

ONE HEALTH INTERVENTIONS FOR ANTIBACTERIAL RESISTANCE IN DENMARK, ENGLAND, AND SENEGAL: A MATHEMATICAL MODEL COMPARISON

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Summary (148/150 max)

Background Determining the contribution of One Health drivers across humans, animals and the environment is key to tackling the global health threat of antimicrobial resistance (AMR).

Methods A deterministic compartmental model was developed and calibrated to data on third generation cephalosporin resistant *Escherichia coli* in three case study countries (Denmark, England and Senegal), then used to estimate the impact of intervention packages.

Results Using the 100 parameter sets that allowed the model to most closely align to data for each country, we found that the biggest impact on resistance levels came from targeting overall spread of bacteria, as well as those aimed at the environment, however uncertainty was large.

Conclusions This research emphasises the importance of targeting transmission to reduce AMR levels but highlights how limited our understanding of the One Health dynamics are due to the lack of similar, longitudinal, detailed AMR prevalence and antibiotic usage or exposure data across multiple settings and sectors.

Keywords antimicrobial resistance; mathematical model; One Health; transmission; antimicrobial usage; Senegal; Denmark; England

Science for Society (121/1000 words)

Antimicrobial resistance (AMR) is a highly important One Health issue, with antibiotics being a vital component of care for humans and animals. Antibiotic residues have been found in many different environmental settings likely driving AMR selection, and hence a source of AMR transmission to humans.

In this article, we use a new One Health mathematical model to ask what intervention packages would have the biggest impact on AMR, providing further evidence for interventions to target spread and transmission of bacteria to control AMR. In addition, by using a single model to compare over three country settings we highlight the common lack of sufficient One Health data on AMR and advocate for more data to understand the contributions of different settings to AMR burden.

Highlights

- We present a comparison of outcomes of hypothetical intervention packages targeting third generation cephalosporin resistant *E. coli* across Denmark, England, and Senegal.
- By fitting the same mathematical model we can find similarities and differences in parameter distributions such as the level of spread or antibiotic effect, across the three settings and three countries which can then be used to target interventions.

- However, we are highly limited by the amount of comparable data and have high uncertainty in the model fit and hence in the accuracy and detail of the model results.
- Intervention packages that result in a reduction in the spread of resistant bacteria and that tackle AMR selection in the environment are predicted to have the highest impact across all three countries.

Introduction

Antimicrobial use (AMU) has significantly enhanced our ability to treat and prevent human and animal disease across the world and has played a key role in transforming food production systems^{1,2}. However, the increased use of antimicrobials has likely contributed to the increase in antimicrobial resistance (AMR). This has led the World Health Organisation (WHO) to classify AMR as one of the top global public health and development threats³, leading to calls for restrictions in use of critically important antimicrobials.

One such group of critically important antimicrobials are third generation cephalosporins (3GCs) widely used in humans^{4,5} and veterinary medicine⁶. *Escherichia coli* (*E. coli*) is one of the most common causes of the most serious types of infections in humans and can be commonly spread between animals and humans^{7,8}. *E. coli* are common colonisers of the intestinal tract of livestock^{9,10}, with food believed to be an important source of drug-resistant *E. coli* due to its detection in animals raised for meat consumption and in meat products^{11–13}. 3GC-resistant *E. coli* are a particular public health concern, listed as a “critical” pathogen-drug combination for future research and development into antibiotics by the WHO¹⁴. 3GC-resistance in *E. coli* is reported to be mainly disseminated via the transfer of mobile genetic elements^{10,15}.

Due to the interconnected nature of bacteria, resistance genes and antimicrobial compounds, a One Health approach is crucial in understanding the transmission and selection of AMR and overall dynamics^{16,17}. In particular, there is an increasing focus on interventions to limit antibiotic use within food-producing animal systems or transmission between food-producing animals and humans in order to combat the increasing number of infections with drug resistant bacteria in humans^{18,19}. Quantifying the likely impact of such interventions to optimise resource use is an important evidence gap in the One Health AMR field. Previous mathematical models addressing this have provided broad results emphasising the need to understand the connectedness of different settings, the importance of antibiotic usage to resistance selection within a setting (e.g. human / environment) but have also often called for more One Health data to quantify intervention impact^{20–22}. More data is also needed to determine the functional form of the link between AMU-interventions and human and agricultural AMR levels^{23,24}, which is a necessary parameter input to cost-effectiveness analyses, which in turn is necessary for making efficient resource allocation decisions²⁵. The unknown interplay between sectors is also likely to vary in importance and functional form between countries, meaning that One Health considerations for intervention evaluation should be country-specific. However, previous analyses have not fitted the same model to data from multiple countries to infer and contrast dynamics vital for informing intervention impact.

This evidence is vitally needed as AMR is a global problem³ and many countries need to implement interventions within their own specific National Action Plans (NAPs)²⁶. Each country has inherently different livestock systems, antimicrobial usage policies, resistance profiles and other key characteristics. Hence different strategies have been implemented

and would be considered to halt the spread of AMR, though few NAPs consider the natural environment²⁷. For example, Denmark, which produced over 30 million pigs in 2020²⁸, has highly regulated AMU, with a voluntary but highly effective pork industry ban on the use of 3rd and 4th generation cephalosporins introduced as early as 2010. Similarly, the UK NAP to 2024²⁹ and wider industry efforts were highly successful in reducing antimicrobial use, particularly in the poultry sector, with new UK NAP targets building on this progress¹⁹. In Senegal, studies show extremely high levels of 3GC-resistance in infections³⁰. The Senegal NAP focuses on increasing laboratory capacity, surveillance of infections, combatting healthcare-associated infections (HAIs), ensuring rational management of antimicrobials, and raising awareness of antimicrobial resistance³¹, but includes no specific percentage reduction targets in usage as in previous English and Danish NAPs. These three examples highlight the varying country priorities and capacity to implement different strategies.

These three countries were chosen for this analysis to estimate the potential One Health impact of different AMU interventions as they have (i) differing agricultural and health systems, (ii) a commitment to tackling AMR using a One Health approach, and (iii) at least some available, published data across sectors^{19,31–33} as well as being one least developed country and two high developed countries³⁴. The aim of this mathematical modelling study was to estimate and contrast the potential impact on 3GC-resistant *E. coli* burden of different AMU and AMR interventions across the One Health system in Senegal, Denmark and England.

Results

Model development

We built a new simple mathematical model, building on previously published compartmental models to describe the AMU, AMR levels and transmission between the three settings of humans, animals, and the environment^{20–22} (Figure 1). The model is fit to data on 3GC-resistant *E. coli*, has been adapted to Senegal, Denmark and England and includes inputted time-varying antibiotic exposure.

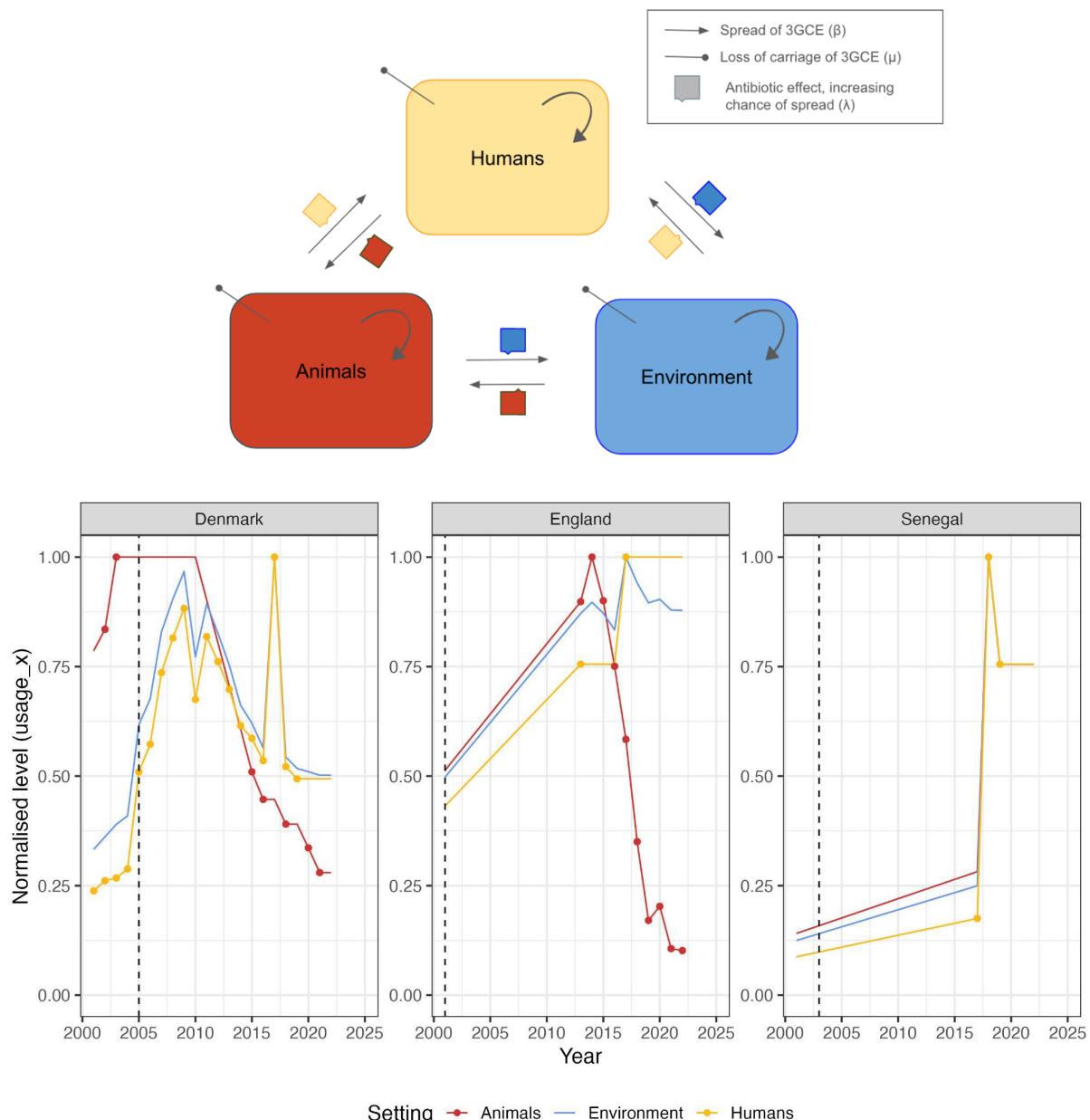


Figure 1. Model structure (top) and antibiotic exposure patterns (bottom). Model structure (top) shows how third-generation cephalosporin resistant *E. coli* can spread and be removed from the three settings humans (yellow), animals (red) and the environment

(blue). Resistant bacteria can spread at a background rate, with an additional rate dependent on antibiotic exposure. Carriage is lost at a constant rate. The trend of antibiotic use over time (bottom) is normalised by dividing by the maximum level in each setting in each country and used as an input to the model. The dashed line shows the start of the model run for each country based on resistance data availability.

Model fit

To determine the parameter values that allowed our proposed model structure to recreate the situation in our three countries, we searched the literature for data on prevalence of resistance to third generation cephalosporins utilising both national reports and individual studies as necessary (points in Figure 2, Supplementary 2). The simple model could broadly capture the trends in resistance in each setting (Figure 2). In particular, the model could capture the levels of resistance in the isolates from humans. With limited data from animal and environmental settings, the uncertainty in model output for these is much higher. Possibly because of the trends in antibiotic usage in animals (Figure 1), the fit to the data in animals in Denmark is not as good as the fit to the levels in humans (Figure 2).

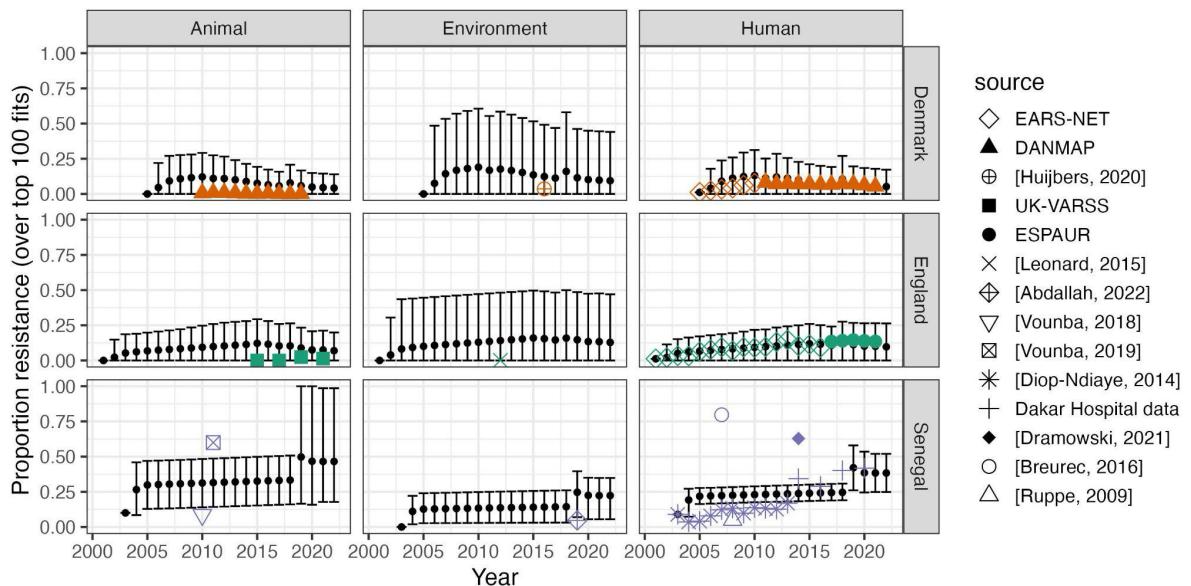


Figure 2: Model fit. Black points indicate the annual mean over runs for the 100 best fitting parameter sets with 95% range shown in error bars. Coloured points indicate data on prevalence of 3GC resistance in *E. coli* samples from each of the three settings and three countries with shape indicating data source.

Best fitting parameter sets

From the range of potential parameters, those parameters that allowed the model output to align most closely with the data were broadly similar across our three countries (Figure 3). However, for most parameters, the distribution for Denmark and England was more similar as might be expected. For example, there was a more uniform distribution of possible values for the spread (β_{YZ}) from environment ("E") to humans ("H") and to animals ("A") (β_{EH}, β_{EA}) in Senegal, with a lower similar distribution of values for Denmark and England. Surprisingly, but potentially in line with the relatively increasing levels of resistance in humans, the distribution of spread within humans (β_{HH}) was lowest in Denmark, higher in England and highest in Senegal. In terms of the parameter values, it is interesting that often spread from animals to humans (β_{AH}) is often higher than from the environment to humans (β_{EH}).

The relationships between the parameters was also similar within each country (correlation analysis, Supplementary Figure S13). As would be expected, the clearance rate and spread rate within each sector (β_{XX} and μ_X) were positively correlated (Supplementary Figure S13). Interestingly, for Denmark and England (and to a lesser extent for Senegal), there was a negative correlation between spread from animals to humans and vice versa (β_{AH}, β_{HA}). Also impact of antibiotic exposure (λ_X) was negatively correlated with within setting spread (β_{XX}).

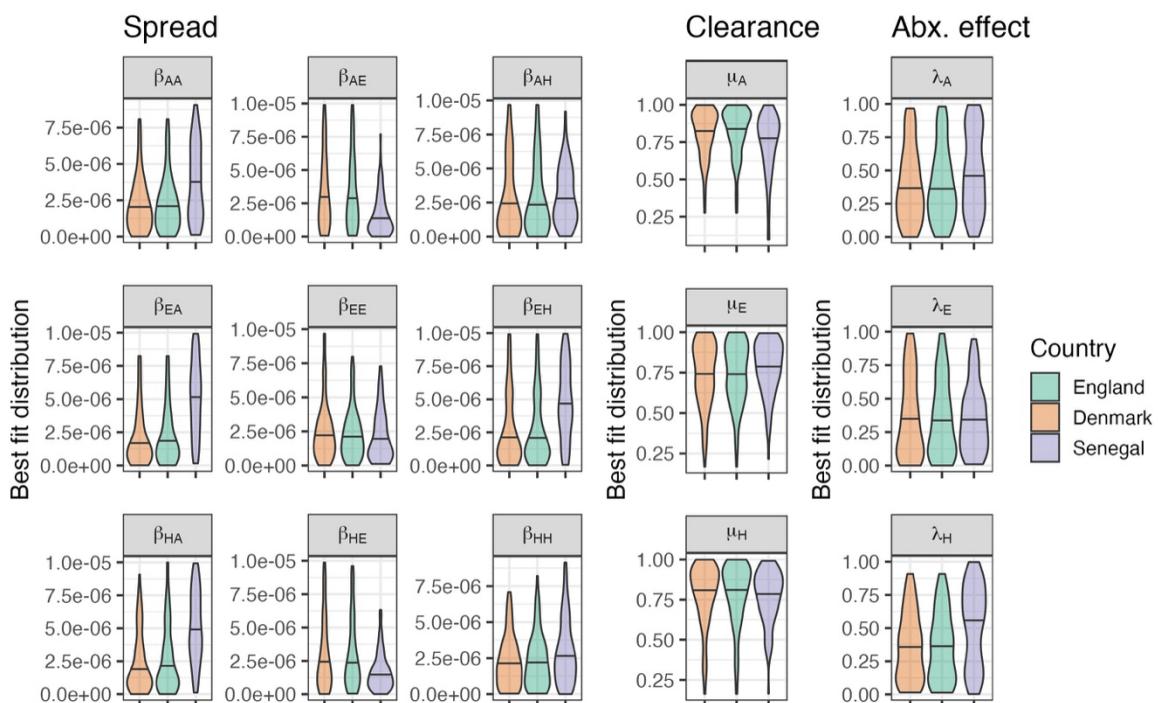


Figure 3: Variation between parameters from best 100 fits for each of the three countries. A Ranges for the best 100 parameters shown in violin plots for each country (colour). β_{XX} and β_{YZ} parameters are for spread within or between settings of animals (A), humans (H)

and the environment (E) respectively. λ_x are the scaling levels of the impact of antibacterial usage on successful transmission with μ_x being clearance rate of resistance from each setting.

Intervention impact

To determine the impact of hypothetical intervention packages, we used the model and parameter sets that best aligned with the resistance data to simulate different scenarios. The hypothetical intervention packages are assumed to achieve particular targets (Table 3) based on national action plans (NAPs), literature targets and expert opinion. For example, we explore how big an impact reducing antibiotic use in animals by 30% would have on AMR comparing the burden over 5 years of achieving this target versus that of no change. The interventions had the greatest absolute reduction in resistance proportion in humans in Senegal (Figure 4A) due to the higher initial resistance levels which, over the 100 best parameter sets were 0.05 (mean, SD = 0.05), 0.1 (0.08) and 0.4 (0.1) for Denmark, England and Senegal respectively (Figure 2).

However, looking at percentage reductions in resistance (Figure 4B, Table 1), in Denmark most interventions were predicted to remove nearly all resistance in humans (percentage reduction of 100%). Reducing antibiotic use in animals alone (by 30%) had a small impact across all countries (Figure 4, Table 1). Targeting antibiotic use alone (reduced by 50%, dark green, Figure 4) had a smaller impact in all countries than reducing all spread (reduced by 50%, bright green, Figure 4) which was able to reduce burden by 100%. Of the combined interventions, the “England package” and “Environment target” packages had the highest level of impact. Comparative analysis on the impact of levels of spread (Supplementary Figure S3, exploring reductions of 10-30% of all spread), suggests that the main driver of the impact of the “England package” was the component of the package that resulted in a 20% reduction in all spread. In Senegal, England and Denmark, for 17, 16 and 6 of the 100 best parameter sets the “Senegal package” resulted in higher levels of resistance after 5 yrs (negative absolute reduction values Figure 4A). For Senegal, a further 2 parameters sets had higher 5 year levels for the “A-H spread down 50%” and 1 for each of “Farm target” and “Antibiotics usage in animals down 30%”.

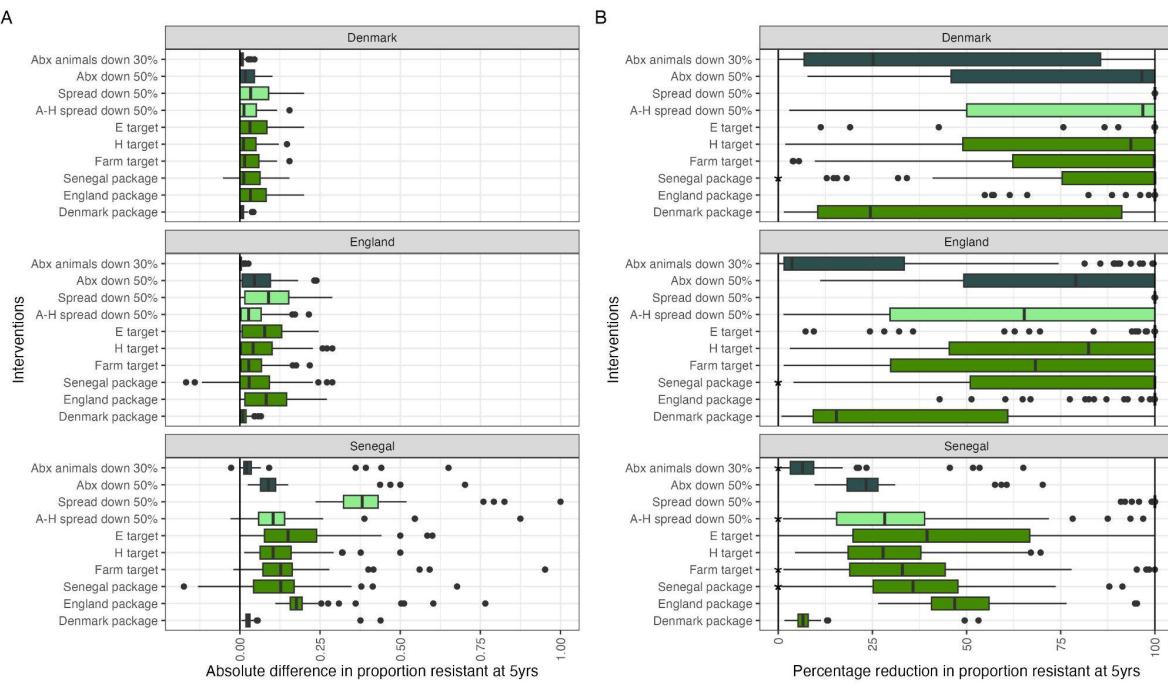


Figure 4: Intervention impact as an absolute difference (A) and percentage reduction (B) in proportion resistant in humans after 5yrs of holding the parameters at intervention values for the three countries (panels) over the 100 best parameter values vs. parameter values that reflect the intervention package target. The boxplot shows the median (central line) with the box showing the 25th-75th percentiles, with the whisker indicating up to 1.5 times this interquartile range. Dark green indicates an intervention reducing only antibiotic use, light green an intervention reducing only spread parameters and medium green for interventions that are a combination of antibiotic use and spread reductions. E = environment, H = Human. * = some parameter values gave a percentage increase where resistance was greater after 5yrs (not shown).

TABLE 1 Percentage reduction after 5yrs of interventions in levels of 3GC resistant *E. coli* within humans (median with 95% confidence interval) over the 100 best parameter sets. Corresponding tables for animals and environment are in the supplementary (Table S1, S2) .

Intervention	Reductions	Denmark	England	Senegal
Denmark package	Human AMU 10%, Animal AMU 5%, Transmission Animal->Human 10%	24.4% (3.7%, 99.7%)	15.5% (2.7%, 99.6%)	6.5% (2.1%, 13.1%)
England package	Human AMU 5%, Animal AMU 30%, Transmission 20%	100% (59.2%, 100%)	100% (62.5%, 100%)	46.8% (31.7%, 74.9%)
Senegal package	Human AMU by 5%, Animal AMU by 5% Transmission by 10%	100% (-19.8%, 100%)	95.7% (-475.1%, 100%)	32.9% (-18%, 70.8%)
Farm intervention	Human<->Animal spread by 50%	99.8% (7.5%, 100%)	68.3% (5.7%, 100%)	32.9% (3%, 96.5%)
Hospital	Human AMU by 50% Human-Human transmission 50%	93.6% (10.4%, 100%)	82.8% (11%, 100%)	27.8% (5.8%, 63.6%)
Environment sanitation	20% reduction in env. antibiotic exposure, Env<->Human by 50%	100% (58.3%, 100%)	100% (26.1%, 100%)	39.5% (2.4%, 99.9%)
Humans and animals	All human<->animal by 50%	96.8% (6.4%, 100%)	65.3% (4.2%, 100%)	27.9% (1.4%, 83.1%)
Transmission	All spread 50%	100% (100%, 100%)	100% (100%, 100%)	100% (94.8%, 100%)
Usage intervention	All usage 50%	96.5% (11.2%, 100%)	79% (15.4%, 100%)	23.3% (11.1%, 58.4%)
Animal antibiotic use	Animal usage 30%	25.2% (0.7%, 100%)	3.6% (0.2%, 96.4%)	6.4% (0.2%, 48.8%)

Our focus was on reducing AMR burden in humans (Figure 4), however our model also captures the AMR burden in animals and the environment. We explored how similar the impact of the intervention packages were across each setting. In all three countries, interventions tended to impact all settings similarly, showing a high level of interdependence between the settings (Figure 5), as well as a high level of uncertainty. This comparison emphasises the high level of impact of the “Spread down 50%”, “England package” and “Environment target” intervention combinations across all three countries.

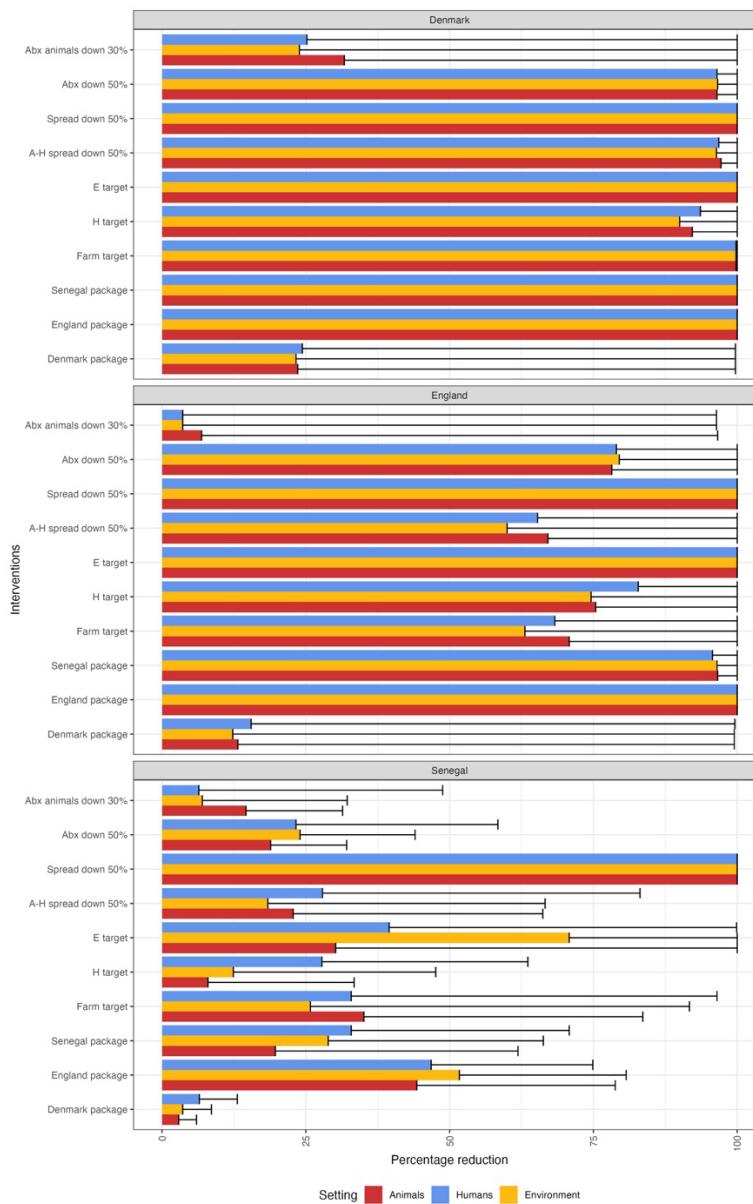


Figure 5: Intervention impact as a percentage reduction in proportion resistant in each of the three settings (colours) after 5yrs of holding the parameters at intervention values for the three countries (panels) over the 100 best parameter values. The bar shows the median with 95% range. For the Senegal package, for some parameter sets the resulting level was higher than the initial level and hence the error bars reach to negative values

and are not shown here. E = environment, H = human. The blue bars reproduce the results shown in Figure 4 above for the impact in humans.

Sensitivity analyses

To determine whether our results were robust to variation in key parameters, we extracted the parameter sets that contained the maximum and minimum values for each of the 15 parameters for each country from the 100 best parameter combinations. We then simulated the model using these parameters and compared the levels of resistance in humans in 2022 and the impact of reducing antibiotic use in animals. In this univariate parameter sensitivity analysis (Figure 6), it can be seen that the variation in individual parameter values and associated levels of resistance vary by country (Figure 6A). The biggest variation in resistance over a single parameter range in Denmark and England is due to usage and spread parameters, whilst in Senegal the top three include two rate of loss parameters. This almost reverses for the parameter ranges with the biggest variability in the percentage of resistance after 5yrs of the “Abx use down 30%” intervention which is large for rate of loss of resistance in the environment and humans (μ_E, μ_H , Figure 6B) in Denmark and England, but large for usage and spread parameters in Senegal. This variation is similar for other intervention sets (Supplementary Figure S4) but not universally true. We did not account for the differences in correlation between parameters in the best fitting parameter sets and the wide level of variability emphasises that there is not clear universal ranking of parameter importance. The importance of this correlation and the nonlinear relationship for a single parameter with these impacts can be seen for example in Denmark for β_{EH} (Figure 6B). There the level of intervention impact is high for parameter sets with the maximum and minimum value of β_{EH} , but is much lower for middle values that exist in the results from other parameter combinations shown.

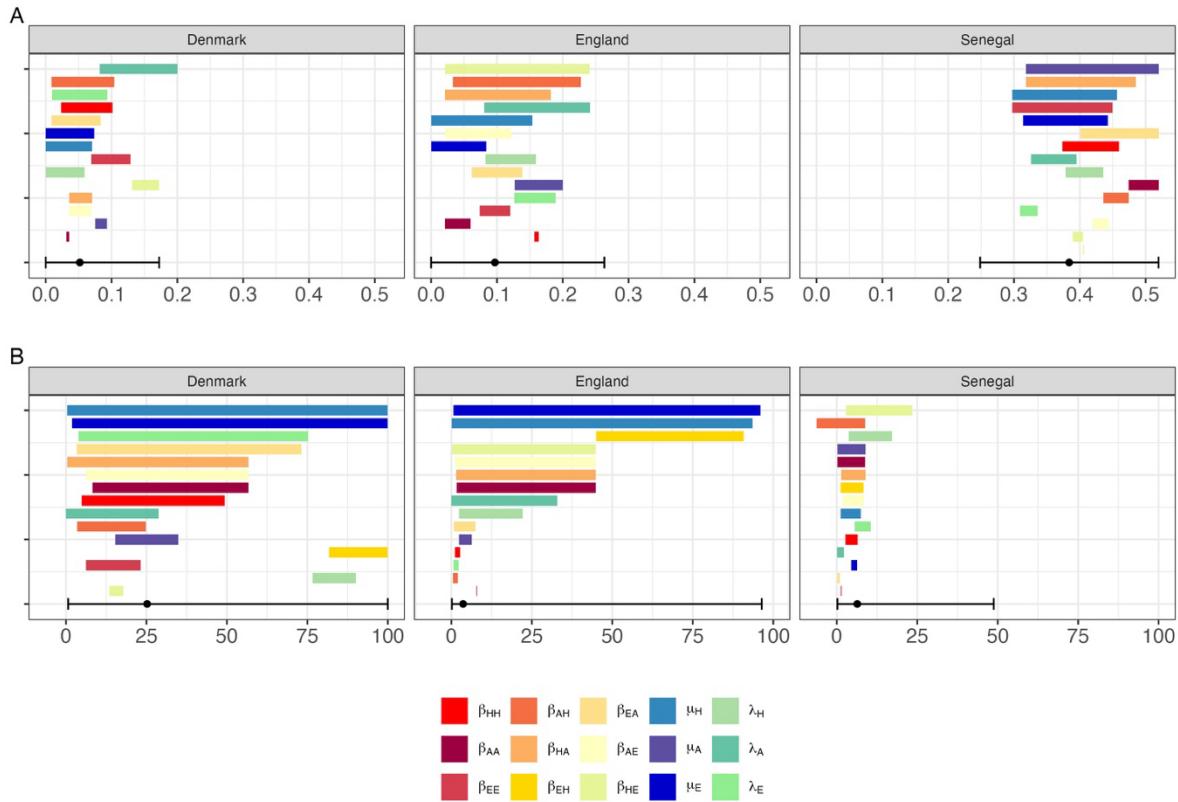


Figure 6: Univariate sensitivity analysis: the levels of resistance in humans predicted by the model in 2022 (A) and after running the “Abx use in animals down 30%” intervention (B) when each of the 15 parameters (colours) are at their minimum and maximum values within the 100 best parameter sets for each country (panel). Black point and line indicate median and 95% range over 100 best parameter sets. Green palette colours indicate usage parameters, blue palette are rate of loss of resistance parameters and orange palette are spread parameters. See equations in methods for a key to exact parameter values. Note here that the greater range for some parameter values within the 100 best parameter sets is not corrected for as the range is similar for many parameters (see Figure 3).

To explore the sensitivity of our results to the inputted data and to some key model assumptions we explored fitting to different datasets and assuming a time-varying transmission rate. We fitted the model to data on only resistance levels in animals and humans and, as would be expected with a least squares fitting method with no weighting, the model produced a slightly better fit for humans and animals, but a much variable range of levels for resistance in the environment (Supplementary Section 6). The impact on the overall intervention impact estimation was mostly small but always positive (always more of an impact on resistance when don't include environment in fit). The biggest change was for Senegal, and in particular for the “England package” with a difference in percentage reduction of 25%.

When including a time-varying transmission rate between humans and animals in the model, we could better recreate the data from Senegal leading to an even stronger correlation in the human and animal sectors for transmission and clearance parameters (Supplementary section 7). The impact of the intervention packages was greater than for Senegal but slightly smaller for Denmark and England, particularly for the Environment and “England package”.

Discussion

Understanding the relative contributions of selection and transmission of antimicrobial resistance (AMR) in different settings from a One Health setting is vital to improve intervention targeting and to control this global public health priority. In this work we aimed to improve the evidence base for such targeting by developing a mathematical model to investigate and compare the same set of intervention packages in three countries (Senegal, Denmark and England). We found that parameterising and fitting a simple mathematical model was highly difficult due to a lack of data across One Health sectors.

From our simple model, our results support targeting overall transmission between settings, in particular from the environment. This suggests that the environment is an important reservoir for the development of resistance^{24,35} but also that transmission may be the main driver of resistance levels, as has been found in previous one health AMR models³⁶. As expected, our most ambitious intervention combination (“England package”) had a high impact but this is likely driven by the impact on spread. The sometimes negative impact of the “Senegal package” likely represents an effectively zero impact of this low level of reductions which was unable to curb the trend of increasing resistance. Our sensitivity analyses suggest that uncertainty in the impact of interventions is greatest for Senegal and that the greatest variation in impact is seen for the Environment and England intervention packages.

Our result that resistance in Denmark could often be reduced to zero, as well as the 100% reduction from other interventions (such as the “spread package”) highlight a key structural limitation and uncertainty for models of AMR dynamics that needs exploring and quantifying in future work: when has resistance plateaued? There is some evidence that, once resistance has built up or become endemic, reductions in AMU may do little to reduce levels of AMR (at least in the short term)³⁷. However, this notion is not well understood nor quantified and hence was not included in the model. Moreover, we need more information on the balance between reducing antibiotic use and animal health, with how far can biosecurity measures go in reducing or stopping transmission?^{38,39}

Our intervention packages are aspirational, we provide no health outcome or cost estimations but have tried to link them to existing National Action Plans and discussion with key stakeholders. This reflects the wider poor evidence base for One Health Interventions, and how to rank them. We hope that our estimates, although highly uncertain, help identify where more evidence is needed: in particular our results emphasise the importance of the often underexplored loss of resistance rates. This is something that is likely to vary by setting and within each setting (e.g. may be higher in some environmental settings such as water than soil), and a rate which would be hard to influence in some settings (e.g. removal from gut microbiome). Expert opinion on the details of intervention choice and implementation now need to be considered e.g. how would we reduce spread from environment to humans and animals as proposed in the highly impactful “Environment” package? This may involve better water sanitation, or could be fundamental investments in

WASH packages. The model result pointing to the importance of targeting spread suggests that interventions such as infection prevention control (IPC), vaccination and biosecurity may be highly effective in reducing AMR.

This modelling study is highly limited both in the simplicity of the model and the availability of parameters to input and prevalence to fit to resulting in many unidentifiable parameters. The AMR field needs to work hard, using initiatives like in Kenya⁴⁰ with interdisciplinary partners, to tackle this lack of cross-sectoral data in order for modelling tools, such as the one developed here and those used in the COVID-19 pandemic, to support intervention design and policy decision making⁴¹. Despite this simplicity we still had 15 parameters suggesting that a more complex One Health model would struggle to be parameterised and highlighting both the intricate and multiple relationships that AMR involves. Future work should focus both on accurately assessing one part of the system and pairing with other general models such as this to build an ecological understanding.

We inputted varying antibiotic use parameters as well as fitting to longitudinal AMR prevalence data but found such data highly hard to source. Even when it was available, it was at a national level and often only from select populations or settings. The latter may cause bias issues if for example human data is only from patients with the most serious infections (e.g. neonates) or if environmental data is only from coastal areas which is obviously not representative, or if data collection has changed over time. We had no information on this bias and so could not account for it. For Senegal, the data was highly sparse and uncertain. Using (and modelling) only annual national level data is also an issue as it is an average over a huge amount of population and geographic-linked variation⁴², including that linked to seasonality, rural/urban, intensive farming etc. These are likely to be hugely important in driving variation in transmission and selection effects that will be key to understanding the One Health contributions to AMR prevalence with subtle targeted interventions. Surveillance systems need to be established and connected over One Health settings to generate necessary data over a substantial period of time.

A key limitation of this work is the simplicity of the model populations capturing only three “settings”, grouping highly diverse populations and sectors (e.g. soil and water) together. This allows for broad interpretations of the spread of AMR in the One Health space, but means that variation within geographical settings or across species is missed. Moreover, whilst we were able to include an approximation to past antibiotic exposure, we did not predict trends going forward (assuming that antibiotic use remains at current levels during the intervention period).

Other limitations link to the time-varying nature of some of the parameters: whilst we fitted to time-varying AMR prevalence data where available and included time varying usage, we only had “kgs” used and did not account for population size changes. We know that animal populations are likely to have varied over time, which may have affected our “force of usage” shape parameters (Figure 1). Moreover, averaging use in humans and animals to give an environmental level may miss cumulative effects in certain environmental settings. In

sensitivity analysis, we varied transmission rates between humans and animals using proxy data to reflect changes in farming intensity which led to slightly better model fits for Senegal, but little impact on intervention impact except for the most ambitious targets. Future work should explore how closely these proxy indicators capture true changes in transmission - our current indicator may reflect intensification more than true contact changes. Moreover, fundamentally more data is needed on levels of resistance across the three settings. In particular, from the “environmental” setting, and in longitudinal datasets to enable exploration of “loss” of resistance rates.

Care should be taken when interpreting our model outputs. As has been mentioned above, a 100% reduction is very unlikely, and thresholds are likely to play in at low levels of resistance as seen in Denmark in particular. The broad and similarity in distributions of best parameters (Figure 3) is also unexpected and suggests that there was insufficient data to narrow down the parameter values to truly capture each individual country, though we could see some differences between our high income European settings and Senegal. The strength of providing more data to such a general model as this, which could be applied to the three countries, would be clear parameter differentiation between countries which could then point to context specific intervention targets. Future models should expand deterministic structures to explore stochastic effects such as rare but initiating spread movement of AMR from animals to humans.

Previous models attempting to capture the One Health spread of AMR are limited⁴³. Our model is similar to that used to explore resistance in Thailand which suggested that targeting transmission and ABU simultaneously would be effective²⁰. However, our model does not assume that spread is always dependent on antibiotic use which likely explains our lower impact of reducing antibiotic exposure, as has been seen in other work³⁶. Instead our work shows a similar high impact of transmission (or “spread”) and the importance of the environment as results from previous models^{21,36,44}. The main difference between the latter model²⁰ and the one here, was again the inclusion of a forcing term for resistance dependent on antibiotic exposure (i.e. resistance could be acquired de novo) which we did not include as we assumed that resistance here is on a mobile genetic element not mutational (all resistance is acquired via transmission). Taken together with some of the earliest modelling work in this area³⁶, these models collectively emphasise the importance of targeting transmission and the likely small impact of reducing antibiotic use in animals expect in some settings where it is already highly unregulated (potentially in Senegal).

In conclusion, our simple model supports the importance of targeting transmission and spread of bacteria across the One Health settings to have the biggest reduction in AMR prevalence in humans. Model structures such as these need to be supported by detailed sub-analysis of individual parameter values and how they vary by individual settings to support wider use of generalisable frameworks. Our intervention impacts should be

interpreted as an indicator of hierarchy within the wide error ranges on our model's ability to capture resistance trends across the One Health settings.

Methods

Model

The model considers the fraction of the *E. coli* population in humans (H), animals (A) and the environment (E) that are resistant to third generation cephalosporins (3GC). We chose this resistance due to their “critical” importance and based on input from our the SEFASI Knowledge Hub. It assumes that resistant strains are transmitted between these three settings. As previously^{20,22}, resistance is spread via transmission within and between environments, as well as by an additional acquisition rate which is dependent on exposure to antibiotics, capturing the impact of selection on the chance of successful transmission within that setting. We assume, due to the nature of the resistance gene (on a mobile element⁴⁵), that *de novo* resistance development is not possible. We model “spread” rather than ‘transmission’ because our parameterisation captures both transmission and replication within a setting.

The basic model structure is shown in the equations below:

$$\begin{aligned}\frac{dH}{dt} &= (1 + \lambda_H \text{usage}_H(t))\beta_{HH}H(1 - H) + (1 + \lambda_H \text{usage}_H(t))\beta_{AH}A(1 - H) \\ &\quad + (1 + \lambda_H \text{usage}_H(t))\beta_{EH}E(1 - H) - \mu_H H \\ \frac{dA}{dt} &= (1 + \lambda_A \text{usage}_A(t))\beta_{AA}A(1 - A) + (1 + \lambda_A \text{usage}_A(t))\beta_{HA}H(1 - A) \\ &\quad + (1 + \lambda_A \text{usage}_A(t))\beta_{EA}E(1 - A) - \mu_A A \\ \frac{dE}{dt} &= (1 + \lambda_E \text{usage}_E(t))\beta_{EE}E(1 - E) + (1 + \lambda_E \text{usage}_E(t))\beta_{HE}H(1 - E) \\ &\quad + (1 + \lambda_E \text{usage}_E(t))\beta_{AE}A(1 - E) - \mu_E E\end{aligned}$$

The dynamics are the same for each setting (humans, animals, environment): resistance can spread into setting X through transmission between individuals or bacterial growth of 3GCE within that setting (humans, animals, environment) at a rate β_{XX} or by transmission from other settings (from humans at a rate β_{HX} , animals at a rate β_{AX} or from the environment at a rate β_{EX}). The impact of time varying antibiotic exposure in that population (usage_X) is to increase the chance of such spread in this setting at some relative level (λ_X) and thus an additional term is included with a multiplicative antibiotic exposure term ($\lambda_X * \text{usage}_X$) which multiplies the spread rates to and within this setting ($\beta_{XX}, \beta_{YX}, \beta_{ZX}$) (e.g. as in⁴⁶). This captures the assumption that antibiotic exposure has an effect on the recipient (increasing the chance of successful transmission) more than the transmitter. A background rate of attrition of 3GCE is assumed to be different in each setting (μ_X) and independent of antibiotic exposure. As 3GC resistance is usually on a mobile genetic element not mutational we did not include a background mutation rate to resistance.

The model is written in R version 4.2.3, with open source code available on GitHub⁴⁷. We built a deterministic simulation model with discrete time steps of 1 week, as we assumed that this would be less than the average length of time successful carriage of 3GCE would persist⁴⁸. We calculated a yearly average proportion of *E. coli* with resistance in each setting to compare to the national yearly data available.

Parameter values and data

For parameter inputs, due to uncertainty in many transmission and antibiotic effects we varied many across the full range possible (Table 2). Unlike in (11), we made no assumptions about relative size of the spread parameters (i.e. did not set $\beta_{HH} > \beta_{AH}, \beta_{EH}$ and $\beta_{AA} > \beta_{HA}, \beta_{EA}$).

We searched the literature for data on resistance to third generation cephalosporins from the three countries. We used phenotypic resistance (instead of presence of e.g. *bla* genes) where possible (Supplementary 2).

For humans in Denmark, we obtained data from the DANMAP reports⁴⁹ from 2011 onwards. Prior to that we used the data from European Antimicrobial Resistance Surveillance Network (EARS-Net) which is for bloodstream infections only, assuming that this resistance prevalence is true for all infection types and colonisation⁵⁰. For Danish animals, we pooled the data for cefotaxime resistance (the only tested 3GC) from samples from beef/cattle, broiler meat/broilers and pigs/pork as available from 2010⁵¹. We could only find one environmental sample data point (from a multicountry wastewater survey) for 2016⁵².

For England we obtained data from the ESPAUR reports for humans from 2017⁵³ and from EARS-NET before then. This was data from bloodstream infections. For consistency, we used the only longitudinal data available for food-producing animals, which was from pigs⁵⁴. We could only find one environmental sample point (from a coastal water survey)⁵⁵.

For Senegal, for humans we had data from a large hospital in Dakar to approximate recent resistance levels from blood and pus samples from 2014⁵⁶. Before 2014, we extracted data from community urinary tract infections from a single study⁵⁷. This was also supplemented by three single time point studies^{30,58,59}. We had only one wildlife sample for resistance from the environment⁶⁰. For animals we had data from two studies for two time points^{61,62}.

Advancing previously published models^{20,22}, we included time varying AMU as a proxy for antibiotic exposure in each setting ($usage_X(t)$, Figure 1). For the human and animal settings we took estimates for the amount of cephalosporins, and where possible 3GC cephalosporins, used in humans and animals in kilograms per year at the national level. For Denmark, we used total cephalosporin use from DANMAP for humans and all animals⁶³. One anomalous high data point in 2017 in human use was included (3104 kg vs ~1660 kg the year before and after). For England, for animals we used the 2022 VARSS report⁵⁴, whilst for humans we used the data in the One Health report⁸, although only available for 2013 and 2017. For Senegal, we had data only for humans from the MAAP 2022 report⁶⁴ (Supplementary section 1) for 2017-

2019. For animals in Senegal, we had no data on kilograms used (only some data on low levels from OIE reports⁶⁵). To calculate AMU in animals, we searched for evidence for the ratio of animal to human use. For Denmark and England the average ratio of animal to human use was 0.279 and 0.263 respectively. However, Denmark and England are outliers in terms of antibiotic control in livestock. Hence we used a global ratio of approximately 70% of antibiotics being used in livestock, 30% in humans^{66,67}. We used this ratio ($70/30 = 2.3$) to generate approximate data for animal use in Senegal from human use. As this was ultimately normalised to provide a trend that was then multiplied by the exposure term the relative levels should make little difference.

For AMU or antibiotic exposure over time in the environment, we could find little data on 3GC levels or residues. Hence for the AMU exposure parameter in the environment, we assumed that antibiotic residues in the environment is proportional to animal and human usage. Hence the exposure in the AMU was some proportion (fitted) of the sum of the total of animal and human use.

For the model, the trend of the exposure is key, as the scaling term (λ_x) influences the relative impact on spread (Figure 1B). Hence, we normalised the usage over time by dividing by the maximum value of the usage data available for that country and that specific setting. As we needed a value for usage in each week, we filled in gaps in the data on usage assuming it would be the same as previous years until a new data point. 3GC were developed in the late 1970s⁶⁸ with global sales increasing dramatically during the 1980s. We chose to assume introduction of use in 1985 with linear scaling of use to the first data point (though not all these calculations were needed depending on resistance availability - see below). The calculations to generate input usage data are in the file `0_usage_data.R`⁴⁷.

Due to the limit on 3GC use in Denmark for food-producing animals from 2010, but open access data available only for 2003 and 2015, we assumed a constant level of use from 2003 to 2010, and then fitted a decreasing line between the 2010 level and 2015 level. Resistance to 3GC can confer resistance to other generation cephalosporins, hence, we still assumed there would be usage that may select for 3GC resistance despite this ban.

Initial conditions and model fitting

We started the model in different years for each country depending on the availability of data. This was set to be the earliest year that we had data on 3GC resistance prevalence in *E. coli* being greater than zero in any setting. For England this was in humans in 2001, in Denmark in humans in 2005 and in Senegal humans and animals in 2003 (see file `0_initial_conditions.R`) (Figure 1).

To calibrate the model, we used Latin Hypercube sampling to sample 100,000 parameter sets from the parameter ranges identified for each parameter (Table 2). For the scaling of

antibiotic exposure and proportion loss per time step the full range from 0-1 was used. For the spread parameters, an upper limit of 1×10^{-5} was set.

The deterministic model was then run until 2022, with a timestep of a week, for each parameter set for each country separately. The distance between the annual average resistance proportion from the model and data on resistance prevalence in samples from each setting was calculated, and the 100 parameter sets that gave the smallest squared distance were extracted.

Intervention package impact

The model was then run for a 5 year time horizon (2022 - 2027) for all countries using the best-fitting 100 parameter sets for all of the hypothetical intervention packages that are assumed to achieve particular targets (Table 3). The targets that the hypothetical intervention packages were assumed to achieve were chosen based on quantified targets from National Action Plans for Denmark and England, reasonable combinations from discussion with the SEFASI Knowledge Hub for Senegal⁶⁹ and explorations of the potential impact of focused but more extreme combinations (e.g. of reducing transmission between two settings to zero).

The “England package” was informed by the recent UK NAP, which has a target of a 5% reduction in total human AMU by 2029¹⁹. RUMA (Responsible Use of Medicines in Agriculture) has targets for antibiotic use in agriculture in the UK in place until 2024 which vary pragmatically by sector based on data on existing levels of use (harder to reduce already low levels). Here, we approximate the England package agriculture AMU reduction target based on the lowest indicated reduction target by the RUMA, which is 30% in pigs. This approximated target is lower than the 40% goal reduction in gamebirds (only other named category) and higher than anticipated achievable target in other categories, such as poultry (e.g. poultry⁵⁴).

For the “Senegal package”, we surveyed the SEFASI Knowledge Hub⁶⁹, using the most commonly suggested values to design a potential set of targets based on existing data and ambitions.

For the “Denmark package”, substantial targets and reductions in antibiotic use have already been achieved across sectors in Denmark⁵¹ so we developed a package inspired by current and potential targets. We used targets from the most recent National Action Plan for AMR for food production for 2021-2023³²: a 2% reduction in antibiotic use per year in pigs (2019-2022), which we approximate by a 5% reduction over the 5yrs of our simulation for all animals. There was also a focus on biosecurity from animals to humans specifically to stop MRSA, but presumably would impact on other resistant bacteria. We approximated this as a 10% reduction in spread from animals to humans (β_{AH}). We used the most recent National

Action Plan for AMR with targets for humans of a 10% reduction in critically important antibiotics⁷⁰ to inspire a reduction in human antibiotic use of 10%.

Alongside these we considered “Farm target”, “Hospital/community target” and “Environment target” packages reducing antibiotic exposure in humans / animals / environment compartments and linked between-setting transmission parameters. This was set at an aspirational 50% level except for the environment AMU which was presumed to be harder (so set at 20% reduction). We also considered intervention sets which just targeted spread by reducing rates by 50% for “Human + animal contact” or all spread parameters (“Spread intervention”). Finally, we had a set of two intervention packages which looked at reducing all antibiotic usage by 50% and one directly linked to SEFASI which explored a 30% reduction in antibiotic usage in animals only based on the Lancet Commission on AMR targets (10/20/30⁷¹).

Sensitivity analyses

We explored the impact of individual parameter variation (a univariate sensitivity analysis) on (a) the underlying level of resistance in 2022 and (b) the impact of the key intervention of reducing antibiotic use in animals by 30%. To do this we determined the parameter sets within the best 100 for each country which contained the maximum and minimum value of each parameter and then visually compared the levels of (a) and (b) for these values from the model with this parameter set. We did not control for correlations between parameters in these best fitting parameter sets.

A first sensitivity analysis changed the data for the model fit: as we had few data from environmental samples, we explored the impact of interventions on a model fitted to only the human and animal resistance prevalence. We also explored a time-varying transmission parameter rate between humans and animals, linked to changes in meat production volumes and practices, as well as population sizes over time (see Supplementary Section 2 for calculations).

Table 2: Parameter values for each setting, their symbol and the range chosen from for the latin hypercube sampling

Parameter	Setting	Symbol	Range (units)
Scaling impact of antibacterial usage on successful transmission	Human	λ_H	0-1 (none)
	Animal	λ_A	
	Environ.	λ_E	
Spread rates within settings	Human	β_{HH}	0 - 1 x 10 ⁻⁵ (probability of successful transmission on contact per week and replication)
	Animal	β_{AA}	
	Environ	β_{EE}	
Spread rates between settings	Human <-> Animal	β_{HA}, β_{AH}	Upper limit set from initial parameter explorations.
	Animal <-> Environment	β_{AE}, β_{EA}	
	Environment <-> Human	β_{HE}, β_{EH}	
Rate of loss of resistant bacteria	Human	μ_H	0 - 1 (proportion who lose colonisation per week)
	Animal	μ_A	
	Environ	μ_E	

Table 3. The intervention set explored in this model to run from 2022 - 2027

Interventions reduce:	Antibiotic exposure			Transmission
1. Denmark package:	human by 10%	animal by 5%	/	animal->human by 10%
2. England package:	human by 5%	animal by 30%	/	all transmission by 20%
3. Senegal package:	human by 5%	animal by 5%	/	all transmission by 10%
4. Farm target:	/	animal by 50%	/	all human-animal by 50%
5. Hospital/community target:	human by 50%	/	/	human-human by 50%
6. Environment target: 50%	/	/	env by 20%	env.-human, env-animal by
7. Human + animal contact:	/	/	/	all human<->animal by 50%
8. Spread intervention:	/	/	/	all transmission reduced by 50%
9. Antibiotic usage intervention:	all reduced by 50%			/
10. Antibiotic usage in animals:	/	animal by 30%	/	

Resource availability

The datasets generated and/or analysed during the current study are available in the relevant Github repository, https://github.com/gwenknight/SEFASI_transmission_model.

The open data the model was fit to is included in Supplementary 2.

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Authors' contributions

GK: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, software, supervision, visualisation, writing - original, review and editing.

RB: Data curation, formal analysis, software, writing - original draft preparation, review and editing.

EE: Supervision, methodology, writing - original, review and editing.

All others: writing - review and editing

Declaration of interests

The authors declare that they have no competing interests

Supplemental information

Document Supplementary 1 contains additional results.

Supplementary 2 Excel file with available data that the model was fit to.

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