shit case studies
  + Salmonella and foodborne pathogens are likely an unusual case study with global food tradfe really obviously affecting this 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
* Carcasses are used as proxies for food products – and we assume a single eta parameter can link together livestock caecum
* An assumption that domestic livestock antibioptic usage changes are linked to human health – worst case scenario if it wasn’t really related to human health – then the efficacy of curtailment would be even lower to begin with (as domestic resistance would be quite low) – and the majority of improvement would be to import trading policy (this is still an important message).

**Overall Conclusion Paragraph**