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Article

A Quantitative Framework for Evaluating the Societal Impact of Antimicrobial Use Reduction in Agriculture

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Abstract:

Antimicrobial resistance (AMR) is an increasingly pressing threat to human, animal, and environmental health. Reducing the use of antibiotics in agriculture has been identified as a key way to curb the spread of AMR. However, the effect of such policies on AMR prevalence, and their broader impacts on agricultural, health, and economic outcomes at the population level have proven very difficult to estimate and compare.

This paper draws on and formalises ideas presented at the JPIAMR New Perspectives on Bacterial Drug Resistance workshop in June of 2022. With reference to emerging literature on the topic, it proposes a quantitative framework for estimating the relevant causal relationships needed to quantify the cross-sectoral impacts of AMR policies in agriculture, and for comparing these outcomes in like terms in a way which can feed directly into policy decision-making, notably without prohibitive data requirements.

The ability of researchers to apply frameworks such as this will be increasingly necessary in order to holistically capture the impacts of AMR policies and to situate them in the broader policy context; especially where the mechanisms of transmission are opaque or complex, where data availability is limited; and where policymakers must allocate scarce resources among many competing objectives.

Keywords: AMR; agriculture; One Health; health economics; policy; modelling

1. Background

Antimicrobial resistance (AMR) is an issue which affects all sectors of society and must be addressed by policy measures. As the FAO-OIE-WHO-UNEP Quadripartite has emphasised, this process falls ultimately into the hands of national governments(1). Crucially, national policymakers have a range of health-related and non-health-related objectives, and must decide how to allocate scarce resources among them.

A large portion of antimicrobial use (AMU) is directed into agriculture, particularly in food animal production. This has been suggested as a major contributor to the level of AMR in humans, and a number of interventions and policies have been introduced to try to reduce agricultural AMU(2–7).

Naylor et al.(8) provide an excellent exploration of AMR interventions as they relate to the One Health system, and recommend the use of multilevel compartmental models to explore such interventions. This was the approach taken in Emes et al.(9), who simulate the health-economic impact of hypothetical AMR interventions in agriculture in

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countries of different income levels. However, due to constraints in the extant literature and available data, this paper did not derive the shape and size of the statistical relationships between variables such as AMU in farms, human AMR, and all-cause morbidity and mortality[1]. Instead, it explored different feasible scenarios based on the available literature, inputting these into a mechanistic compartmental model. Morel et al. provide an extremely comprehensive exploration of the pathways by which AMR affects all sectors of the One Health nexus. They suggest a mechanistic mathematical framework for calculating this impact in a bottom-up way, and detail the data required to parameterise such an analysis.

In this paper, we propose a framework which combines agnostic top-down statistical modelling with the more traditional "bottom-up" mechanistic mathematical approach explored in the above literature. The aim of this is to facilitate analysis which is able to estimate the causal relationships needed to understand the pan-sectoral impact of AMR and AMR-related interventions, but with fewer data requirements and with less need to explicitly model each step[2]. Our approach to statistical modelling is informed by an earlier paper from Emes et al(11).

2. Rationale

Given the One Health nature of AMR and agriculture, pan-sectoral analyses of policies targeting AMR in agriculture should be able to answer the following :

- What effect will this policy have on the incidence of resistant infections in humans?
- What will be full the societal effect of this change in the incidence of resistant infections, including
  - The life years lost to morbidity and mortality?
  - The costs saved to healthcare?
  - The morbidity and mortality avoided by freeing up healthcare resources?
  - The labour productivity lost to infection?
  - The safety of chemotherapy for cancer, and of invasive surgeries, as influenced by the level of AMR?
  - Other indirect human health pathways?
- What will be the effect of the policy…
  - On agricultural productivity?
  - On the welfare of farmers?
  - On morbidity and mortality via food security?

A few problems arise when considering all of this together. For one, these various outcomes of policies to combat AMR are not easily comparable. For example, it is difficult to compare, in like terms, an averted incidence of disease with an increase in food security or a change in farm productivity.

Secondly, the approaches taken by the AMR literature so far often do not feed well into policy decision models of this type(11). Studies may approach the issue from a mi-

[1] Previous works have sometimes overcome the opacity of these statistical relationships by making the assumption of a unit elasticity of AMR prevalence with respect to systemwide AMU(10)

[2] For example, in this framework it is not necessary to explicitly model the growth cycle of animals, the mechanism by which antibiotics resistance is developed in these animals, and the subsequent mechanism by which this resistance is transferred to humans. Rather, we can simply estimate at the macro level the relationship between antibiotic use in animals and the incidence of antibiotic-resistant infections in humans at the population level

crobiological lens, investigating the relatedness of bacterial communities from small samples of humans and animals, which does not allow us to understand the population-level effect of a change in agricultural AMU on the incidence of AMR infections in humans. Where the burden of AMR is estimated, only human health outcomes are consistently considered (e.g. incidences of disease, number of deaths, and sometimes quality-adjusted life years (QALYs). When economic methodologies are applied, the techniques may rely on rules of thumb when it comes to discount rates and willingness-to-pay thresholds(12), and only some economic impacts (e.g. the cost to healthcare and the valuation of QALYs) may be considered.

Finally, the statistical relationships which must be estimated in support of frameworks like this (detailed in the next section) are often not known and have not been estimated at the population level. While the effect of antimicrobial withdrawal on farm productivity may be recorded in disparate small-scale trials, there has been little effort to characterise this relationship at the population level. When considering the effect of agricultural AMU on the incidence of AMR infections in humans, prominent studies may simply assume that all AMU has the same effect regardless of where it is used, and that there is a unit elasticity of the portion of AMR in human infections with respect to systemwide AMU(10). Also, assuming that the amount of total infections will stay the same when AMR becomes more or less prevalent is highly problematic(13).

3. Our Causal Framework

To inform policy in a pragmatic, feasible, flexible and comprehensive way, we have created this framework. It proposes a causal framework (below), as well as a two-step modelling process for use in real-life policy analysis. The aim of this paper is not to provide a complete theoretical explanation of the different ways in which antimicrobial resistance can impact society (Morel et al., 2020 does this very well(13)). Rather, it aims to provide the simplest possible framework that still comprehensively estimates the societal impact of AMR policies in agriculture. It is meant as a practical guide for researchers to use in future work, which is feasible with currently available data.

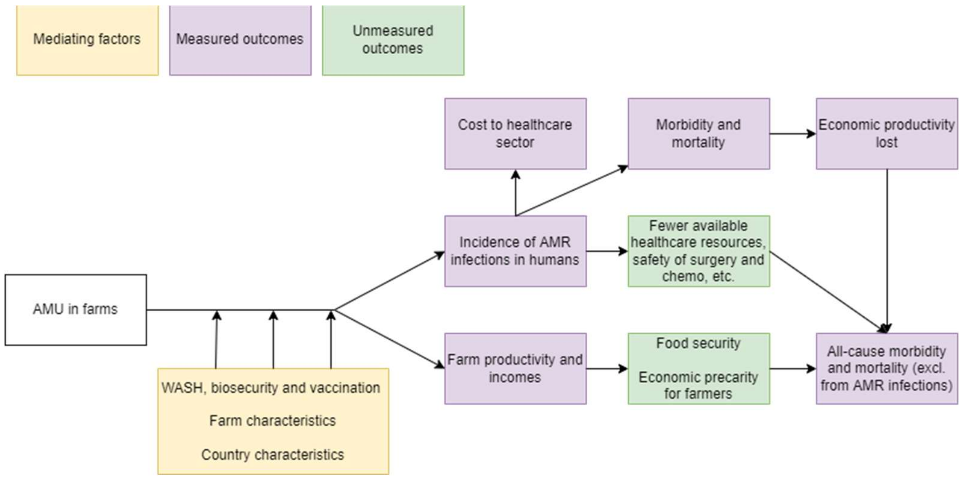

Figure 1. Causal framework for evaluating the pan-sectoral impact of policies targeting AMR in agriculture.

Here, the proposed policy (reducing antimicrobial use in farms) has two direct effects: one on the incidence of AMR infections in humans, and one on farm productivity. These effects will be mediated by country characteristics. For example, if there is generally a very high standard of water, sanitation and hygiene (WASH) infrastructure and rigidly enforced food preparation regulations, then the transfer of pathogens through

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the food chain may be limited, meaning that a change in agricultural AMU may not be felt in the general population. The effect on farm productivity will also be mediated by farm characteristics and any other interventions which are paired with the AMU reduction. For example, if antimicrobial use on farms is already restricted to necessary therapeutic use, then a reduction in antimicrobial use may result in an increase in untreated on-farm infections and a fall in productivity. Conversely, if the reduction in AMU is paired with an investment in WASH infrastructure or an increase in vaccination, then infections may be averted through non-antimicrobial means, and a decrease in farm productivity may be averted, or productivity may increase outright.

The effect on farm incomes is a major outcome, as is the effect on the incidence of AMR infections in humans. Lower agricultural productivity can influence food security and nutrition, resulting in higher all-cause morbidity and mortality. Lower incomes for farmers and vulnerability to output shocks (e.g. due to outbreaks in flocks and herds) can also result in increased economic precarity for (what is often) a large part of the population.

The increase in the incidence of resistant infections in humans will be associated with a number of deaths, incidents of sickness, and incidents of sequelae. People who die or are sick are also less able to work (in both paid and unpaid work), and this loss of productivity can also be estimated. An increased number of infections will also incur a cost to the healthcare system needed to treat those infectected. There will also be an indirect effect of these infections on all-cause morbidity and mortality, for example because a higher level of AMR can make invasive surgery less safe, or because more AMR infections will place strain on scarce healthcare resources.

The causal framework introduced here is similar to the one used in Emes et al., 2021(14). However, it is expanded somewhat to include more causal pathways. It is also different in that it involves statistical estimation of the main causal relationships, as will be explained in the following section.

4. The Two-Step Modelling Process

4.1 How to interpret this framework

Practically applying this framework can be done using a (relatively) simple two-step process which does not have prohibitive data requirements. First, statistical modelling is used to estimate the main causal relationships considered. Then, the results of these statistical models, along with other parameters, are fed into a mathematical meta-model which produces results with a direct cardinal interpretation for policymakers.

Let us briefly clarify the scope of this section. Here we do not aim to present a detailed pre-analysis plan, rather we present an overview of the modelling process that we propose. The reasons for this are a) that presenting a complete pre-analysis plan would likely double or triple the length of the paper and greatly exceeds our present scope, and b) this framework is general, and can be applied to a range of systems depending on the goal(s) of the researcher(s) using it.

When practically applying this framework, a number of considerations will have to be taken.

1) For one, the regression equations listed in the following subsection are simplified illustrations. In reality, a number of specifications should be explored to determine the most appropriate functional form. Statistical tests should be ap-

plied as relevant, for testing for the presence of heteroskedasticity and multicollinearity, using a Hausman test(15) to determine which kind of panel regression is most appropriate, examination of autocorrelation coefficients and partial autocorrelation coefficients to determine which lags are most appropriate, etc.

2) Secondly, the way that data are cleaned to fit into these equations will need careful consideration. For example, will AMU be coded as the number of defined daily doses (DDD) nationwide per unit of human population, or as the total expenditure on antibiotics, or in some other way?
3) Where will these data come from?
4) What is the best way of expressing outputs such that it has a cardinal interpretation which can feed into the health economic analysis of the mathematical meta-model? It is not enough just to establish the presence of an association between (for example) the prevalence of AMR and the use of antibiotics in pigs. Rather, we need to know what specific change in the latter we can expect after a given change in the former. Similarly, will the analysis look at the incidence of all antibiotic-resistant infections together, or will there be a separate regression for (for example) infections of different levels of severity, or different types of infection?

These considerations have no definite answers, and are not exhaustive. In all likelihood, the answers will depend on the setting concerned and on the goals of the researcher(s) applying the framework.

Below, we elaborate on the framework itself.

4.2 Stage 1 of 2 – statistical modelling

First, we estimate the relationship between on-farm AMU and farm output, controlling for WASH, vaccination, biosecurity, and other relevant covariates. This could be done through large-scale farm trials where antimicrobial stewardship (AMS) interventions are implemented, both alone and in combination with complementary interventions. It could also be done using large national datasets on agricultural AMU, farming practices, and farms' economic performance, either cross-sectionally or in panel format, e.g.

$$\text{productivity}_{i,t} = \beta_0 + \beta_1 * \text{AMU}_{i,t} + \beta_2 * \text{WASH}_{i,t} + \beta_3 * \text{WASH}_{i,t} * \text{AMU}_{i,t} + \boldsymbol{\beta} * \text{controls} + \varepsilon_{i,t}$$

We then estimate the relationship between farm output and population-level morbidity and mortality (via food security, nutritional uptake, and farmers' economic precarity) by regressing all-cause morbidity and mortality on farm output. Because this regression would be highly endogenous (e.g. industrialisation may be related both to a fall in farm output and a fall in all-cause morbidity and mortality), we use weather shocks to instrument for changes in farm output, capturing only the exogenous component using second-stage least squares, i.e.

$$\text{farm.output}'_t = Z_0 + Z_1 * \text{rainfall}_t + Z_2 * \text{temperature} + u_t$$

$$\text{pop.mortality}_t = \beta_0 + \beta_1 * \text{farm.output}'_t + \boldsymbol{\beta} * \text{controls} + \varepsilon_t$$

Next, we estimate the relationship between AMU in livestock and the incidence of AMR infections in humans, e.g.

$$\text{incidence.AMR}_t = \beta_0 + \beta_1 * \text{AMU.livestock}_t + \beta_2 * \text{AMU.humans}_t + \boldsymbol{\beta} * \text{controls} + \varepsilon_t$$

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Finally, we estimate the indirect effect of the policy on morbidity and mortality (via strained healthcare resources, the safety of invasive surgeries, etc.) by regressing all-cause morbidity and mortality on AMU in agriculture, controlling for the incidence of AMR infections in humans and all other relevant covariates, e.g.

$$\text{pop.mortality}_t = \beta_0 + \beta_1 * \text{AMU.livestock} + \beta_2 * \text{AMR.incidence} + \boldsymbol{\beta} * \text{controls} + \varepsilon_t$$

All together, these statistical models will tell us: the direct and indirect effect of the proposed policy on population morbidity and mortality; and the effect on the economy via farm productivity, healthcare costs, and labour hours lost to disease.

4.3 Stage 2 of 2 – mathematical modelling

We now create a population-level Markov state transition model for farms and humans, with transition probabilities parameterised using country-level data, e.g.

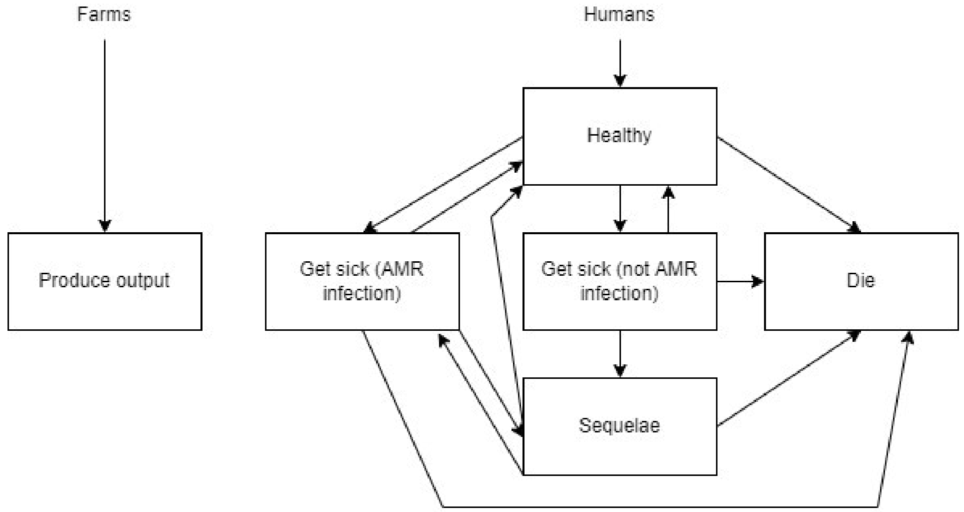

Figure 2. Example of state transition[3]

Using the statistical relationships estimated in stage 1, we allow the intervention to affect the transition probabilities as well as farm output. We can assign values to individuals in each state, including: an economic productivity, a QALY value, a cost to healthcare. We can assign a monetary value to these QALYs using a willingness-to-pay (WTP) threshold appropriate to the national healthcare system(16). We can run this model over an appropriate time horizon, allowing values such as the background growth in AMR, the level of labour productivity, agricultural output etc. to evolve over time as appropriate to the context. We can also estimate an implementation cost of the intervention; lump-sum, annually, or in any other modality of implementation. We then discount the values assigned to each state, as well as farm output and the implementation cost, using a discount rate appropriate to the national context(17). We do this for a scenario where the intervention is not implemented and for one where it is, and thus estimate the net societal utility gained from (i.e. the net monetary benefit of) the intervention.

5. Potential Applications and Concluding Thoughts

[3] Note that, depending on the type of infection modelled, more states might be added (e.g. 'immune', 'exposed').

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This modelling framework would allow us to see how the proposed intervention would affect each stakeholder (the general public, farmers, the healthcare system, the public sector). We can thus see if the intervention would generate 'losers', if it would be politically and socially acceptable, and if the financial commitments required would be feasible and worthwhile. This allows AMR interventions to be compared directly with unrelated alternative policies, and can help to prioritise AMR on the national policy agenda.

It also allows us to gain a holistic understanding of the societal effect of AMR policies without focusing on just one outcome type or stakeholder group. It also allows us to consider both the direct and indirect pathways by which AMR-related interventions impact human health. This builds on the findings of Emes et al., 2022(9), who highlight that the effect of such interventions on agricultural output and labour productivity can be just as significant as the direct effect on human health, and note the importance of economic methodology in determining apparent cost-effectiveness.

Whilst the framework proposed here focuses on AMR as it relates to antimicrobial use in agriculture, it could equally be modified to look at interventions related to healthcare or the environment. For example, it could consider the effect on pharmaceutical revenues from regulatory changes concerning the sale of antibiotics. Or, it could consider the effect on the replenishment or depletion of natural wealth stores from environmental interventions. It could factor in the effect on the incidence of susceptible bacterial infections from a reduction in therapeutic or prophylactic antibiotic use in humans, and so on. See the appendix for some examples of how the causal framework could look in those scenarios.

We hope that this framework can play a role in agenda-setting for future research, for example by increasing our awareness of the need for large-scale farm trials to help estimate the effect of AMR-related interventions on farm productivity, or by encouraging population-level analyses of the determinants of AMR in humans which could feed into future policy analysis. This framework is far from concrete, and we encourage other researchers, policymakers and other stakeholders to draw from, critique, and improve it.

Supplementary Materials: There are no supplementary materials to note

Author Contributions: This research article was authored by only one author

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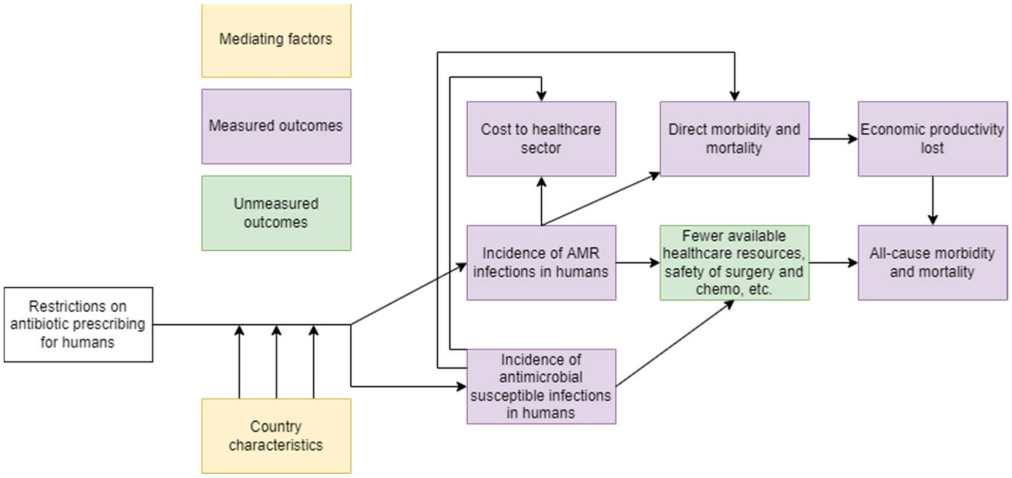
Appendix 1 – examples of application to other issues

Increased regulation of antibiotic prescribing



Prohibiting dumping of AMR-promoting compounds into environmental reservoirs