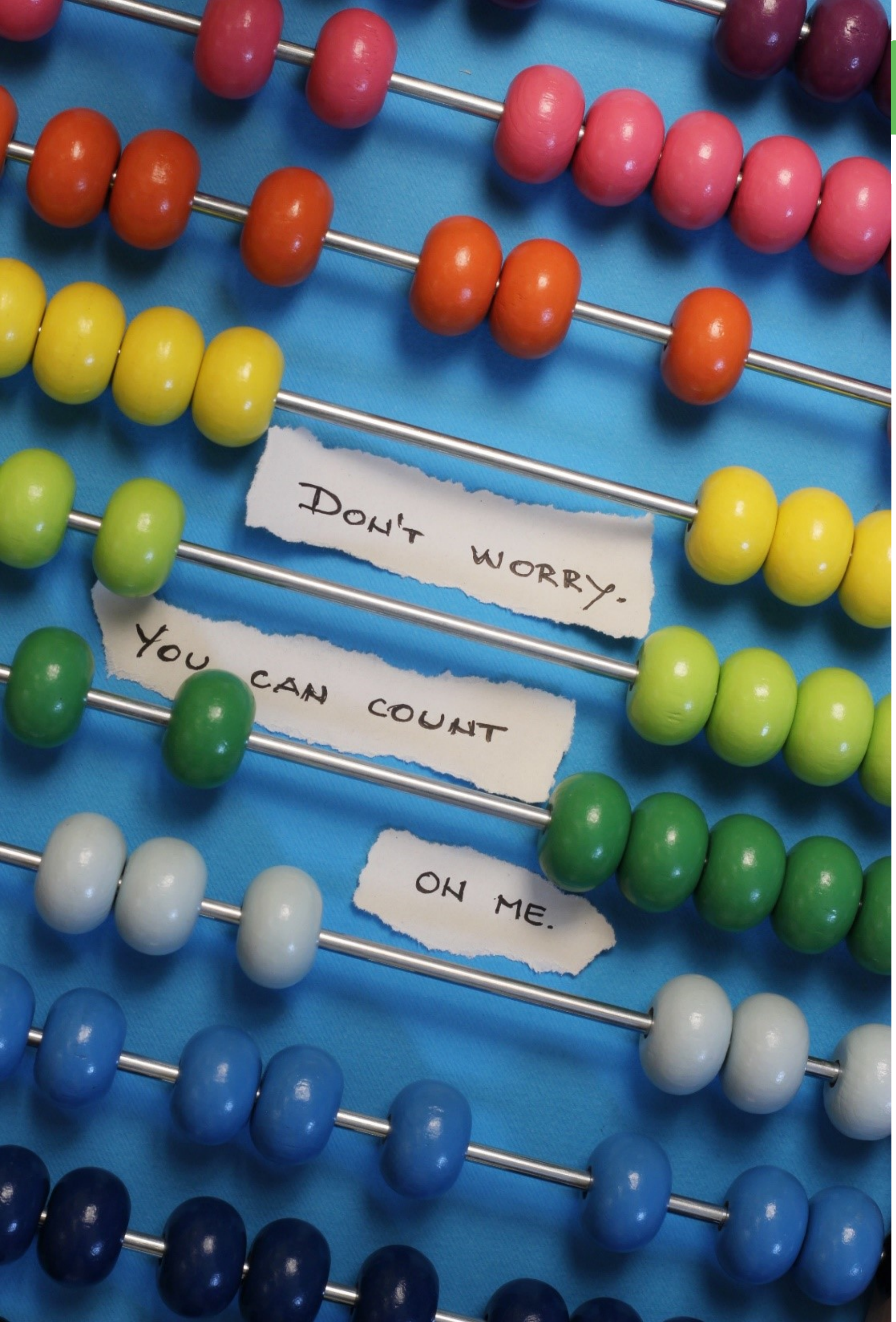


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THE UNIVERSITY of EDINBURGH
Royal (Dick) School of
Veterinary Studies

# Antibiotic Resistance in a One Health setting.

## Can we learn from models?

Bram van Bunnik

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Biotechnology and
Biological Sciences
Research Council

# What is the issue?

- Increasing levels of antimicrobial resistance worldwide.
- Transition to intensive animal production systems rapidly growing in many regions.
- Volume of antibiotics consumed by animals is approaching the volume consumed by humans.
- > 70% of the antibiotics deemed medically important for human health sold in the US are used in livestock (and > 50 % in most other countries).

  (FDA, 2012)
- Calls to reduce levels of antibiotics in food animals.


NEWS

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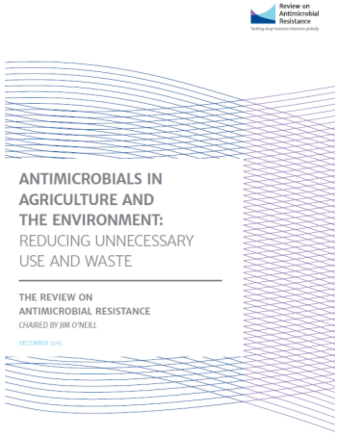
Health

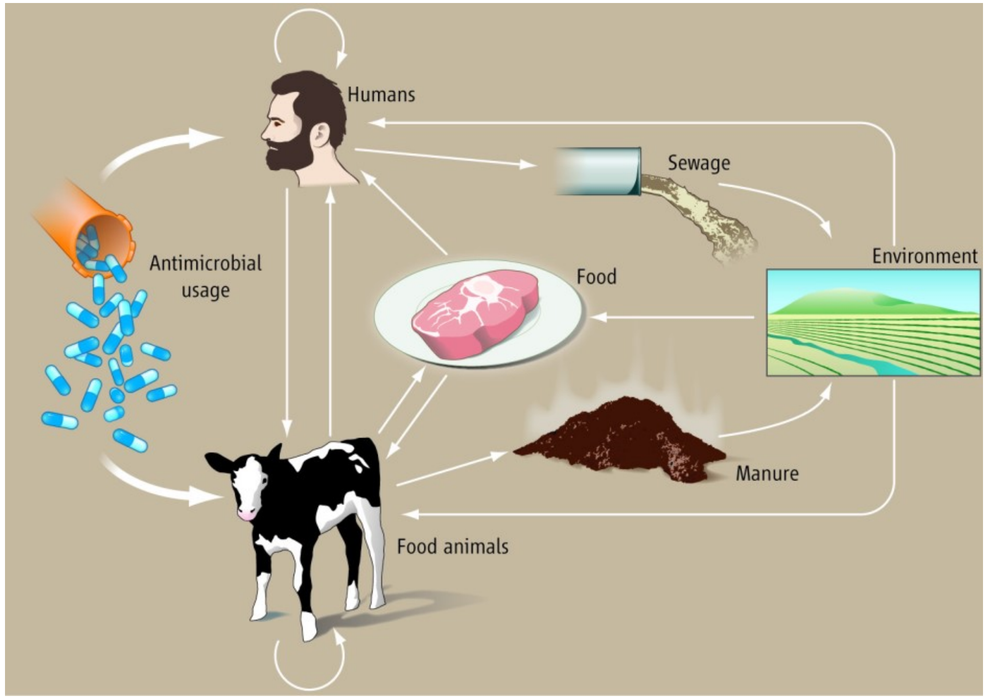
**Farmers urged to cut antibiotic use**

By James Gallagher
Health editor, BBC News website



# The Challenge

- Highly complex problem with myriad drug-bug-host combinations and multiple ways of movement.




- Different ways of movement:
  - Bacteria
  - Mobile genetic elements
  - Drug residues

In:

- Different hosts
- Different routes
- Different environments

- Better understand the dynamics of antibiotic resistance moving between food animals and human populations.

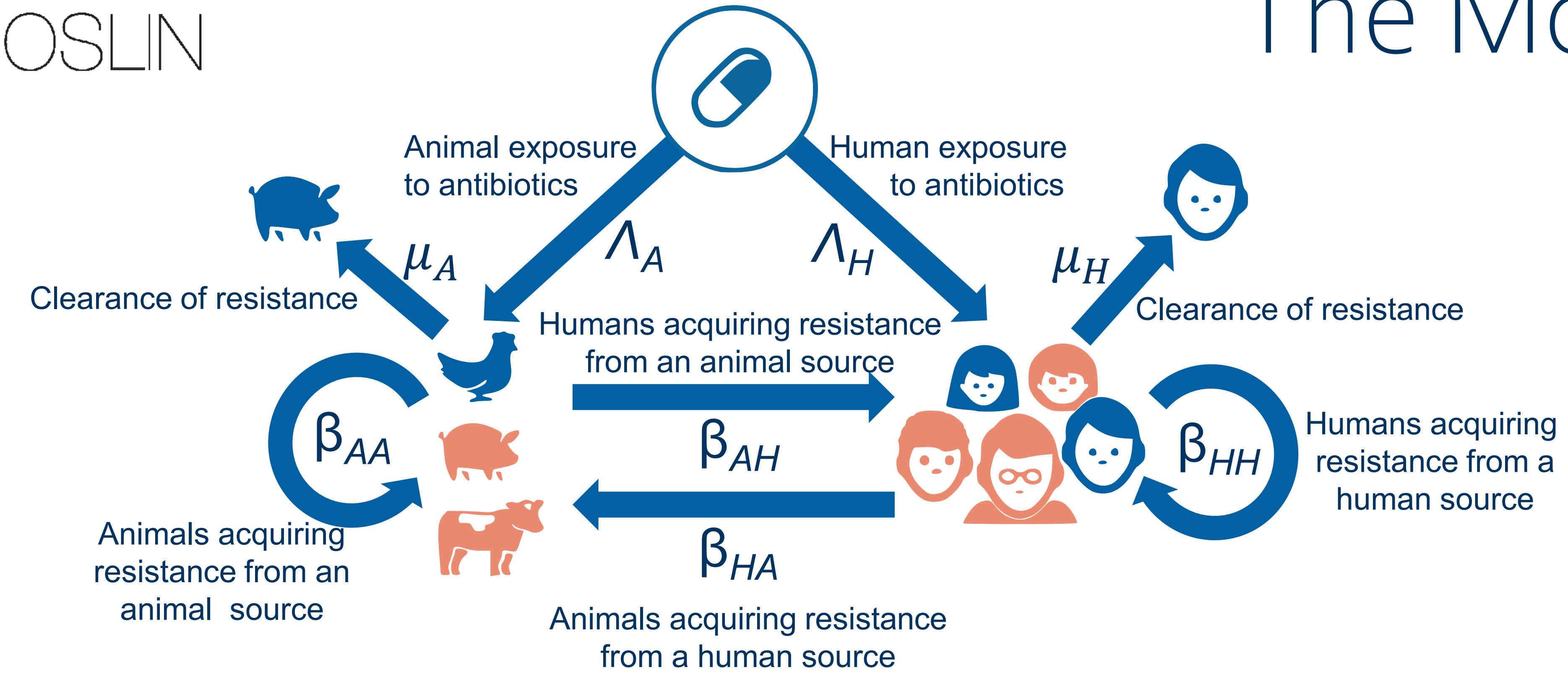
# The Approach

- Simple mathematical models to explore the relationship between a.b. consumption by livestock and levels of resistant bacteria in humans.

- Which model parameters have the greatest impact on the system.

- For which (modifiable) parameter combinations do we expect to see the greatest impact of reducing a.b. consumption in livestock.

# The Model




$$\frac{dR_H}{dt} = \Lambda_H(1 - R_H) + \beta_{\mathrm{HH}} R_H (1 - R_H) + \beta_{\mathrm{AH}} R_A (1 - R_H) - \mu_H R_H$$

- $\Lambda_H(1 - R_H)$: Acquire resistance through direct exposure
- $\beta_{\mathrm{AH}} R_A (1 - R_H)$: Acquire resistance through animal contact
- $\mu_H R_H$: Clearance of resistance

$$\frac{dR_A}{dt} = \Lambda_A(1 - R_A) + \beta_{\mathrm{AA}} R_A (1 - R_A) + \beta_{\mathrm{HA}} R_H (1 - R_A) - \mu_A R_A$$

van Bunnik et al, RSOS, 2017

# Methods

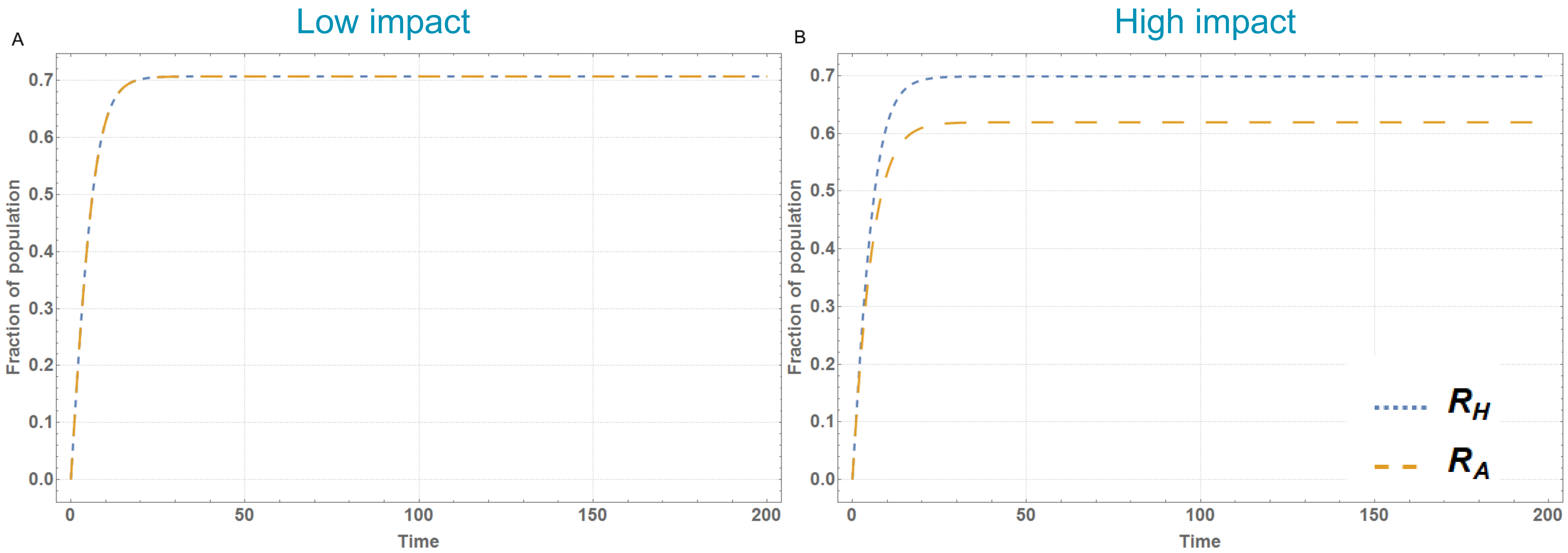
- Interested in steady state of the system to explore long term effects of changing parameter values.

- For this calculate $R_H^*$ by setting $dR_H/dt$ to 0 and solve for $R_H$

- To measure the potential impact of curtailing antibiotic usage in animals define $\omega = 1 - \frac{RC_H^*}{R_H^*}$, with $RC_H^*$ = $R_H^*$, with $\Lambda_A = 0$

- Two scenarios:
  1) Low impact scenario ($\beta_{HA} = 0.1$)
  2) High impact scenario ($\beta_{HA} = 0.001$)

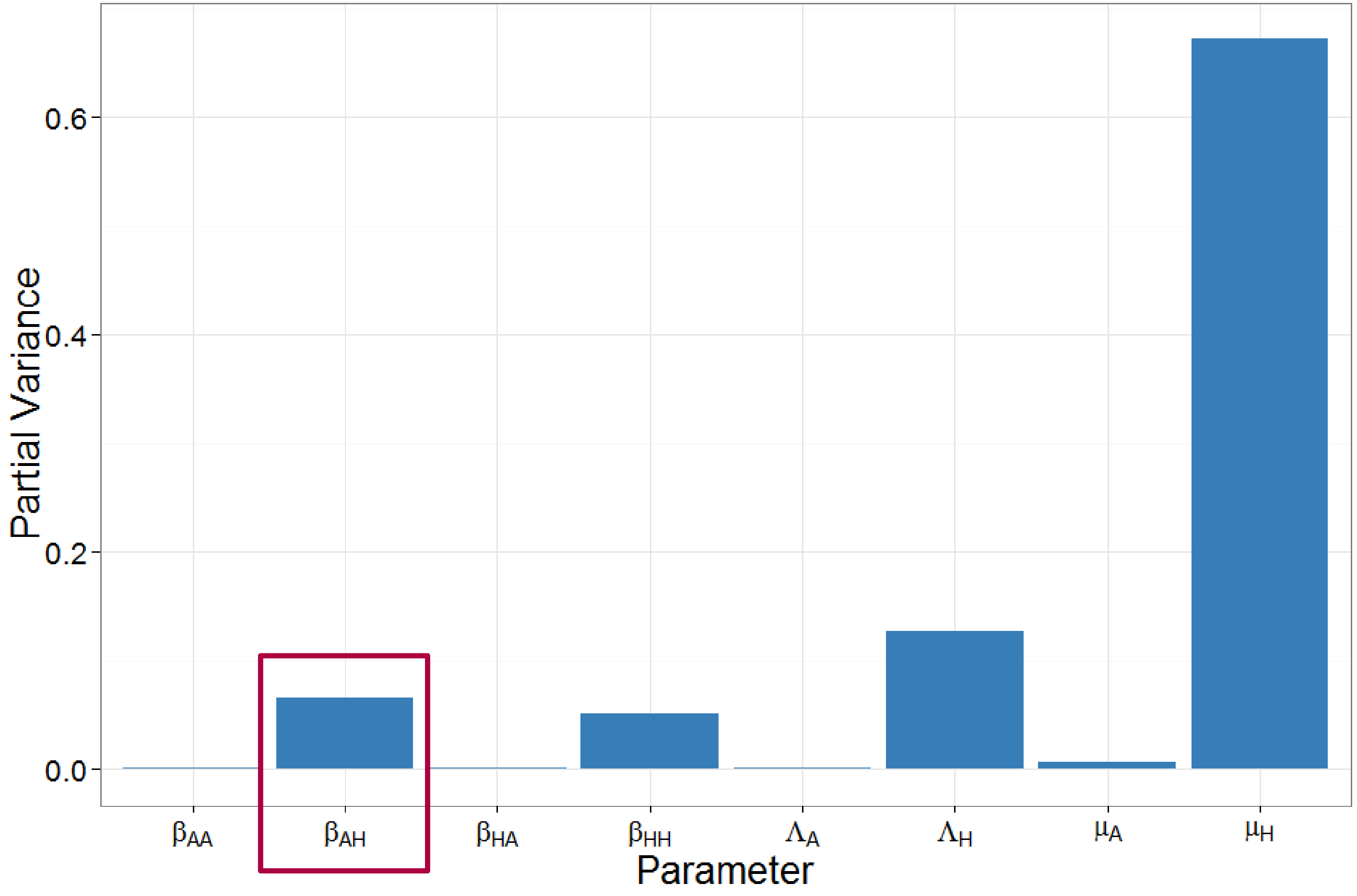
# Trajectories of scenarios




Baseline parameter values were chosen such that the long-term prevalence of the fraction of the human population that is affected by resistant bacteria is roughly 70%. Consistent with the situation of bacterial resistance to ampicillin in the UK, where both humans and food animals show similarly high level of resistance

van Bunnik et al, RSOS, 2017

# Sensitivity analysis

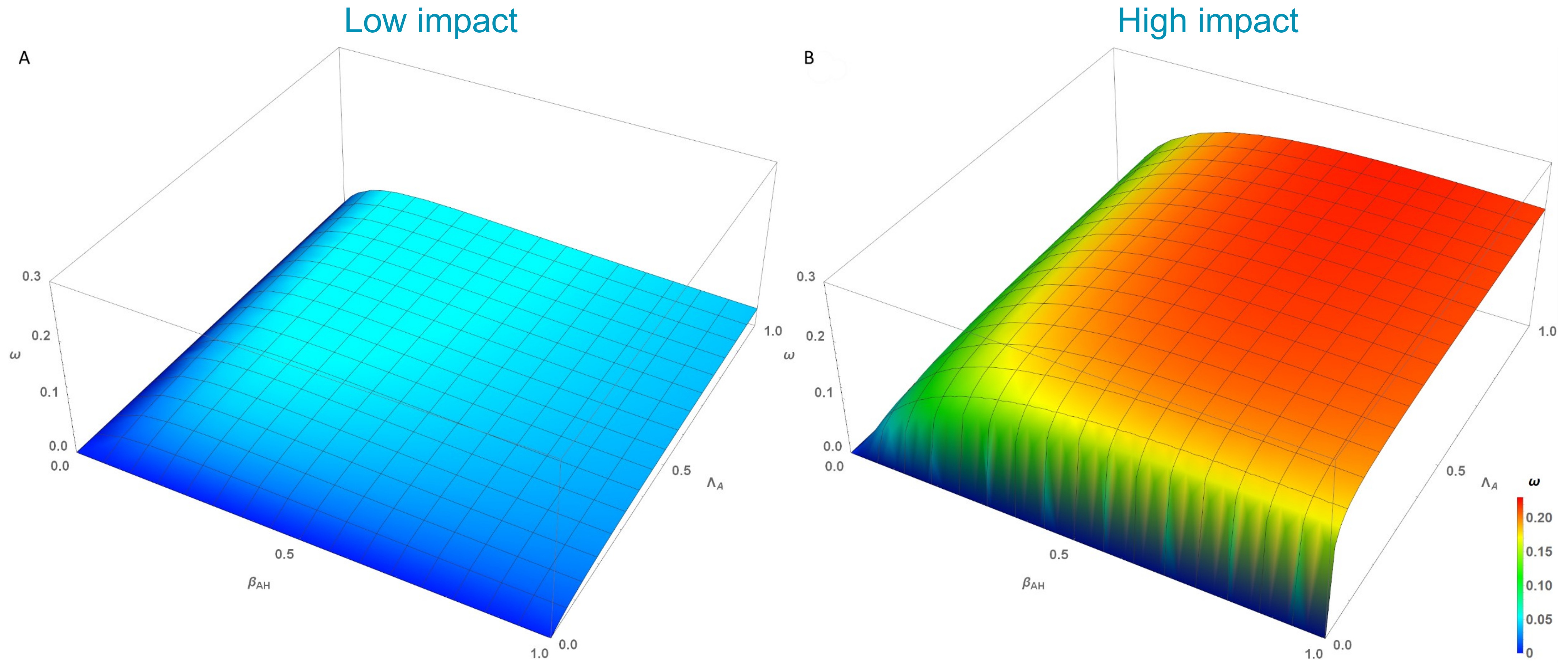



**Sensitivity of $R_H^*$ to changes in parameter values.**
Sensitivity analysis performed using FAST procedure.

Obvious sensitivity to changes in $\Lambda_H$ and $\beta_{HH}$, but more interesting also to changes in $\beta_{AH}$

van Bunnik et al, RSOS, 2017

# Impact of curtailing antibiotic resistance in livestock




Virtually no impact of reducing $\Lambda_A$ in the low impact scenario (high $\beta_{HA}$) while in the high impact scenario (relatively low $\beta_{HA}$) there is a much more obvious benefit.

van Bunnik et al, RSOS, 2017

# Conclusions

- Useful insights into a highly complex problem like antibiotic resistance can be obtained by using a simple mathematical model.
- Although widely regarded as intuitively obvious, reducing antibiotic consumption in animals does not decrease levels of antibiotic resistance in humans for a wide range of scenarios (i.e. parameter space), especially if this intervention is made in isolation.
- It is not enough to only lower the consumption of antibiotics in food animals, the transmission both from and to food animals should also be limited in order to maximise the impact of this and other interventions.
- Formal, quantitative analyses are needed to assess the expected benefits to human health of reducing antibiotic consumption by food animals.

# Limitations

- Model used is very simple.
  - However, by taking the simplest possible mathematical model as a starting point, we are able to make a first step in trying to understand this highly complex system and gain some robust and useful insights into its behaviour.

- Shape of the relationship between consumption and $\Lambda$ is left undefined as we are only interested in the specific alternative scenario where $\Lambda_A = 0$.

- Not properly fitted to data.
  - Limited availability of data and results of the simple, generic model presented here are robust in the sense that they apply over a wide range of parameter space that we expect to cover many real world scenarios.

# Modelling the effects of livestock antibiotic usage on antibiotic-sensitive/resistant human food-borne disease

(an extensions to the previous model)

Alex Morgan

# Introduction

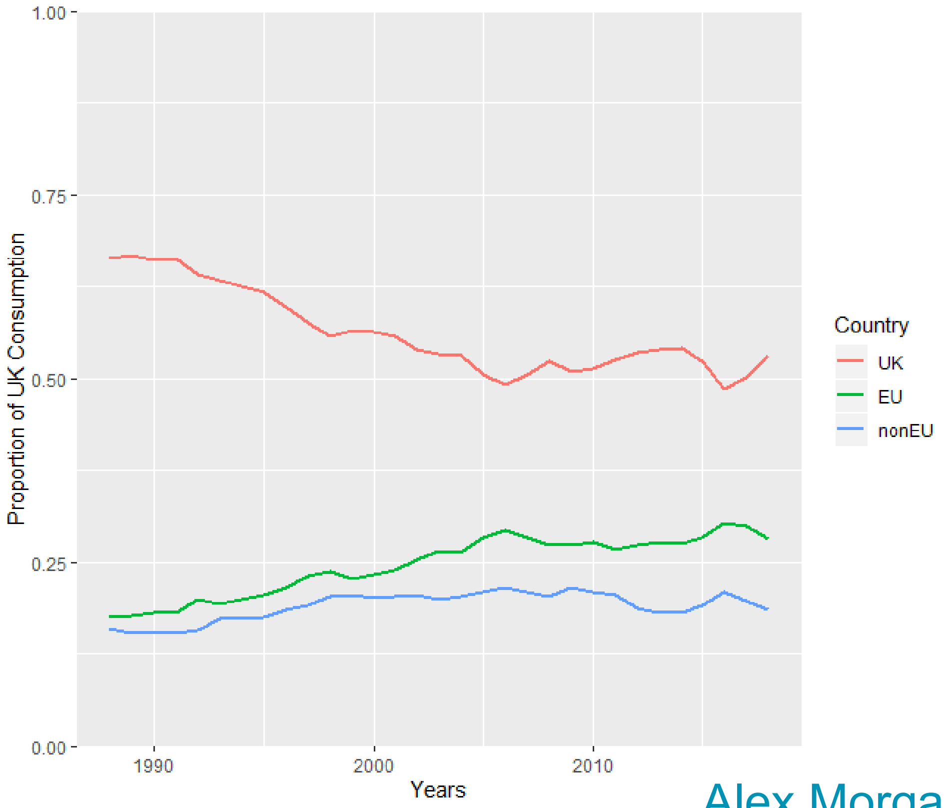
- The risk of AMR transmission through the food chain is poorly understood.
- Food Standards Agency (2016) – Systematic Review of AMR bacteria in food at UK retail:

  "There is a need for more studies to quantify the contribution of both domestic and imported foods to AMR occurrence…"

- Excessive livestock antibiotic usage has been identified as a potentially important driver of AMR in human populations
- Relationship between livestock antibiotic usage and antibiotic-resistant/sensitive human food-borne disease is poorly understood
- Use of mathematical models to understand the complexities of livestock antibiotic usage on human health

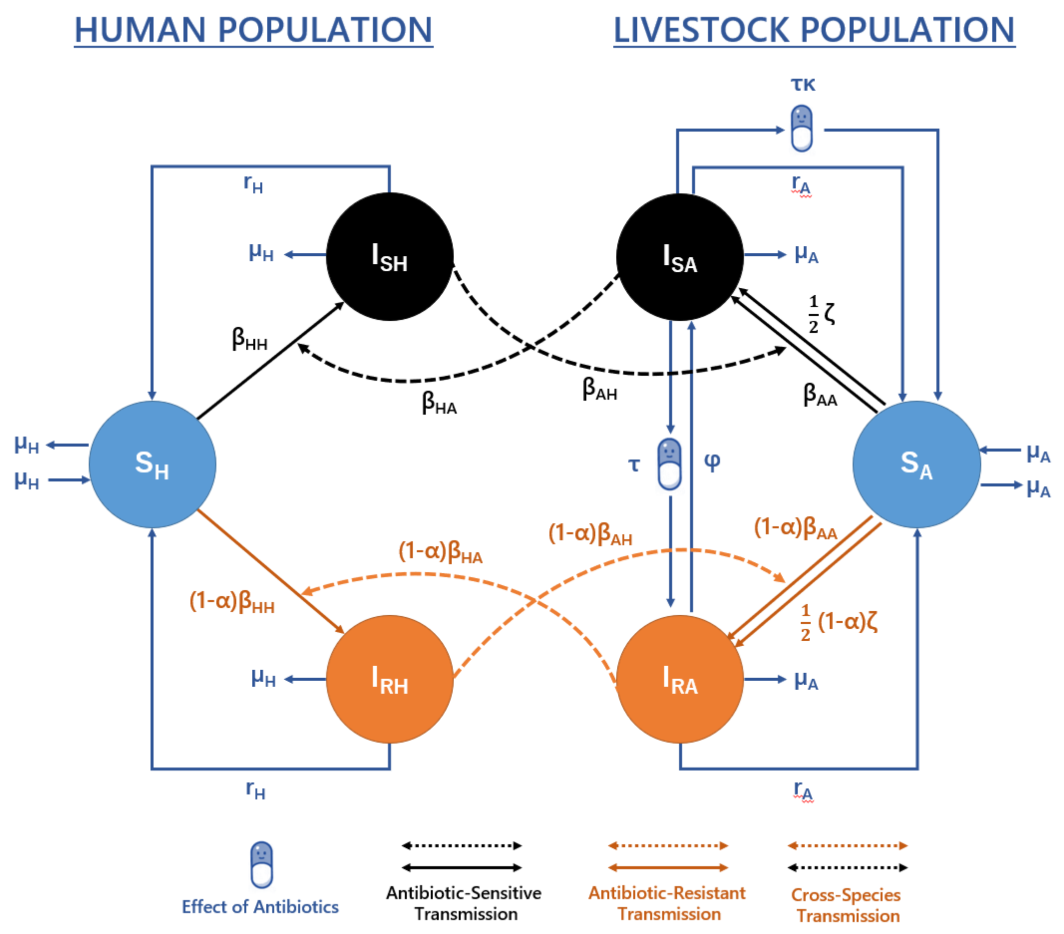
**How a no-deal Brexit threatens your weekly food shop**

UK reliance on EU food imports is a major risk if the country crashes out of the union



# Model Overview

- Deterministic SIS-model for the transmission of a.b.-resistant & a.b.-sensitive food-borne bacteria within/between livestock and humans




<u>Model Outputs</u>

1. Overall level of antibiotic-resistant and antibiotic-sensitive foodborne infection in HUMANS
2. Proportion of antibiotic-resistant HUMAN foodborne disease

| Parameter | Description |
|---|---|
| $\beta_{i,j}$ | Per capita rate of direct/indirect transmission between infectious population j and susceptible population i. |
| $\tau$ | Per capita livestock antibiotic usage rate. |
| $\alpha$ | Relative fitness cost (transmission) of resistant strains relative to sensitive strains. |
| k | Efficacy of antibiotic-mediated recovery. |
| $\phi$ | Antibiotic-resistant to antibiotic-sensitive reversion rate. |
| $\mu_x$ | Per capita birth/death rate in population x. |
| $r_x$ | Per capita rate of recovery in population x. |
| $\zeta$ | Background transmission rate |

Alex Morgan

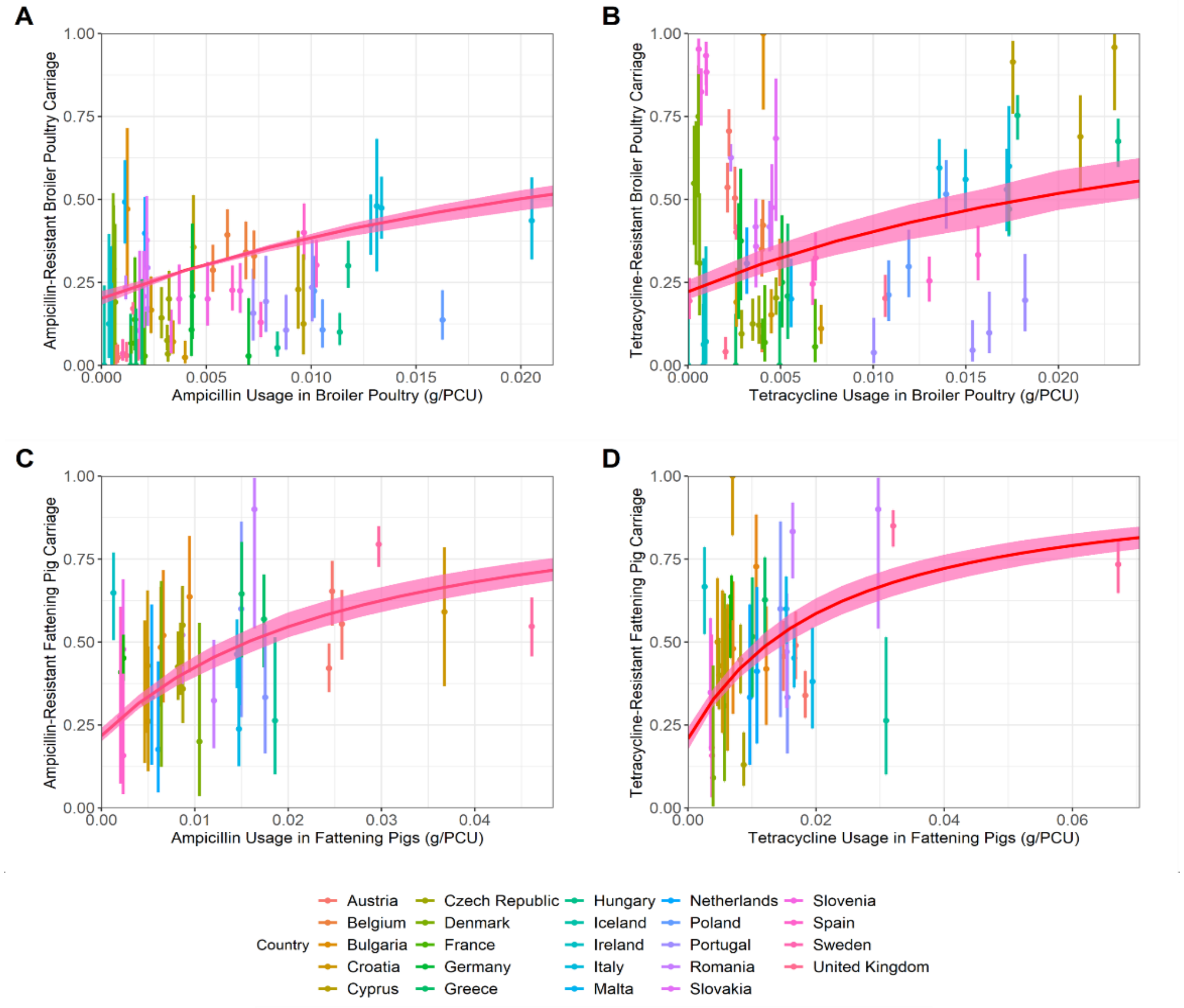
# Aims / Hypothesis

**What are the effects of livestock antibiotic usage on human health?**

Assumption: Antibiotic pressure reduces carriage of harmful bacteria

- Reducing antibiotic usage removes this pressure?
- What are subsequent effects in human populations?

**Hypothesis – Decreasing livestock antibiotic usage will have adverse human health effects**

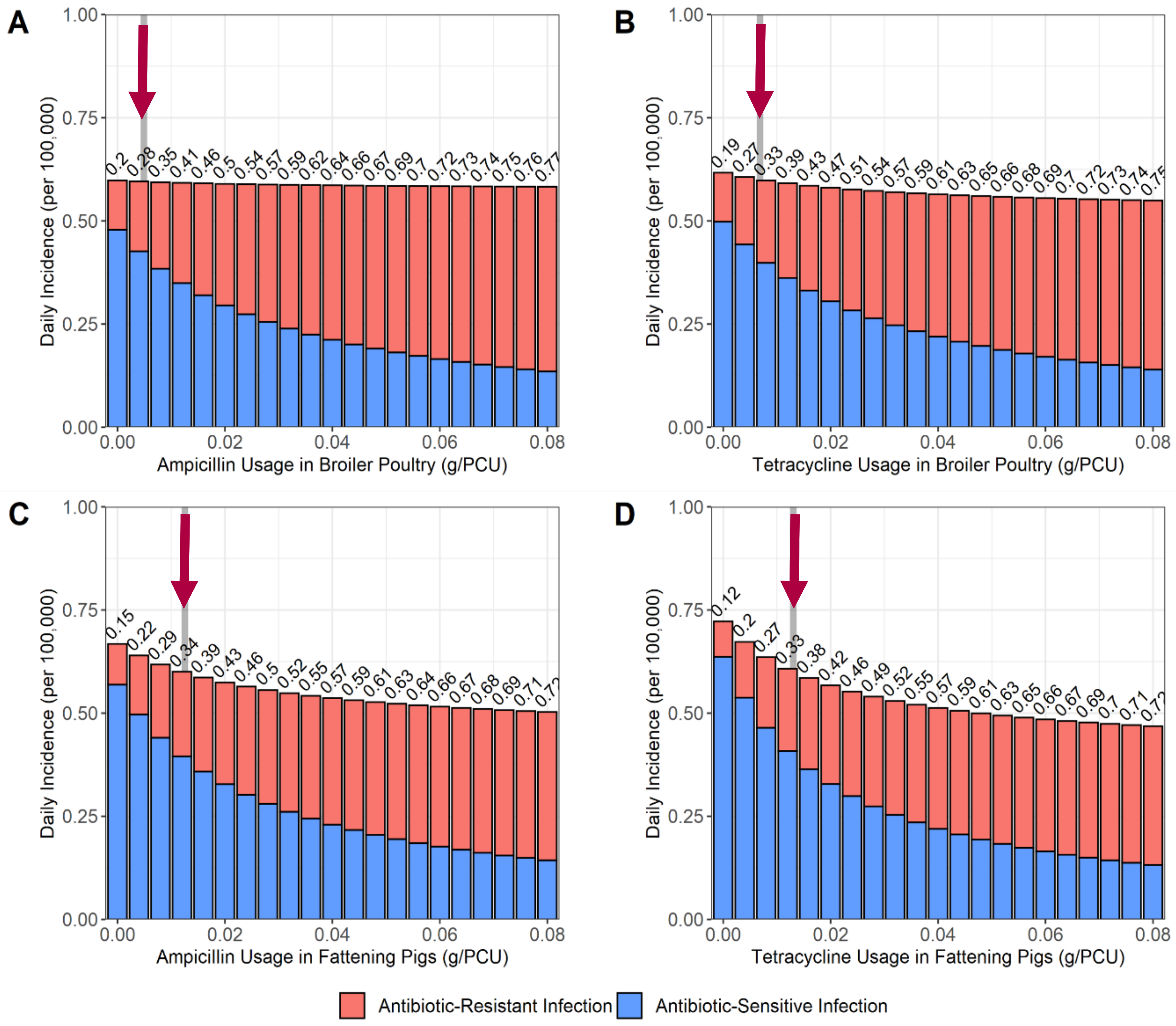



**Observed and estimated relationship between livestock antibiotic usage and the prevalence of antimicrobial-resistant salmonellosis in humans.**

Solid red lines and ribbons represent model fit resulting from the approximated posterior distribution using ABC-SMC and the corresponding 95% HDI.

(Data from ESVAC on antibiotic sales data)

Alex Morgan

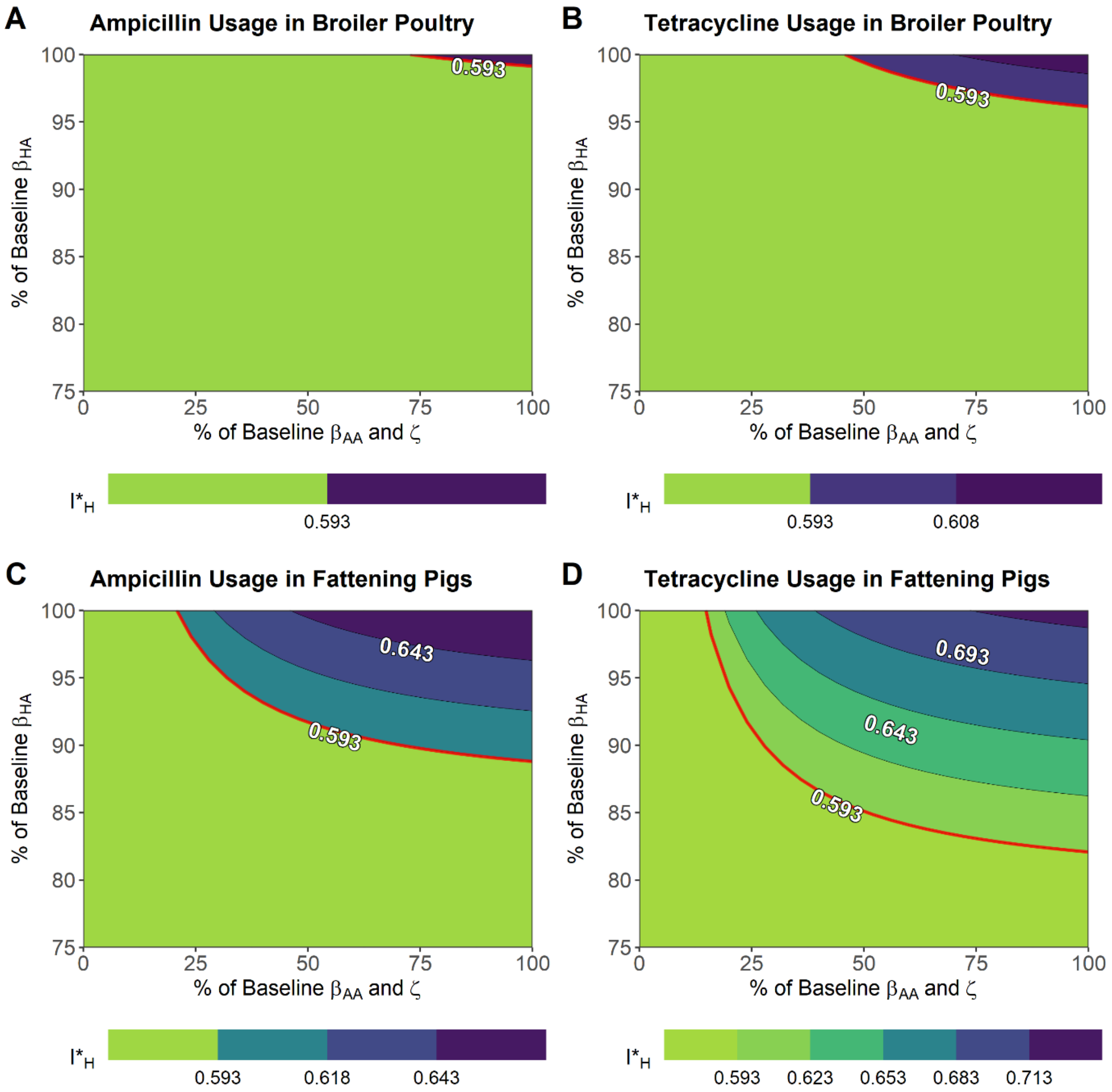



**Decreases to livestock antibiotic usage from baseline levels results in increases in overall human food-borne disease and a decrease in the proportion of resistant food-borne infection.**

Red arrows represents baseline livestock antibiotic usage.

Alex Morgan

# Possible mitigation of these effects?




**Reductions in $\beta_{HA}$ and (to a lesser extent) $\beta_{HA}$ & $\zeta$ can mitigate increases in overall human food-borne disease following livestock antibiotic curtailment.**

- The light-green area represents food-borne disease at baseline livestock antibiotic usage.
- Red line indicates represents the threshold at which daily incidence is below current levels (0.593 per 100,000).

Alex Morgan

# Conclusions

- Livestock antibiotic usage curtailment can increase overall levels of human foodborne illnesses and decrease the proportion of foodborne illnesses that is antibiotic-resistant.

- This increase in foodborne illnesses upon curtailment is scenario-specific and will be determined by a combination of influential parameters.

- Increase in human food-borne disease upon curtailment can be mitigated using livestock biosecurity interventions (alterations to $\beta_{HA}$ and $\beta_{AH}$).
  - Improvements to agricultural biosecurity are currently ongoing – continuation of these measures may prevent human health risks from future livestock antibiotic curtailment.

- Future predictive modelling requires improved epidemiological data (for model fitting) and empirical evidence to identify the current AMR situation in the explored parameter space.

# Limitations

- Constant rate of antibiotic usage in livestock assumed
- Livestock antibiotic usage assumed to be the sole driver of resistance in common food-borne infections
- Homogenous mixing within-populations

# Overall conclusions

- Reducing antibiotic consumption in animals does not decrease levels of antibiotic resistance in humans for a wide range of scenarios.
- Livestock antibiotic usage curtailment can increase overall levels of human foodborne illnesses.
- But can be mitigated using livestock biosecurity interventions.
- Simple mathematical models can be useful to gain quantitative insights in transmission between livestock and humans.
- However, future predictive modelling requires improved epidemiological data (for model fitting) and empirical evidence to identify the current AMR situation in the explored parameter space

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# Acknowledgment

THE UNIVERSITY of EDINBURGH

- Mark Woolhouse
- Alex Morgan
- Hannah Lepper
- Epigroup members

WAGENINGEN UNIVERSITY & RESEARCH

- Dik Mevius

UMC Utrecht

- Rob Willems
- Jaap Wagenaar

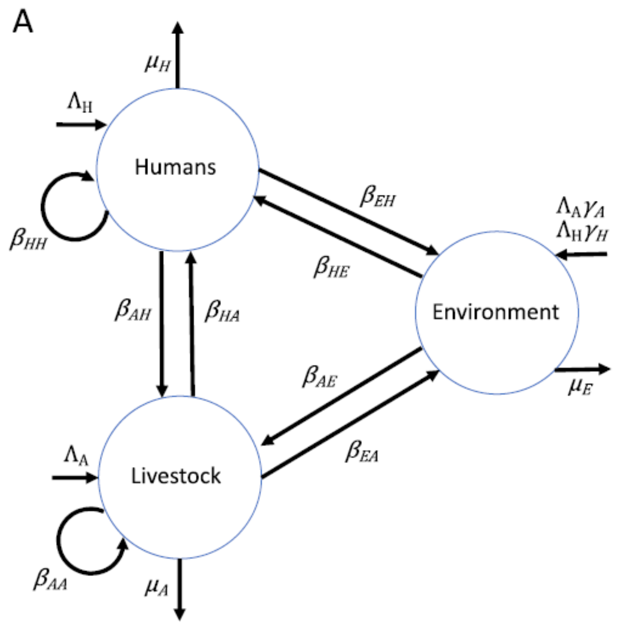
**Funding:**

Compare

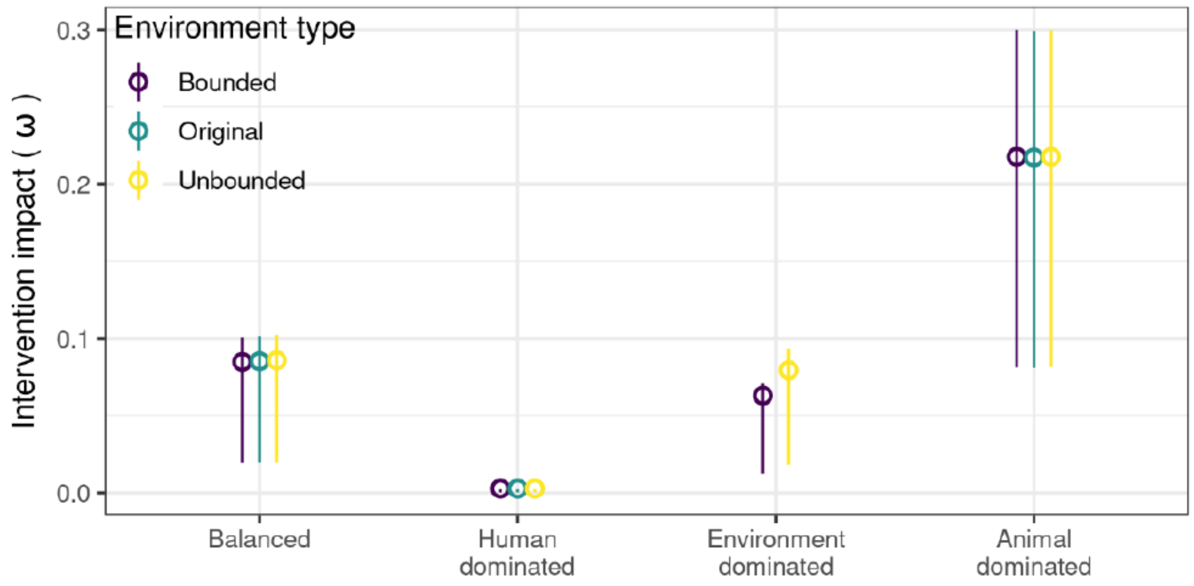
STARCS

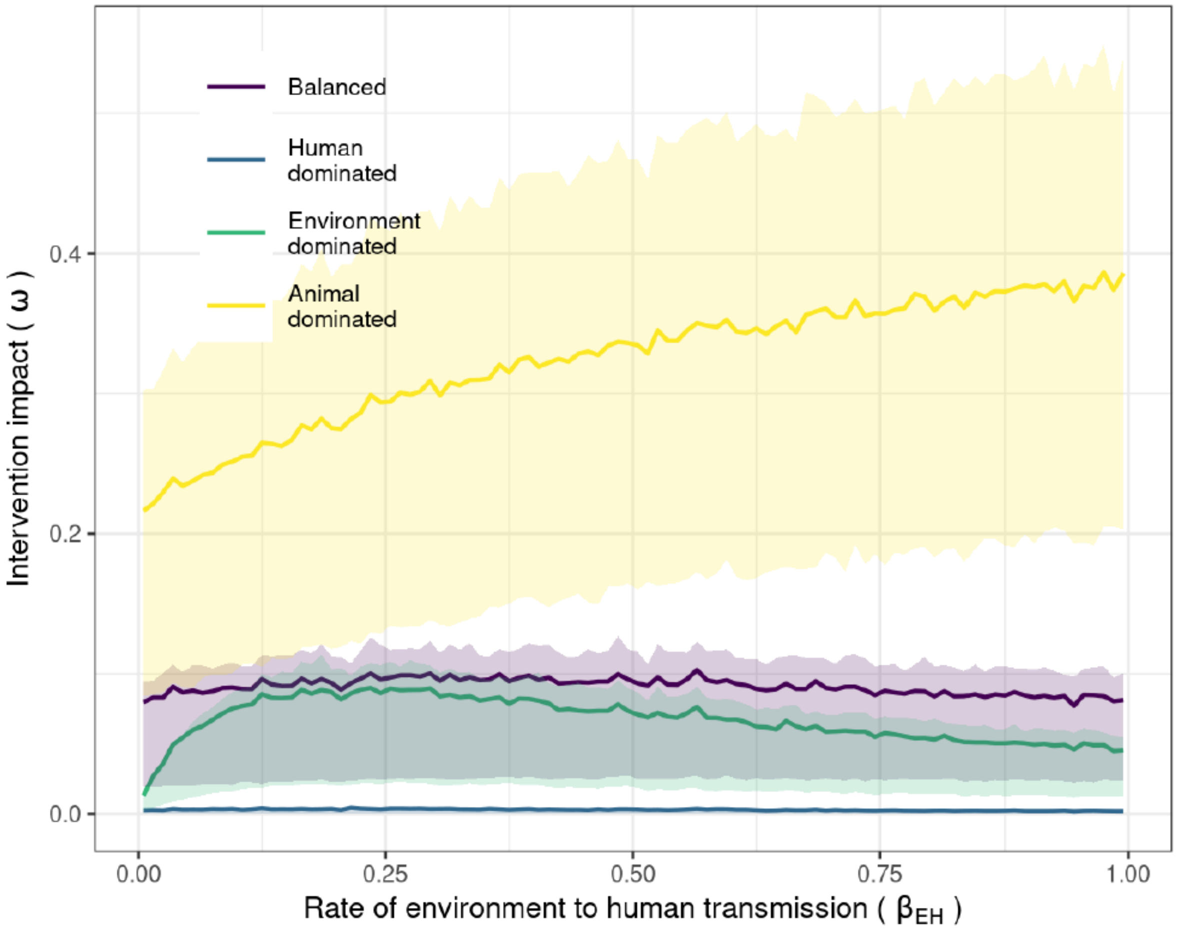
MRC Medical Research Council

jpiamr JOINT PROGRAMMING INITIATIVE ON ANTIMICROBIAL RESISTANCE



A
μ_H
Λ_H
Humans
β_HH
β_EH
β_HE
Λ_A γ_A
Λ_H γ_H
Environment
β_AH
β_HA
β_AE
μ_E
β_EA
Λ_A
Livestock
β_AA
μ_A


Environment type
Bounded
Original
Unbounded
Intervention impact ( ω )
0.3
0.2
0.1
0.0
Balanced
Human dominated
Environment dominated
Animal dominated



Balanced
Human dominated
Environment dominated
Animal dominated
0.0
0.2
0.4
0.00
0.25
0.50
0.75
1.00
Intervention impact ( ω )
Rate of environment to human transmission ( βEH )