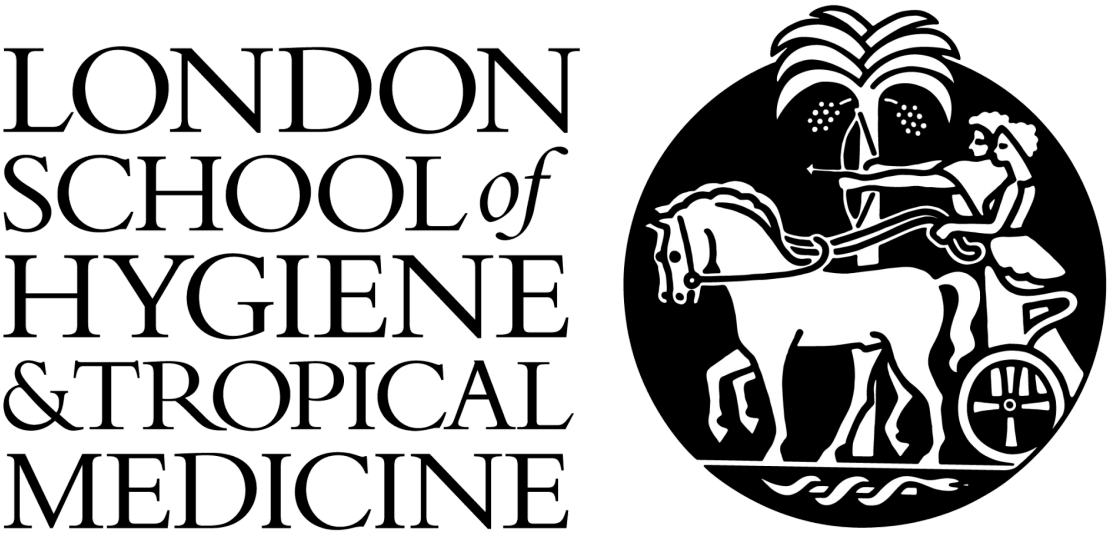
Revisiting key assumptions about animal antibiotic use and human health from a One Health perspective



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Declaration

I, Eve Emes, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis

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Abstract

Antimicrobial resistance is a major and growing concern to human health, as well as animal and planetary health. Globally, most antimicrobials used are in the form of antibiotics given to food-producing animals. This use is often divided into ‘therapeutic’ (curative) use and ‘nontherapeutic’ (prophylactic, metaphylactic, growth-promoting) use. The latter is seen as unnecessary and irrational - its elimination is often targeted by stewardship initiatives in order to reduce the human health burden of resistance.

However, such antibiotics may be important for safeguarding animal health and productivity in livestock farms. Further, our understanding of the ecological relationship between antibiotic use in animals and antibiotic resistance in humans is poor, and we do not know that such reductions in animal antibiotic use will be sufficient to reduce the human health burden of resistance. Finally, existing methods for One Health health-economic evaluation of AMR are limited, and our ability to capture the holistic effect of AMR interventions in agriculture is not sufficient to make such policy decisions with confidence.

This thesis seeks to address these knowledge gaps through a series of papers written as part of my work with the SEFASI Consortium. First, I design, present and demonstrate a holistic model for the health-economic evaluation of AMR interventions in agriculture (the AHHME model). I then analyse survey data from smallholder livestock farms to evaluate the effect of antimicrobial use and other practices on animal health and productivity. Finally, I analyse AMR surveillance data from humans and livestock animals to investigate the ecological relationship between animal antibiotic use and antibiotic resistance in humans.

These works suggest that even nontherapeutic antibiotic use may be important for animal health and productivity, and identifies potential complementary interventions which could make antibiotic stewardship on farms safer and more acceptable to farmers. While some ecological link was identified, reductions in animal antibiotic use alone may be insufficient to reduce the human health burden of resistance, especially in the short term. Finally, models such as AHHME should be used to capture a wider range of outcomes in our health-economic analysis of AMR (and other) interventions, and should feed into a participatory and mixed-methods policy decision-making process.

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Thank you also to all of the experts and stakeholders who were consulted as part of the SEFASI knowledge hub meetings, to all of the collaborators who have provided data and worked with me to design studies, and to all of the livestock farmers who have participated in the AMUSE surveys. Thanks as well to the JPIAMR, the MRC, and everyone else who has funded me over the past four years.

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Whoever wants to know a thing has no way of doing so except by coming into contact with it, that is, by living (practising) in its environment. ... If you want knowledge, you must take part in the practice of changing reality. If you want to know the taste of a pear, you must change the pear by eating it yourself.... If you want to know the theory and methods of revolution, you must take part in revolution. All genuine knowledge originates in direct experience

Máo Zědōng (毛泽东),
“On Practice”, July 1937

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Glossary

ABR	Antibiotic resistance
ABU	Antibiotic use
ABS	Antibiotic stewardship
AGPs	Agricultural growth promoters
AHHME	Agriculture Human Health MicroEconomic Model
AHHME-B	Agriculture Human Health MicroEconomic Model-Burden
AMR	Antimicrobial Resistance
AMU	Antimicrobial Use
AMUSE	Antimicrobial Use in Livestock Production survey tool
AMS	Antimicrobial stewardship
APHA	UK Animal and Plant Health Agency
ARGs	Antimicrobial resistant genes
CGIAR	Consultative Group for International Agricultural Research
DALY	Disability-adjusted life year
ESBL	Extended spectrum beta-lactamase
FAO	United Nations Food and Agriculture Organisation
FPAs	Food-producing animals
GAP	Global action plan (on AMR)
GDP	Gross domestic product
HEA	Health-economic analysis
ILRI	International Livestock Research Institute
IPC	Infection prevention and control
JPIAMR	Joint Programming Initiative on Antimicrobial Resistance
KAP	Knowledge, attitudes and practices

LSHTM	London School of Hygiene and Tropical Medicine
MDR	Multidrug resistant
NAPs	National action plan (on AMR)
OH	One Health
OIE	Organisation Internationale des Épizooties / World Organisation for Animal Health
QALY	Quality-adjusted life year
RVC	Royal Veterinary College
SEFASI	Selecting Efficient Farm-Level Antimicrobial Stewardship Interventions from a One Health Perspective
UKHSA	UK Health Security Agency
UNEP	United Nations Environment Programme
WHO	World Health Organisation
WTP	Willingness-to-pay

Chapter 1 - introduction and literature review

1.1 Introduction

This analytical commentary is submitted for my PhD by Prior Publication, alongside a portfolio of four connected publications, all connected to a One Health (OH) analysis of antimicrobial use (AMU) in food-producing animals (FPAs). I have authored these publications largely as part of my work on the Selecting Efficient Farm-Level Antimicrobial Stewardship Interventions from a One Health Perspective (SEFASI) consortium (1). SEFASI is a JPIAMR-funded project based at the London School of Hygiene and Tropical Medicine (LSHTM), which aims to conduct holistic One Health analysis of farm-level antimicrobial stewardship (AMS) interventions in England, Senegal and Denmark, eventually ranking them using multi-criterion decision analysis. Until April 2022, I was involved on a similar grant funded by the CGIAR (Consultative Group on International Agricultural Research) dedicated to evaluating the societal health and economic impact of interventions to reduce agricultural antimicrobial use. Prior to this, I trained in development economics and worked in economic research and public health policy. I use this background to apply a cross-disciplinary approach which uses political economy, statistical and mathematical modelling, and OH lenses to address issues in global public health.

Antimicrobial resistance (AMR) is the capacity of microbial pathogens to survive in the presence of antimicrobial medicines (antiseptics, antibiotics, antivirals, antifungals, antiparasitics)(2). Antibiotic resistance (ABR) refers specifically to the capacity of bacterial pathogens to survive in the presence of antibiotics, and is the focus of this commentary. Antibiotics are given to food-producing animals (FPAs) for a number of purposes, including to cure infection, as a prophylactic or metaphylactic to prevent infection, or added to feed in order to promote growth, such antibiotics being referred to as agricultural growth promoters (AGPs)(3). Prophylactic, metaphylactic, and (in particular) growth-promoting AMU is often referred to as ‘non-therapeutic’, contrasting it with curative use(3,4).

While ABR exists in nature, the use of antibiotics (ABU) can select for resistant bacteria. Resistance can spread among hosts through the transfer of resistant pathogens and antibiotic-resistant genes (ARGs), collectively referred to as resistomes. Antibiotic stewardship (ABS) and antimicrobial stewardship refer to efforts to use antimicrobials in optimal and responsible ways, minimising the emergence and spread of resistance while maximising the present and future efficacy of antimicrobial drugs.

Questions of AMR and AMS are sometimes approached using the framework of ‘One Health’(5), which sees human, environmental and animal health as interlinked and requiring interdisciplinary collaboration. AMR can have impacts on health across all three OH ‘sectors’: most straightforwardly, resistant infections are harder to treat and therefore incur greater morbidity and mortality for humans. This incurs a cost to healthcare systems and places strain on their resources. The risk of resistant infections can also make other aspects of healthcare (chemotherapy for cancer, use of catheters, nosocomial infections, invasive surgery) more risky, and the human health burden of resistance affects people’s ability to do both marketised and non-marketised work.

The presence of resistant infections on farms can also reduce agricultural productivity, farmers' economic security, and broader food security, as can the removal of antibiotics from farms(6). Finally, the environment acts as a reservoir for the development and spread of resistance, and the presence of antimicrobial residues and other pollutants can select for resistance in pathogens in the environment. One way of evaluating these impacts is health-economic analysis (HEA), either to assess the burden of resistance or to evaluate the cost-effectiveness of interventions combating AMR.

There has been a global drive to create a coordinated policy response to AMR. Among the key actors involved is the 'Quadripartite', a coalition of the Food and Agriculture Organisation of the United Nations (FAO), the World Organisation for Animal Health (OIE), the World Health Organisation (WHO), and the United Nations Environment Programme (UNEP)(5). The Quadripartite is a multilateral effort to coordinate a policy response to AMR from a OH perspective, and has created a 'Global Action Plan' (GAP) on AMR. They work in tandem with national governments, many of which have National Action Plans (NAPs) on AMR, as well as with other actors.

One Health, as a concept, is sometimes difficult to define. Discourse on OH from influential organisations makes mention of zoonoses, the link between human and animal health and food security, the impact of climate change and environmental degradation of food systems and human health, and the ability of AMR pathogens to spread between the three OH compartments(5). This approach sees efforts to safeguard animal, human and environmental health as connected and interdependent, requiring a coordinated effort from stakeholders and practitioners within these spheres and beyond(7,8). This framework, outlined by the WHO and by the Quadripartite more broadly, identifies a set of five key principles (equity, sociopolitical and multicultural parity, sociological equilibrium, stewardship, and transdisciplinary and multisectoral collaboration) underpinning One Health efforts(7).

While OH can be taken to mean simply 'human, animal and environmental health are connected', there are drives to generate a deeper and more transformative definition of health(9,10). Some authors, notable Raj Patel and Rupa Marya, write about conceptions of 'deep medicine' which see these three healths as a single ecology, rejecting the rationalist desire to separate 'self' from 'environment' and seeing the human body itself as an ecosystem which is not discretely separable from the broader ecosystem that we inhabit(10). I use 'One Health' throughout this thesis to refer to efforts to consider human, environmental and animal health together, while acknowledging that this falls short of a truly integrative approach.

1.1.1 Thesis angle

During my time working in the OH AMR space, I identified several assumptions (which I refer to in this thesis as 'themes') that were prevalent in the policy and research discourse but which I felt were potentially inaccurate and not sufficiently founded in existing evidence. Thus, throughout this thesis and the work presented here, I have chosen to review the basis for these assumptions, to interrogate them, and to propose alternative lines of thinking where relevant.

These assumptions are namely:

1) The notion that ‘nontherapeutic’ AMU in FPAs, particularly in the Global South[1], is inappropriate and unnecessary
2) The tendency to view AMR as primarily a human health concern, and to apply a human health perspective to health-economic evaluations of AMR and related interventions
3) The notion that reducing AMU in FPAs is an effective way to bring the human health burden of resistance down to desired levels

In section 1.2, I review the prevailing discourse on AMR and agriculture, highlighting the presence of these three assumptions and elaborating on them. In section 1.3, I then review existing knowledge about these three themes, before presenting my work in Chapter 2, and concluding in Chapter 3. Throughout this thesis, when talking about agricultural AMU and AMU in animal health, I focus on antibiotic use in food-producing animals. While non-antibiotic antimicrobials are used in agriculture, and antimicrobials are used in plant production and other forms of agriculture, these fall outside of the scope of the work presented here.

1.2 Discourse around AMR and agriculture

1.2.1 Nontherapeutic antibiotic use in livestock

AMR, the ‘silent pandemic’, is increasingly acknowledged as one of the greatest threats to human health; estimated to have contributed to five million deaths in 2019 with this number projected to grow considerably(12–15). There is widespread acknowledgment of the need for a globally coordinated One Health approach to fighting AMR, as manifested in the FAO-OIE-WHO-UNEP Quadripartite Global Action Plan on AMR(5,16,17).

Most global AMU is in animal health(18), and the centering of a One Health approach to AMR has led to increasing policy attention on the role of animal AMU(5,19–21). This AMU is assumed to be a major contributor to the human health burden of AMR(6,21–30), and there is a global policy drive to improve animal antibiotic stewardship(22,31–35).

Specifically, there is a tendency to divide animal AMU into ‘therapeutic’ and ‘nontherapeutic’ use(36,37). The latter is viewed as irrational[2] and inappropriate, and much policy discourse explicitly targets ‘excessive’ or ‘unnecessary’ use, often defined with respect to what is deemed ‘medically necessary’ for curative purposes (19,23,29,30,35,36,38–47). Conventionally, the spread of AMR has been attributed to the ‘abuse and misuse’ of antibiotics, despite the role of other factors(48): the influential 2015 O’Neill report explicitly references ‘unnecessary’ use in its title, even claiming that AMU reductions in agriculture can be done without damaging animal health or productivity, and referencing the ‘real of

[1] Throughout this thesis, I use the terms ‘Global South’ and ‘Imperial Core’ as used in world-systems theory(11), rather than terms such as ‘high-income and low-income countries’

[2] To elaborate, different conceptions of ‘irrationality’ exist. Referring to ABU, ‘irrational’ can mean antibiotics used which ‘[exceed] medical use(38). In economics, ‘rational’ may describe any behaviour which an actor has a material incentive to do. Thus, (medically) irrational antibiotic use may be (economically) rational, depending on the material incentives faced by farmers and other stakeholders

perceived' need for agricultural AMU to imply that much agricultural AMU is simply not needed(47).

Such claims differ in their treatment of countries in the Global North and Global South. There is frequent reference to rising meat consumption in the Global South driving the growth of global AMR(25,27,28,38). The influential O'Neill report explicitly references agricultural AMU in the Global South, and mentions that excessive AMU is a problem 'in many areas'(47), with other studies referencing high levels of AMR in the Global South and claiming that AMU in those settings drives global AMR by '[exceeding] medical use'(38). The Global South is seen as lagging in terms of antimicrobial stewardship, seen as having less awareness(49), with claims that stewardship efforts have been less successful there(33) due to differing priorities(49) and 'less developed hygiene and production practices'(27).

There is, nonetheless, acknowledgement in the literature of the necessity of AMU on farms, the lack of proven alternatives, and the potential dangers of removing them(50). There is some acknowledgment of the need for better knowledge and practice on infection prevention and control (IPC), biosecurity, husbandry, and antibiotic alternatives in reducing the need for antibiotics and allowing safer ABU reduction on farms(24,32,34,45,51,52). Removing antibiotics without these assurances could endanger animal welfare, worsen farmers' economic precarity, harm food security, and lead farmers to resort to more deleterious counterfeit antibiotics(24,32,45,53). This picture is complicated by the fact that the line between therapeutic, prophylactic and growth-promoting AMU is blurred and these uses are often employed concurrently(37). It is also uncertain if any level of AMU can be sustainable in the long run(50).

Despite a widespread desire to reduce agricultural AMU, knowledge gaps exist on how antibiotics are used on farms(42), the precise role of different kinds of AMU in determining farm-level outcomes(4,36), optimal or safe levels of use(50), strategies for reducing AMU(36,54), understanding farm IPC from a OH perspective(52), and the safety and efficacy of antibiotic alternatives(32,34,50). Taken together, these factors undermine the idea that the dangers of agricultural AMU to human health can be avoided by straightforwardly reducing it to some 'medically necessary' quantity (theme 1).

Despite the emphasis placed on simply reducing agricultural AMU, there exists a body of literature which takes a whole-system approach, recognising the complicated political economy of farm AMU. This includes recognising the role of creditors and landlords in influencing farmers' decision-making(20) and the need to involve animal health professionals in stewardship policy(26), recognising that economically precarious farmers may not invest in stewardship without demonstrable cost-effectiveness(55). Woolhouse and colleagues argue the need for an intergovernmental body on agricultural AMS, marrying scientific research with economics, social science and law; and the involvement of industrial stakeholders, government, animal health professionals, farmers, pharmacists, and patients in decision-making(50).

1.2.2 Health-economic methods in the OH AMR space

Policymakers face the problem of optimally allocating scarce resources to improve public health, weighing the costs and benefits of interventions and policy decisions using

health-economic analysis. There is a widely acknowledged need for health-economic evaluation in AMR by national governments and multilateral organisations(56). This includes quantification of the costs and burden of AMR(56–58) as well as cost-effectiveness evaluation of AMR interventions(57). It is acknowledged that this is needed in order to effectively allocate public resources(57,59) as well as to demonstrate the economic acceptability of agricultural stewardship interventions to farmers and to promote uptake(55).

That being said, an evidence gap exists in health-economic analysis (HEA) of AMR. For many AMR interventions, no cost-effectiveness evidence exists(23), and cost-effectiveness evidence is limited even for major intervention types such as hospital AMS programmes(60) or vaccines as a tool to combat AMR(61). Economic evaluations of antibiotics rarely include the cost of resistance(62). There is also a lack of evidence on the economic burden of AMR at the societal level, in the Global South, and in primary care(63).

Where analysis of the burden of AMR takes place, it has generally been limited to human health outcomes and costs to the healthcare system, failing to capture the societal impact of AMR and with no OH costing of AMR(14,56,57). The WHO's large-scale expert consultation on the health burden of AMR in 2018 suggested comparing disability-adjusted life years (DALYs) to policy implementation costs: of the 8 projects included in the report, only two mentioned healthcare costs and none included cost-effectiveness analysis(59).

Another group of economic evaluations have taken the approach of estimating the effect on gross domestic product (GDP) through the reduction in 'labour supply' arising from AMR mortality and (sometimes) morbidity, including the 2017 World Bank report(64), the 2015 O'Neill report(47), and the 2014 KPMG report(65). This approach does not place value on the loss of human life, but estimates its effect on economic output. The 2013 report by the US CDC simply included extra illnesses and deaths from AMR, as well as healthcare expenditure(66).

There is some acknowledgment of the need for a OH societal-level analysis of the impact of AMR and AMR interventions. Several papers propose frameworks for doing so, e.g. Morel *et al*.(56), Naylor *et al*.(67), and Noyes *et al*.(31). While some recent literature has expanded to include costs such as labour productivity, trade outcomes and livestock productivity(56), truly One Health analyses of the AMR burden remain elusive, driven in part by a lack of available data on the AMR burden(59).

1.2.3 The ecological relationship between animal AMU and human AMR

The design, evaluation and prioritisation of AMS policies requires an understanding of how AMU relates to AMR at the ecological level(68–71). While it is intuitive that the quantity of AMU in animals should influence the level of human AMR(37,38,70,72,73), a knowledge gap exists in terms of quantifying the extent of that relationship at the ecological level(17,36–38,70–72,74,75), due in part to a lack of available and appropriate data(36,38,50,70).

Little attention has been paid to this ecological relationship, and the assumption that it exists often rests on consensus rather than evidence(37) - some publications (e.g. O'Neill,

2015(47) take the correlation between human AMU and human AMR as evidence that the same must be true between humans and animals as well.

The transmission of resistomes between animal, human and environment is poorly understood and controversial(17,75). There are also reasons to believe that changes to animal AMU may have a very limited impact on human AMR for certain drug-pathogen combinations, at least in the short run(70). Once resistance has emerged and resistant strains become endemic, they may cease to be dependent on continuous selective pressure from AMU by humans and may therefore become decoupled from the quantity of AMU(47). AMR is also determined by factors other than AMU, including socioeconomic and public health factors and non-antibiotic environmental conditions, leading to an overestimation of the role of AMU(48,73).

Finally, we don't yet know if *any* amount of antibiotics can be used sustainably without leading to unacceptably high levels of AMR(50). Understanding the ecological relationship is therefore essential as it tells us if we should target a specific level of AMU or focus more heavily on other factors which determine AMR.

Where does this leave us?

In summary, the importance of AMR to human (as well as environmental and animal) health) is widely acknowledged, leading to a coordinated global policy initiative. This has led to initiatives to reduce animal AMU, especially nontherapeutic AMU which (particularly in the Global South) is thought of as irrational and unnecessary. Such AMU reductions are assumed to be beneficial for human health. Despite these assumptions, there is insufficient evidence on what impact such stewardship efforts would have on farm outcomes, and the extent to which they would be successful in reducing the human health burden of AMR. When HEA of AMR and AMR takes place, it is generally from a human health perspective. There is a sometimes-acknowledged need for a more comprehensive OH HEA of AMR, but efforts to do so have been limited.

From here, I draw out the three key assumptions described in section 1.1.1. For each assumption, there is a connected knowledge gap. Namely:

1) *Assumption*: the notion that 'nontherapeutic' AMU in FPAs, particularly in the Global South, is inappropriate and unnecessary

   Knowledge gap: we are uncertain what impact antibiotics (especially nontherapeutic antibiotics) have on farm outcomes, and on the impact of alternative interventions

2) *Assumption*: the tendency to view AMR as primarily a human health concern, and to apply a human health perspective to health-economic evaluations of AMR and related interventions

   Knowledge gap: there is a lack of One Health HEA of the societal impact of AMR and AMR interventions

3) *Assumption*: the notion that reducing AMU in FPAs is an effective way to bring the human health burden of resistance down to desired levels

   Knowledge gap: we are uncertain how (human and animal) AMU relates to human AMR at the ecological level, and therefore of the likely human health impact of AMU reductions

The papers in this portfolio aim to assess the validity of these assumptions and to fill the associated knowledge gaps. Before presenting these papers, I present a brief literature review scoping the current state of knowledge on these three questions (chapter 1.3). Specifically, it aims to answer 1) *what is our current knowledge about the role of AMU and its alternatives on farm outcomes?*, 2) *what health-economic methodologies exist in the AMR space?*, and 3) *what is our knowledge on the ecological relationship between (animal and human) AMU and human AMR?*

This review is more a narrative review than a full systematic literature review which, given the breadth of the topics reviewed, would greatly exceed the scope of this commentary. The purpose of the review is to scope out the state of our knowledge on these three questions, to situate my work in the context of the existing literature, to justify the existence of the research gaps to which my work responds, and to help understand the contribution of the papers I present in chapter 2.

1.3 Literature review

1.3.1 Search terms

Prior to conducting a literature search on databases, I searched through my Zotero(76) library (552 sources) and identified (by title and abstract) any sources which may be relevant to these three questions, as well as including any recent relevant reports from the Quadripartite organisations.

Subsequently, on 17 - 18 June 2024, I searched PubMed. Sources published in the last five years were included. The search was divided into three themes: 1) *the role of nontherapeutic AMU and its alternatives on farms*, 2) *health economic methods used in AMR*, and 3) *the ecological relationship between AMU and AMR*. The search terms used, and the inclusion and exclusion criteria, are described in table 1.

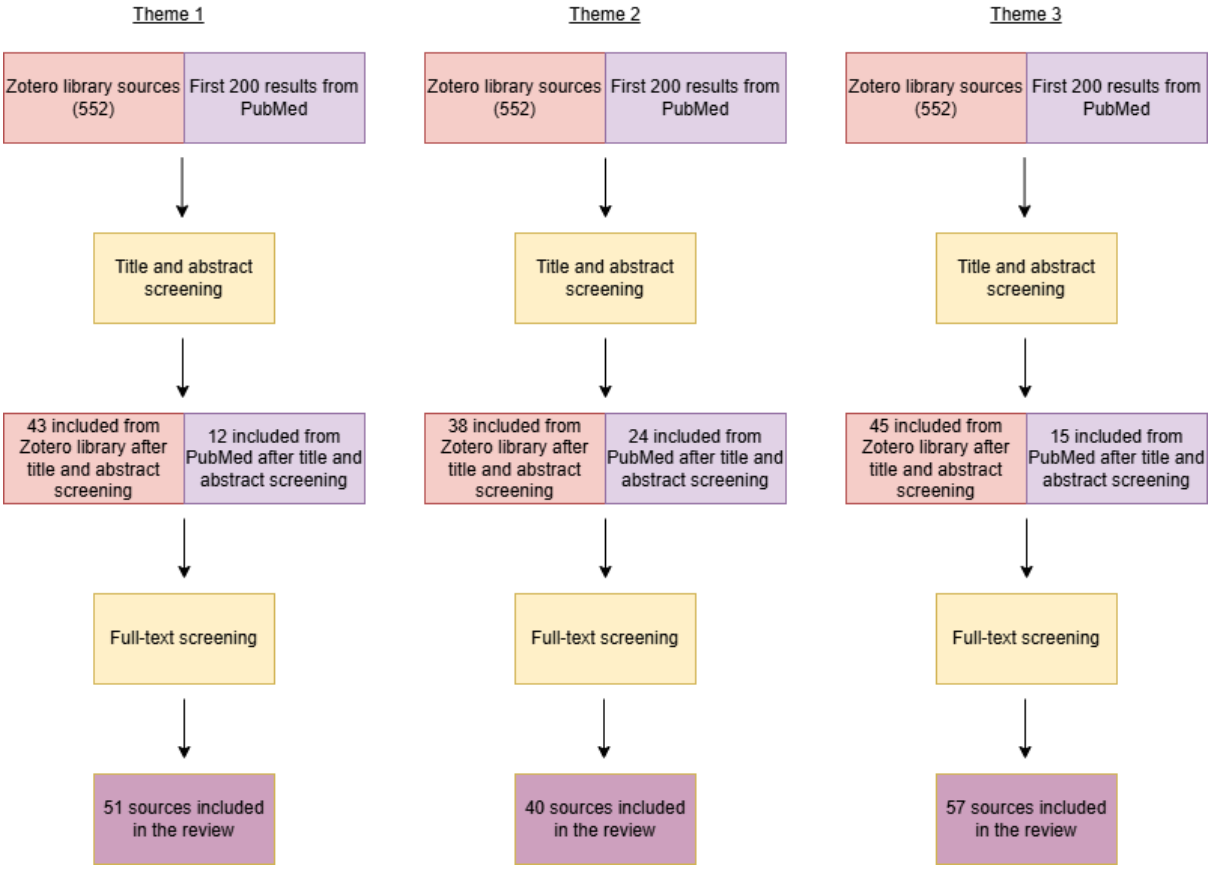
Table 1 - search terms

Theme	Search terms	Inclusion and exclusion criteria
1) The role of nontherapeutic AMU and its alternatives on farms	Antibiotic use OR antimicrobial use OR growth promoters OR biosecurity OR antimicrobial replacement OR antibiotic replacement AND health OR productivity OR disease	- A trial, data analysis or review which describes the impact of AMU, AMS, and/or other farm practices (which could potentially be paired with stewardship interventions) on animal health and productivity on livestock farms

	AND farm OR animal OR livestock OR agriculture OR animal production	
2) Health economic methods used in AMR	AMR OR antimicrobial resistance OR ABR OR antibiotic resistance AND Cost OR economic OR economics OR health economic OR health economics OR economic evaluation	- Actual health-economic analyses of AMR problems - Guidelines on health-economic methods for AMR problems
3) The ecological relationship between AMU and AMR	AMR OR antimicrobial resistance OR ABR OR antibiotic resistance AND determinant OR relationship OR link OR association AND Antibiotic use OR antimicrobial use OR AMU OR ABU	- Quantifies, measures or models the ecological link between AMU (in humans or animals) and AMR in humans - Studies otherwise measuring the determinants of human AMR or the link between human and animal resistomes were set aside to help describe the state of the literature

The first 200 results for each topic, as well as the 552 sources from my Zotero library, were screened by title and abstract, leading to the selection process described in Figure 1. The sources selected after title and abstract screening were subjected to full-text screening, leading to the final body of literature included in the review.

Figure 1 - literature selection process



As notes were taken on all sources for which I did full-text screening, many of those sources have also been cited in section 1.2, in the discussion (chapter 3), and elsewhere throughout this commentary.

1.3.2 The role of nontherapeutic AMU and its alternatives on farms

In accordance with the prevailing narrative (of nontherapeutic AMU being irrational), some studies suggest that nontherapeutic AMU in FPAs has little benefit for, or actively harms, farm-level outcomes. In smallholder chicken farms in the Mekong Delta, overall AMU was not associated with morbidity in one study(77) (although curative AMU guarded against mortality). Another study in the same setting found that prophylactic AMU never reduced the likelihood of disease, consistently increased the likelihood of diarrhoea, and increased the likelihood of disease for some antibiotic classes(4). In Europe and the US, some studies found that the economic consequences of removing AGPs have been minor(27,78), especially for production systems with stronger biosecurity(27).

That being said, there is a scientific basis for expecting nontherapeutic AMU to be beneficial. Antibiotics can bolster growth via modulating intestinal microflora when used at clinical

doses(78), and via other pathways when used below clinical doses, consistently aiding growth across species and production systems(79). In addition, many smallholder livestock farms exist in a state which necessitates antibiotic use. Economic precarity, lack of access to stewardship and biosecurity resources, high risk of infectious disease, and increasing demand for animal products may make antibiotics necessary to guard against risk and bolster productivity(6,28,38,43,80,81).

Regardless of their financial status, farmers often face strong incentives not to reduce antibiotic use. System dynamics modelling of Senegal's poultry production system revealed that ABU can partially compensate for what would otherwise be a lack of profitability(53). Antibiotics are often a very small portion of total expenditure, meaning that they may be worth keeping as a risk-management tool where profit margins are thin and uncertainty can be dangerous(6). After reviewing bans on AGPs in Europe and the US, Laxminarayan and colleagues(27) noted a fall in productivity and profitability of US, Swedish and Danish livestock. Denmark's Yellow Card Initiative, which introduced a quota on AMU in pig production, reduced profits and increased costs, and Denmark's earlier ban on AGPs reduced profits across livestock types(82). This weakens the narrative that biosecurity and stewardship in the Imperial Core are so advanced that antibiotics can be removed without consequences for productivity.

That being the case, there is an argument that reductions in AMU could be beneficial in the long run. While Denmark's Yellow Card Initiative did reduce profits, Belay and Jensen suggest that it will encourage investment in other production technologies and techniques and have long-term benefits(82). Laxminarayan and colleagues(27) make the same claim about Denmark's ban on AGPs.

Despite the potential economic risks of reducing on-farm AMU, there is a strong body of evidence suggesting that AMU can be reduced while maintaining or increasing productivity when this reduction is combined with complementary interventions in biosecurity, farm management, and Water, Air, Sanitation and Hygiene (WASH). Such intervention packages reduced AMU while maintaining or improving health and/or productivity in Belgian and Dutch broiler farms(24), European pig farms(32,83), Belgian pig farms(54,84), and Vietnamese chicken farms(43). In a review of One Health biosecurity and WASH interventions on farms, Pinto and colleagues(51) found that all three interventions which targeted AMU were able to do so while improving productivity. Sweden's ban on AGPs had less economic impact on farmers with stronger hygiene standards, and the negative productivity impacts of AGP bans in Europe and North America were significantly lower in the 2000s than in the 1980s, which some attribute to improvements in biosecurity during that time period(27).

There is also a growing body of evidence on the potential of alternative compounds to replace antibiotics on farms, both as growth promoters and as curative or prophylactic medicines. These include plant-based feed additives and nutritional supplements(34,35,45,85), bacteriophages(35,45,86,87), antimicrobial peptides(35,44,45), probiotics(35,45,88), antimicrobial polymers(89), antivirulence drugs(45), heavy metals(45), monoclonal antibodies(35,45), bacteriocins(35), vaccines(35,45), and alternative therapies such as photodynamic therapy, laser therapy, stem cell therapy, and the breeding of bacteria-resistant animals(35). However, no single compound is likely to replace the various

functions of antibiotics on farms, and there is a need for further research to turn these compounds into viable products(34,86,89).

Replacing agricultural antibiotics will also require a combined One Health approach, involving changes to farm management and biosecurity as well as systems-level changes. The success of stewardship programmes in Denmark and Sweden has depended on interventions to improve vaccine uptake, farm management, animal health, biosecurity, surveillance and monitoring, enforcement, and financial compensation of farmers(49,90).

When reviewing WASH and biosecurity interventions for agricultural AMR, Jimenez and colleagues(52) found varying degrees of effectiveness from different intervention types, with different interventions complementing each other but none consistently returning positive results. This highlights the need for combined interventions. While most interventions in that review were successful in reducing AMU and animal disease, reducing on-farm AMR and pathogen levels was much less successful. This suggests that the level of resistance and infection on farms is largely determined by environmental factors and cannot simply be eliminated at the farm level. In Tien Giang province, a context with a very high level of resistance and widespread AMU, there was no relationship between on-farm AMU and on-farm AMR for poultry farmers(28). A study on a farm which had never used antibiotics found that the ARG load was at least as high as on intensive farms in the same region(91).

Changing AMR-related behaviours on farms must be done from a bottom-up systems-thinking lens, involving stakeholders in a participatory way, proceeding from a bottom-up understanding of farm dynamics, improving farmers knowledge, attitudes and practices (KAP), involving animal health professionals, tailoring interventions to local the context, complementing existing legal frameworks and leveraging existing social networks(33,39,40,42,53). Such interventions should identify social, institutional and infrastructural barriers to stewardship faced by stakeholders and target these(41). A range of reviews and case studies of combined stewardship interventions in Europe note that interventions which take a sociological approach, involve farmers, and provide tailored solutions have had much more lasting success than those which do not(24,41,49,51). Studies also note the need to provide interventions which are feasible and affordable to farmers, which are well-explained, which clearly demonstrate the benefit to farmers, focus on manageable incremental change, and do not vilify AMU - interventions which do otherwise are liable to alienate farmers and may fail to achieve sustained uptake(41,51).

Improving agricultural AMS necessarily involves resolving conflicting incentives of various stakeholders, seeing farmers as part of a network of economic interdependencies(6,38,92,93). Governments may be reluctant to harm agricultural export competitiveness by reducing AMU(82), stewardship comes at a considerable public cost in terms of monitoring and enforcement(90), vets may have an incentive to encourage greater AMU(26,77), and farmers' AMU behaviour is determined in large part by private agrovet drug suppliers and the landlords, poultry dealers, and creditors with whom they have a patron-client relationship(20,39). For this reason, stewardship interventions should involve and consider the entire food chain, supply chain, and institutional environment(6,21,30,38,81,92,93), and may require global-level cooperation to resolve conflicting incentives and make it feasible for farmers and national governments to implement stewardship policies(38,82).

Finally, designing a better agricultural AMS policy is hampered by a lack of data and significant knowledge gaps. The risks and effectiveness of on-farm AMU itself are not well understood or comprehensively studied(37,38), and existing surveillance data often do not distinguish between different types of AMU (prophylactic, metaphylactic, therapeutic, growth-promoting) in a way which could guide stewardship policy(37). While the potential of antibiotic alternatives has been demonstrated, there is a need for much more research and development and assessment of risks, effectiveness and cost-effectiveness before they can become commercially viable(34,45,86). There have been studies on microbial and non-microbial approaches to animal disease management, but trials are often not well-designed, well-executed, consistent, or replicated, and there is a lack of evidence for some intervention types(94). Evidence on farm-level WASH and biosecurity interventions for AMR are generally confined to the farm level, with insufficient study targeting broader agricultural communities or the socio-economic policy environment(52). Evidence gaps also exist on the impact of agricultural AMU on human and animal health, the feasibility and cost-effectiveness of stewardship interventions, structural interventions, the tradeoffs of agricultural AMS; household, subsistence, small-scale, pastoral, and mixed production systems; the role of social and geographical factors, and on applying these questions to the Global South(38,51,52).

Returning to the main themes of this commentary, it is unclear what impact (nontherapeutic) antibiotic use has on animal health and productivity. There is evidence that it may be beneficial, and that complementary interventions would be needed to make its removal safe and acceptable to farmers. While there are many potential interventions that could facilitate this, our knowledge of them must be improved in order to confidently guide policy.

1.3.3 Health economic methods used in AMR

An overarching theme from policy and academic literature is simply that health-economic analysis is not prioritised in the AMR space. The Global Database for Tracking Antimicrobial Resistance country self-assessment survey (TrACSS), a detailed database collecting information about national policies to combat AMR, does not even have a question about economic evaluation(95). After reviewing AMR NAPs from 114 countries, Patel and colleagues found that cost-effectiveness evaluation was one of the areas where countries had the worst governance(96). A similar review found that, of the five objectives from the WHO GAP on AMR, the objective to develop an economic case for sustainable investment was the goal towards which countries had made the least progress(97). Beyond this, there is limited cost-effective evidence on a range of important AMR-related interventions(23,60,61).

When studies look at the burden of AMR, they rarely consider the holistic OH health-economic burden. Studies estimating the ‘burden’ of AMR often include only human health outcomes(14,98,99) or include the ‘economic burden’, defined from the healthcare system perspective as human health outcomes plus healthcare costs(14,56,59,63,100–102) and sometimes lost productivity from mortality(62,103,104). Large studies by multilateral organisations have tended to take a more macro-level approach to estimating the AMR burden. Here, general equilibrium modelling is used, and mortality and morbidity from AMR affect GDP via the ‘labour supply’(13,47,64,65,105). The World Bank model from 2017 goes slightly further, modelling the effect of AMR on the supply of livestock, and subsequently on

food prices and agricultural productivity(64). Overall, estimates of the AMR burden tend not to take a societal perspective or to include a holistic One Health analysis, and instead focus on (usually secondary) healthcare system perspectives in the Imperial Core, with little consistency in the perspectives adopted and outcomes considered(57,63,102).

The situation for evaluation of AMR interventions is similar, tending to come from the healthcare system perspective, including no economic outcomes beyond healthcare costs and occasionally productivity losses, and being primarily focused on secondary care and the Imperial Core(23,60,61,102,106,107) (the 2018 OECD report estimating the future AMR burden also does cost-effectiveness analysis using a macroeconomic framework as described above(13)). Many AMR interventions have had little to no economic evaluation, particularly those related to animal AMU, and interventions overwhelmingly look exclusively at human populations and individual pathogens(23). Methodologically, HEA of AMR interventions tends to favour cost-effectiveness analysis, with cost-utility analysis[3] being relatively neglected, and little consideration for the indirect effects of AMR(23,107). Finally, the quality of data and the consistency and quality of AMR CEA studies is limited(23,107).

In short, the prevailing conception is that the ‘burden’ of AMR refers to the human health burden, with health-economic analysis being limited to a healthcare system perspective and with little consensus on how to perform it. When HEA is done, it treats AMR interventions like trials of a new drug or new surgical technique, rather than as fundamentally ecological in nature.

There are, however, some moves towards a more holistic HEA of AMR. National governments and multilateral organisations acknowledge the need for quantifying the societal cost of AMR; and that this knowledge is needed in order to prioritise interventions, effectively allocate resources, advocate for AMR, and demonstrate the value and feasibility of stewardship interventions to farmers(55–57,59). More recently, HEA in AMR has begun to go beyond simple healthcare costs, incorporating outcomes such as labour productivity, trade outcomes, and livestock productivity(56,62,64,102,103,108).

There are also a number of frameworks for a One Health HEA of AMR, although they have not been widely applied yet. Morel and colleagues(56) create a bottom-up framework for estimating the national OH burden of AMR. They used expert consultation to select dozens of potential costs of AMR from across the three OH compartments. They suggest using epidemiological data to estimate the probability of infection and colonisation across the three sectors, and thence the probability of those costs being incurred. Noyes and colleagues(31) propose a framework for evaluating interventions which considers: the biological effect on AMR, the feasibility of the intervention, unintended consequences, and costs (financial, environmental, societal, health-related). Alarcon *et al*.(22) suggest a framework for economic evaluation of AMU surveillance in livestock. They suggest comparing intervention cost to several performance indicators such as ‘identifying risk factors’ and ‘detecting hotspots’, using this to assist decision-making and incentivise AMU reductions.

[3] To elaborate, cost-effectiveness analysis compares the cost of an intervention to a named outcome (e.g. “dollars per hospital bed day averted”). Cost-utility analysis compares the intervention cost to the value of QALYs saved by an intervention - it can therefore be used to determine the net monetary benefit of an intervention (and thus the extent to which it is cost-effective), and is useful for making decisions around resource allocation.

Finally, Naylor and colleagues(67) review evaluations of cross-sectoral OH interventions, and use this to create a framework for estimating the OH burden of AMR. They begin from a decision tree of intervention options, using a compartmental microeconomic model to determine the intervention effect on the number of people and animals in each health state. This feeds into a general equilibrium macroeconomic model to determine the impact on GDP. Outcomes include cost-utility, GDP, and other outcomes of interest to relevant stakeholders. These feed into a multi-criterion decision analysis (MCDA) that weighs estimated impacts along other chosen outcomes of concern (e.g. equity, uncertainty).

While these frameworks for comprehensive and holistic OH HEA in AMR exist, they have rarely been applied and existing analyses remain much narrower in scope. One potential reason for this is that these comprehensive bottom-up models require an immense amount of data on various outcomes and indicators across the three OH compartments, which are hard to find even within the human health sector(59). From my own experience, I have worked with the SNAP-ONE consortium who aim to apply the model of Morel *et al.*(56) to Zambia and Malawi, and the impossibility of parameterising such a model using existing surveillance networks led to me creating a new top-down model to use instead. Another reason is that, even when we choose to take a more top-down approach, we do not know with confidence what the effect of changes in AMU will be on either human health (discussed below in section 1.3.4) or farm outcomes (discussed above in section 1.3.2). As Hillock and colleagues note(58), while modelling has great potential as a tool for estimating the burden of AMR, not actually understanding the drivers of AMR or being able to predict future rates prevent such potential from being realised.

1.3.4 The ecological relationship between AMU and AMR

It is considered intuitively obvious that agricultural AMU should influence human AMR(37,70,72). We know that animal AMU generates selective pressure for human AMR, that most AMU globally is in FPAs, that many important bacteria can colonise both humans and animals, and that resistant strains of animal origin have spread into human populations(70). Mathematical models of AMR ‘spillover’ also highlight that even small interactions between populations can significantly influence the occurrence of AMR(71).

However, there is a lack of robust evidence supporting this link (72) and most policy is based on consensus and expert opinion rather than concrete evidence(37). Surveillance of AMR in livestock is weak(50) and the pathways of emergence and transmission are poorly understood(70,109,110). Studies on this process have often been inconclusive and are limited by available methodologies and data(75,110), and thus the size and shape of this link is not well understood(74).

There are, simultaneously, reasons to expect that the animal-human link may not be strong, or may be more complicated than a reduction in animal AMU causing a fall in human AMR. For one, the relationship seems to vary considerably by sector, drug and pathogen(111). Resistant strains have sometimes existed in FPAs for a long time without spreading to humans(70), and we have often seen sustained large-scale reductions in agricultural AMU without commensurate falls in human resistance(112,113). Some scholars argue that agricultural AMU may be important for the *emergence* of resistant strains that spread to

humans and that, once these strains have taken hold, future reductions in animal AMU may have limited impact on human AMR(17,114). Due to transmission pathways, the effect of changes to animal AMU may take much longer to affect human AMR than stewardship efforts in human health(70)

While there is evidence demonstrating links between human and animal resistomes(37,115–118), and some animal AMS policies have seen a fall in the prevalence of key resistant pathogens in humans(119,120), quantifying the link between animal AMU and human AMR receives relatively little attention(74). Where studies do investigate this link at the ecological level, results have varied, which I discuss in more detail below.

Several studies have approached this question from the lens of mathematical modelling. Reviewing mathematical models of the emergence and spread of AMR, Birkegård and colleagues(110) note that these tend to focus on humans, with few having multiple compartments or fitting to real-world data. The model of van Bunnik and Woolhouse(72) suggests that reducing animal AMU alone would have little impact on human AMR, and that reducing transmission (within and between sectors) would be more influential. However, that model was not parameterised to real-world data. Booton and colleagues(121) model AMR transmission across OH sectors and apply the model to (very limited) point prevalence data from Thailand for gut colonisation of extended spectrum beta-lactamase (ESBL)-producing bacteria. They find that reducing human AMU was by far the most important factor with the potential to reduce human AMR by 95.4%. Eliminating animal AMU in this model could reduce human AMR by 7.1%, and eliminating human-animal transmission could do so by 7.9%. A risk-assessment model by Opatowski and colleagues(69) suggested that each person would acquire AMR bacteria from livestock 0.98 times per year in a high-income Asian setting and 2.47 times in a low-income one (much less than from water, for example).

This relationship has also been investigated by regression analysis of ecological surveillance data. Allel *et al*.(122), looking across a range of countries and drug-pathogen combinations, find an effect of animal AMU on human AMR for some drug-pathogen combinations. Adda(123) looks at a very large dataset from the USA at the state-drug-pathogen level. They find a consistent link between human AMU and human AMR, but little evidence for animal AMU. This is despite a very large dataset (21000 - 23000 datapoints, using several different methods), and despite animal AMU accounting for the majority of AMU in that country. Rahman and Hollis(124) look at the link between (animal and human) ABU and human AMR in European countries over time for a few key drug-pathogen combinations. They found that human AMR was more sensitive to changes in animal AMU than it was to changes in human AMU. Zhang *et al*.(125), looking at the determinants of fluoroquinolone-resistant *P. aeruginosa* in European countries, find that resistance was positively associated with human AMU but *negatively* associated with animal AMU. Finally, the 2017 JIACRA report(111) looks at AMU and AMR in humans and animals in Europe. It found a consistent link between AMU and AMR within the human population and within the animal population. It also found a link between animal ABR and human ABR (especially for *Campylobacter spp.*), but did not manage to establish a direct link between animal ABU and human ABR. Overall, then, these studies have not consistently or convincingly demonstrated a link between animal AMU and human AMR.

Other approaches have been taken. For Instance, Thorpe and colleagues(17,126) write about large-scale sampling of *K. pneumoniae* isolates in Pavia, where there was little evidence of transmission between animals and humans. When animal-human transmission did occur, there was little evidence of onward transmission to other humans. This was taken to suggest that resistant pathogens may have important adaptations to specific species, and mirrors similar conclusions from studies in the UK for *E. coli*(127) and *E. faecium*(128). A source-attribution model for ESBL-producing *E. coli* in the Netherlands found that 18.9% of human isolates came from food, 7.9% from companion animals, 3.6% from farm animals, and 2.6% from environmental contact, with the remainder attributed to human-human transmission(129). These findings highlight that, while animal-human transmission of resistance does occur, it may not be a major driver of AMR in the human population.

There are some studies which have reviewed this relationship, but they too are inconclusive. Tang and colleagues(130,131) find evidence of animal AMS interventions reducing human AMR, but they are geographically concentrated within the Global North and focus on people in direct contact with animals, rather than the ecological level. The O'Neill report(47) claims that 100 of 139 sources reviewed were in favour of reducing animal AMU, but those studies come from across academia, government and industry and may tell us more about expert consensus than about the actual ecological relationship between animal AMU and human AMR. Finally, reviewing evidence of transfer of AMR from FPAs to humans, Muloi *et al*. (75) found mixed results, with only 8/45 studies actually demonstrating animal-human transmission, and with serious methodological limitations.

Other studies suggest that factors other than AMU may be essential to the equation, and that reducing AMU alone may not be enough to curb the growth of AMR. Some studies have found that socioeconomic factors, and the setup of the healthcare system, may be more important in determining AMR at the national level even than AMU(73,122,125,132–137). Non-antibiotic substances in the environment may also be overlooked as important selectors for resistance(48,138–143). Some studies argue that targeting pathogen emergence and transmission may actually be much more effective than targeting AMU, and that stewardship without complementary strategies to transform a country's economic and agricultural makeup may be ineffective(70,72,74,122,144–146). This could explain why significant reductions in (human and animal) AMU have often been insufficient to reduce AMR in humans, or even to slow its growth in the long run(46,112,147,148).

1.3.5 Where does this leave us?

Having reviewed the discourse and literature on agricultural AMU and human health, we can draw several conclusions. 'Nontherapeutic' AMU, while often asserted to be unnecessary and detrimental to human and animal health, may indeed be important for animal health and productivity, for food security, and for farmers' economic security. On-farm stewardship interventions, combined with improvements to farm practices, could make reductions in animal AMU safer and more viable, although further research is needed to design optimal intervention packages. Such interventions should take a holistic approach, considering both farm-level and systems-level factors and the political economy of agricultural AMR.

Turning to theme 2, health-economic analysis has not been prioritised as an area of research in the AMR space. It tends to focus on the healthcare systems perspective,

sometimes incorporating labour productivity, with a focus on secondary care in the imperial core. Frameworks for holistic One Health health-economic analysis of AMR do exist, but have not been applied. This is partially because of data limitations, and partially because such models require a knowledge of how AMU affects both farm and (ecological) human health outcomes, neither of which is well-understood.

This leads us to the macro-level relationship between AMU and AMR (theme 3). While it is intuitive that agricultural AMU should influence human AMR, this relationship (especially at the ecological level) is not well-understood and existing evidence is inconclusive. There is a scientific basis suggesting that this link may not be strong, and that reducing (especially animal) AMU alone may be insufficient to curb the growth of AMR.

Mathematical models have suggested that reducing animal AMU alone would have limited impact on human AMR, and that targeting human-to-human and animal-human transmission would be more effective. Statistical analysis of the ecological relationship has produced varied results, but most studies do not show a strong impact of animal AMU on human AMR. Non-AMU factors (including transmission, environmental contaminants, healthcare system design and socioeconomic factors) also appear essential to determining AMR at the ecological level. Thus, while animal AMU may have played an important role in the development of human AMR, there is little strong evidence that animal AMS alone can curb the growth of AMR across drug-pathogen combinations.

Chapter 2 - the portfolio

2.1 AHHME: One Health health-economic analysis of agricultural AMR interventions

2.1.1 Introducing the paper

The papers that I have written as part of this PhD proceed from the state of the literature and discourse on animal AMU and human health as outlined above. This began when I was working at the LSHTM in partnership with the International Livestock Research Institute (ILRI), with the goal of using a One Health approach to evaluate the societal impact of interventions to reduce agricultural antimicrobial use on economic and health outcomes.

The project drew on the ideas laid out in Naylor *et al*.(67), which creates a conceptual framework for how OH health-economic analysis of AMR could be done holistically. It emphasises that the effects of AMR interventions on different sectors need to be taken into account and compared.

Having a background in development economics, where the focus on national-level policy is central, I was frustrated by the lack of health-economic analyses of AMR which

a) Considered the range of outcomes that AMR interventions have on agriculture, human health, the healthcare system, and the macroeconomy
b) Compared these outcomes in like terms to generate estimates of net cost-effectiveness
c) Presented these outcomes in a format which allows for the favorability of policies to be compared, aiding policy design and selection

I was initially tasked with using mathematical modelling to evaluate the impact of prospective AMR interventions in Vietnamese livestock farms. I inherited some initial R code from Dr. Nichola Naylor, who had coded a Markov model which allowed humans and livestock animals to move between health states, and could assign values to each of these health states.

Proceeding from this code, I spent 2021 creating the Agriculture Human Health Microeconomic Model (AHHME). My aim was to produce a tool which responded to the shortfalls identified above, which could be accessed and used by policymakers in different countries, and could be tailored to the local context, allowing a more holistic OH approach to economic analysis in AMR to become more widespread and accessible.

In 2023, along with coauthors, I wrote and published a paper (below) in One Health which presents and explains the AHHME model, applies it to representative data from countries of different income levels, and encourages researchers and policymakers to use the model and other associated tools. After contacting LSHTM Ethics Online (LEO), I was told that I did not need to seek ethical approval for the study because it did not involve human or animal subjects or the collection of new data.

2.1.2 Paper 1

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	2204500	**Title**	Miss
First Name(s)	Eve		
Surname/Family Name	Emes		
Thesis Title	Revisiting key assumptions about animal antibiotic use and human health from a One Health perspective		
Primary Supervisor	Gwen Knight		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	One Health		
When was the work published?	September 2023		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	I am enrolled in the PhD by Prior Publication programme, so the papers that form part of this portfolio were already published at the time of registration		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I was hired to create a mathematical model for the holitsic health-economic evaluation of AMR interventions in agriculture. Building on some preliminary code (around 200 lines) from Dr. Nichola Naylor which created the scaffold of a state transition model, I designed and coded the AHHME and AHHME-B models (around 8000 lines). I parameterised the model and ran it to generate results, which I used to write the paper included in this portfolio, and I incorporated comments from peer reviewers during the process of publication. I had regular supervisory meetings with coauthors during the process of creating the model and writing the paper, and coauthors read and gave comments on drafts of the paper during the publication process

SECTION E

Student Signature	Eve Tresco Emes
Date	22 October 2024

Supervisor Signature	Gwen Knight
Date	22 October 2024

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AHHME: A model for estimating the holistic cost-effectiveness of antimicrobial resistance interventions in food animal production

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ABSTRACT

Antimicrobial resistance (AMR) is considered a global priority for human health, and reducing antimicrobial use in food animals has been suggested as a key area for interventions aiming to reduce resistant infections in humans. In addition to the effect on human health, such interventions may have effects across food animal productivity, healthcare sector costs, and the broader macroeconomy, but these effects are rarely captured in the AMR health economic literature. Without being able to estimate these effects, it is difficult to understand the true cost-effectiveness of antimicrobial stewardship interventions in food animal production, or to correctly design and prioritise such interventions.

We explore and demonstrate the potential use of a novel compartment-based mathematical model to estimate the holistic cost-effectiveness of AMR-related interventions in food animal production from a One Health perspective. The Agriculture Human Health Micro-Economic model (AHHME) uses Markov state transition models to model the movement of humans and food animals between health states. It assigns values to these health states utilising empiric approaches, from the perspectives of human health, food animal productivity, labour productivity and healthcare sector costs. Providing AHHME open-source code and interactive online modelling tools allow for capacity building in AMR intervention modelling.

This model represents a useful framework for capturing the cost-effectiveness of AMR-related interventions in food animal production in a more holistic way: it can allow us to capture the often-overlooked benefits of such interventions in like terms while considering distributional concerns. It also demonstrates that methodological assumptions such as willingness-to-pay thresholds and discount rates can be just as important to health decision models as epidemiological parameters, and allows these assumptions to be altered. We provide example outputs, and encourage researchers and policymakers to use and adapt our code to explore, design, and prioritise AMR-related interventions in their own country contexts.

1. Introduction

Antimicrobial resistance (AMR) imposes a considerable burden of disease globally, affecting human health, economic growth, and food security. This has resulted in international efforts to curb its growth [1,2]. Antimicrobial use (AMU) in food animals has been suggested as a major contributor to the spread of AMR [1]. For this reason, it has been targeted by interventions such as legally restricting the use of antimicrobials in food animal production, encouraging prudent use of

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Acronyms

AMR	Antimicrobial resistance
AMU	Antimicrobial use
WASH	Water, sanitation, and hygiene
AHHME	Agriculture Human Health MicroEconomic Model
QALY	Quality-adjusted life year
WTP	Willingness to pay
QoL	Quality of life
NMB	Net monetary benefit
CEAC	Cost-effectiveness acceptability curve

antimicrobials, replacing antimicrobials with alternative products,[2] or using improvements in animal husbandry, on-farm biosecurity, and on-farm water, sanitation and hygiene (WASH) to reduce the need for antimicrobials [3–5].

However antimicrobials, and especially antibiotics,[3] are often used by food animal farmers as disease management and productivity enhancement tools in food animals [6,7], and reducing their use may harm food animal productivity and farmers' incomes. On the other hand, if reduced food animal AMU leads to a lower level of AMR in human infections, then it will provide gains to human health (and subsequently economic productivity) while reducing healthcare costs [8]. Weighing these outcomes against each other is essential to modelling the effect of AMR-related interventions, and is needed in order to correctly design and prioritise such interventions [8]. This will also give us insight into how the costs and benefits of prospective interventions are distributed among actors, helping us to understand important distributional concerns [9].

For this reason, we created the Agriculture Human Health Micro-Economic (AHHME) modelling tool to model and evaluate the cross-sectoral impact of AMS interventions in food animal production, taking a holistic One Health approach as proposed by Naylor et al. [10]. AHHME aims to evaluate the effect of such interventions on a range of relevant sectors, and thus to determine the cost-effectiveness of those interventions and the amount of funding that governments should allocate towards their implementation. It considers the effect of interventions on food animal productivity, human life years lost to disease, healthcare costs, and labour productivity lost to disease. It compares these outcomes in monetary terms, and it can be parameterised in detail to reflect the epidemiological, agricultural, and economic context of the country being considered. We explain in detail how the model works, giving examples of the types of outputs that can be produced and linking to our free open source online resources for using, exploring, and adapting the model.

2. Methods

2.1. Model structure overview

The AHHME model calculates the cost-utility (from the human health perspective) and cost-benefit (from the food animal agriculture sector, labour productivity, and healthcare cost perspectives) of AMR-related interventions in food animal production. It has epidemiological modules for humans and food animals based on a compartmental state-transition model using difference equations to model movement between health states [10]. It assigns monetary values to these health states from different perspectives using economic modules from four perspectives. Namely: human health, healthcare sector costs, labour productivity, and food animal productivity.

In terms of causal pathways modelled, AHHME considers the impact of a given intervention on the rate of antimicrobial resistance in both humans and food animals, as well as the finishing weight of food animals. It models the resultant change to farmers' incomes, to the number of labour hours lost to illness and death, to the cost of treatment borne by the healthcare sector, and to the life years lost to illness and death (Fig. 1).

AHHME does not mechanistically model the way that farm antimicrobial use interventions influence farm outcomes or the rate of AMR in humans. These intervention impacts vary by intervention and context. Rather, it provides a health-economic framework for understanding the holistic economic impact of these outcomes. The intervention impact on farm outcomes can be parameterised using farm trials or farm-level survey data [3–5,11–14]. The intervention impact on human AMR prevalence can be parameterised using mathematical transmission models [15] and ecological panel regression analysis [16–20].

The model is run both with and without the intervention, and compares the number of humans and animals in each health state in the two scenarios. It assigns a monetary value to these health state outcomes from the four perspectives mentioned, and synthesises them to estimate the cross-sectoral monetary benefit of the intervention being simulated at the population level.

While the model currently allows the intervention to directly impact three parameters (blue boxes), the code can be modified to allow the intervention to impact any of the model parameters. The full set of parameters used in the model are listed in Table 1 (below).

2.2. Epidemiological module

AHHME models human and food animal epidemiology using a population-level Markov chain state-transition model (Fig. 2), which models state transition over one-year periods.[4] Humans and food animals begin life in good health. At the beginning of the period, additional humans are born based on the number of net births in the population, and additional food animals are bought by farms based on the growth rate of agricultural output.

In a given one-year period, non-infected humans may die without infection, or may develop an infection with (antimicrobial-)susceptible or (antimicrobial-)resistant pathogens. Infected humans may die, recover fully, or develop sequelae.

In a given one-year period, food-producing animals may die without infection, or may develop an infection with (antimicrobial-)susceptible or (antimicrobial-)resistant pathogens. Infected animals may die or recover fully. Those alive and well at the end of the production cycle are sold. The model can be run for as many periods as desired, with the default set to twenty periods (years).

The definition of resistant and susceptible infections in the model depends on the drug-pathogen resistance pairs being modelled. For example, one might model an intervention which reduces use of fluoroquinolones in food animal production, and the resultant effect on the rate of fluoroquinolone resistance in human campylobacterioses. It is possible to model different animal species and farm types, with different parameter sets. By default, the model considers poultry and pig farms, each with two production types (smallholder and industrialised). New modules can be written to add different food-producing animal species and farm types can be added as appropriate, and these farms can be

[2] This can include non-antimicrobial food additives, such as nigella seed and silver, as well as treatments such as vaccination and bacteriophages which reduce the need for antimicrobial use

[3] AHHME can model various types of antimicrobial resistance (antifungal, antiviral, etc.), and other antimicrobials are used in food animal production. We focus on antibiotic resistance in this manuscript.

[4] Most livestock species have production cycles which are less than a year in length. We still use one year periods here, but each period may contain multiple production cycles

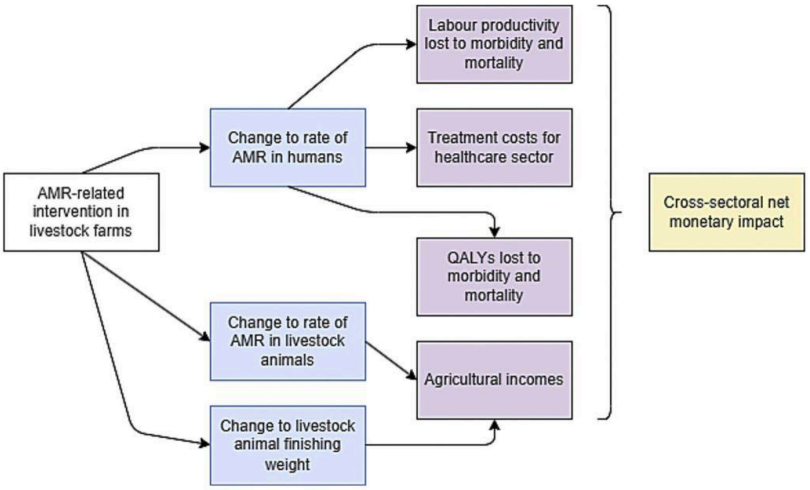

Fig. 1. Causal pathways modelled by AHHME. Blue boxes represent the direct effects of the intervention. Purple boxes represent the four perspectives from which monetary values are assigned to these outcomes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
List of parameters used for AHHME.

Methodological parameters	Timeframe (years), discount rate, willingness to pay per quality-adjusted life year (QALY)
Demographic parameters	Population, annual population growth rate, portion of population in paid employment, average remaining life years, average remaining working years
Agricultural parameters	Population of each food animal species, portion of animals in each farm type (e.g. industrial, smallholder), average size of farms (by farm type and species), animal selling price per kg by species, number of production cycles per year (by farm type and species), animal mortality without infection (by farm type and species), animal mortality with an antimicrobial-resistant infection (by farm type and species), animal mortality with an antimicrobial-susceptible infection (by farm type and species)
Epidemiological Parameters	Incidence of chosen disease, portion of infections from resistant bacteria, growth rate of portion of resistant infections, fatality from resistant and susceptible infections, chance of sequelae from resistant and susceptible infections, subjective quality of life from resistant infections, susceptible infections, and sequelae, hospital length of stay from resistant and susceptible infections
Economic parameters	Labour productivity, labour productivity annual growth rate, ratio of paid work to total (paid + unpaid) work, cost of providing a hospital bed for one day
Intervention parameters	Effect on rate of AMR in human infections, effect on rate of AMR in animal infections, effect on animal finishing weight (by species and farm type)

Examples values given in the supplementary material

parameterised to behave differently.

Due to the difficulty in mechanistically modelling the ecological relationship between AMU and AMR [8], that relationship is not modelled mechanistically by the model. Instead, the intervention reduces the portion of infections which are resistant by a user inputted value (with separate values for humans and food animals). As with other parameters in the model, this value can have multiple values across different scenarios, and can be drawn from a distribution (more on this in the *sensitivity and scenario analysis* subsection).

In order to estimate this value, modellers may assume a unit elasticity of resistance with respect to systemwide AMU as in OECD, 2018 [21], may estimate this relationship using mathematical models as in Booton et al. [15], or may do so using ecological panel data regression analysis of public health surveillance data [8,16–20]. The effect of the intervention on the rate of AMR in food animals and on finishing weight can be estimated using farm-level trials of antibiotic stewardship interventions [3–5], or by using system dynamics models of agricultural production systems [22,23].

2.3. Economic modules

After running the model in both the "intervention" and "no intervention" scenario, AHHME sums up the total number of humans and animals in each health state over the study period, discounting future outcomes using the selected discount rate. It then assigns values to these health states from four perspectives: labour productivity, farm productivity, healthcare costs, and human health.

2.3.1. Labour productivity

The labour productivity module calculates the value of labour lost through morbidity and mortality from AMR infections in the whole human population. The labour productivity lost to death can be estimated using either the friction cost or human capital approaches [24], with the approach used being one of the arguments of the main model function. In the former, it is assumed that there exists a pool of unemployed labour and that, once a working person dies, they will be replaced after a searching period (default six months in this model). In this scenario, a death will incur a loss of productivity equal to that which would have been produced in the search period (e.g. six months' productivity). To calculate the average productivity per person per year, we take the average annual labour productivity of a person in paid employment, multiply this by the labour force participation rate, and adjust this by the ratio of paid to total (paid and unpaid) labour. This includes unpaid housework, unpaid carer duties, volunteerism, etc., and estimates of this ratio in different countries can be found in Alonso et al. (25).

In the human capital approach, when a person dies, the loss of

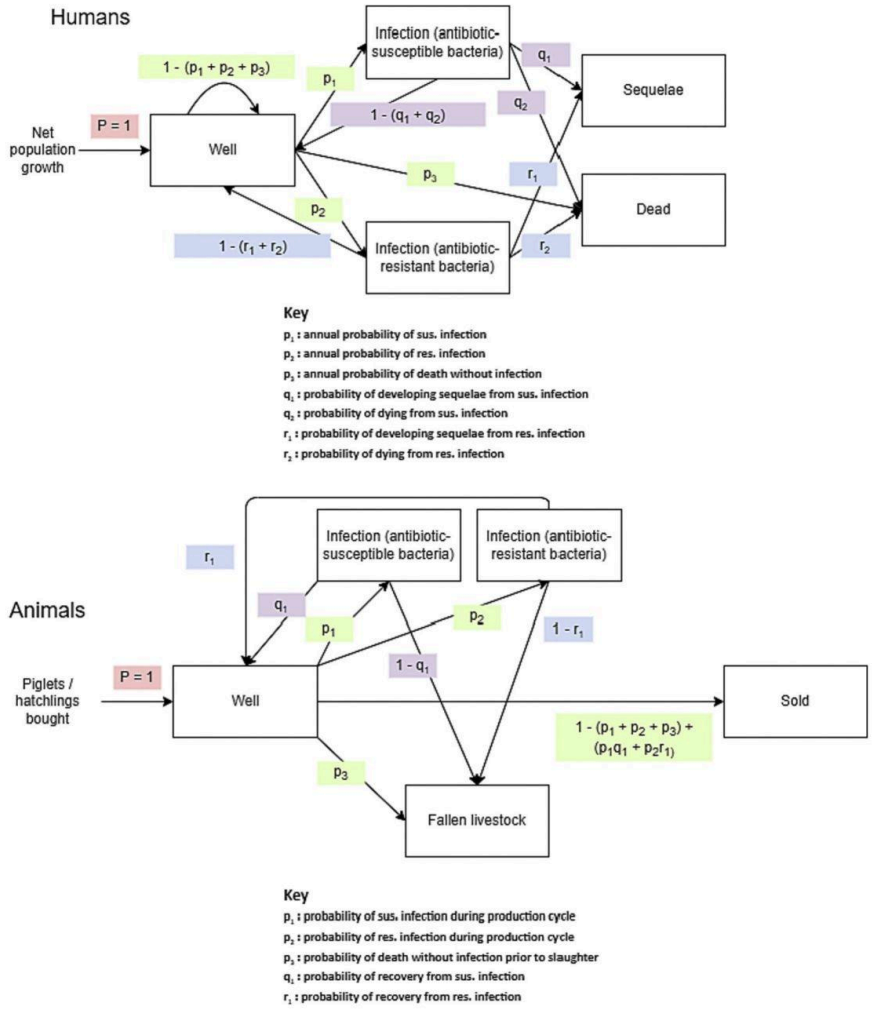

Fig. 2. State Transitions for Humans and Animals.
P = 1 means that individuals who enter the model go directly into the 'well' compartment. Green probabilities (p_x) represent transitions out of the 'well' compartment. Purple probabilities (q_x) represent transitions out of the 'susceptible infection' compartment, and blue probabilities (r_x) represent transitions out of the 'resistant infection' compartment.

productivity is equal to the present value of the labour done by a person of median age during the rest of that person's working life, assuming both a given discount rate and a given rate of per-person labour productivity growth.

Under both approaches, when a person becomes sick but does not die, the loss of productivity is equal to the productivity which would have been created during the time that they are in hospital, assuming given lengths of stay for resistant and susceptible infections respectively. It is assumed by default that people with sequelae have the same life expectancy and labour productivity as those without, although this can be altered (as mentioned earlier, sequelae still affect subjective quality of life and therefore the number of quality-adjusted life years (QALYs) lost to morbidity).

2.3.2. *Farm productivity*

Because the model allows the intervention to affect the prevalence of AMR in food animal infections (which mechanistically affects the number of animals which survive and are sold) as well as animal finishing weight, the impact of the intervention on farm incomes is straightforward to calculate. The sale price per kg of live weight (which can change over time) is multiplied by the finishing weight of animals, then by the number of animals sold in each production cycle, then by the number of annual production cycles, for each period. This total revenue is discounted and summed over the study period, and the difference in

discounted total revenue between the 'intervention' and 'non intervention' scenarios is the net intervention effect on (food animal) farm productivity.

2.3.3. Healthcare costs

For a given cost of providing a bed day in hospital, and a given length of stay from resistant and susceptible infections, we can estimate the healthcare sector cost from providing hospital beds to people with infections[5] of the type being considered, and compare the discounted totals between the 'intervention' and 'non-intervention' scenarios. By default, there is no healthcare cost for people with sequelae once they are no longer infected, although this can be altered.

2.3.4. Human health

We use a given willingness to pay (WTP) for each quality-adjusted life year (QALY) to assign a monetary value to QALYs lived by people in each health state. This is the money amount that the relevant healthcare system is willing to spend in order to gain one year of life in good health. Different countries may have existing guidelines for the WTP used in their health economic evaluations, and otherwise the WTP can be estimated using the formula suggested in Woods et al.(26). We assign a QALY value to each health state (resistant infection, susceptible infection, sequelae) using subjective quality of life (QoL) estimates, assuming a value of 1 for good health and 0 for death.

The QALYs lost from infection are equal to: $\left(QoL^{good\ health} - QoL^{infection}\right) * length\ of\ infection^{years}$.

The QALYs lost from sequelae are equal to the difference between

a) The discounted present value of the average remaining lifespan if lived in good health, and
b) The discounted present value of the average remaining lifespan if lived with sequelae

The QALYs lost from death are simply equal to the discounted present value of the QALYs lived in good health for the average remaining lifespan, which can be estimated using life tables.

The total QALYs lost from infection, sequelae and death across the study period are then discounted, summed and multiplied by the WTP threshold. The difference in this value between the 'intervention' and 'non intervention' scenarios is the value of the intervention from the human health perspective. Assigning monetary values to QALYs in this way allows the human health impact to be considered alongside other perspectives, giving a more holistic picture of the societal impact of AMR interventions.

2.3.5. Calculating final outputs

The value of the intervention for each of the four economic perspectives is presented, as well as their sum, i.e. the total monetary benefit of the intervention. The model also outputs the 'threshold price' of the intervention, i.e. the annual implementation cost which would leave the government indifferent between implementing and not implementing the intervention

2.3.6. Sensitivity and scenario analysis

In addition to these main results, our code performs sensitivity and scenario analysis. This includes investigating the threshold price / net monetary benefit under different intervention impact scenarios, using the human capital vs. friction cost approach to estimating productivity losses from illness, etc. If certain parameters fall within a given feasible range, then the model can perform univariate sensitivity analysis using tornado plots. If parameters are uncertain following a given distribution, then the model can also display the distribution of the threshold price following Monte Carlo simulation. If the chosen outcome is net monetary benefit rather than threshold price, a cost-effectiveness acceptability curve (CEAC) can be produced.

3. Example model outputs

Examples of AHHME outputs are displayed below (Table 2, Figs. 3–4), where we run the model for hypothetical interventions. For demonstrative purposes, we parameterised the model to settings of different income levels. Taking a population of 100,000,000, we let all other parameters be the population-weighted average of the relevant value among all countries in the low-, middle-, and high-income World Bank lending groups(27). Considering pig and chicken farms, using the human capital approach, and using sepsis as our disease outcome of interest,[6] we demonstrate the model applied to a hypothetical intervention which affects animal finishing weight and human AMR prevalence. Examples of interventions that could be modelled include quantitative restrictions on antibiotic use, WASH interventions which limit pathogen transmission to humans, and combinations of AMU reduction with other farm practice interventions such as biosecurity improvements.

3.1. Code and data availability

All of the code and data used to parameterise and run the model are available on our GitHub(28), as well as example applications of the model and instructions on how to adapt the model to one's own country context. A free interactive Shiny App(29) is also available online, which allows users to explore the model by altering parameters manually and observing the results. We encourage modellers and researchers to use and adapt our code, while the Shiny App may be more useful for policymakers and non-modellers to do more exploratory analysis.

4. Discussion

In this paper, we have constructed and demonstrated the use of a cost-effectiveness analysis tool which can help policymakers to understand the potential benefit of AMR-related interventions in food animal production from a One Health perspective, allowing these interventions to be more accurately designed and prioritised. It can also help to understand the importance of methodological and parameter uncertainty, and can be useful for capacity building in the quantitative evaluation space in One Health.

4.1. Strengths

Our compartmental health-economic model provides a comprehensive estimate of the cross-sectoral cost-effectiveness of AMR-related interventions in food animal production. The literature evaluating AMR-related interventions tends to focus on human health outcomes, and sometimes on healthcare cost as well, but broader impacts such as that on the macroeconomy and on food animal productivity are often overlooked, despite being potentially as important as the direct impact on human health [8]. Taking these outcomes into account, we can more comprehensively estimate the cost-effectiveness of AMR interventions; and can select, design, and prioritise them with greater accuracy and confidence.

[5] Note that the 'bed day' approach is only one way of estimating healthcare costs, and may not include all possible costs to the healthcare sector. Using different cost parameters, community and unit costs could be considered as well

[6] In reality, sepsis is generally nosocomial and thus is unlikely to be influenced by antibiotic use in livestock production. However, we selected this for demonstrative purposes due to widespread data availability. In practice, a more useful disease outcome would be a pathogen where most cases are associated with consumption of meat, such as *Campylobacter*. The model can also consider many drug-pathogen pairings together

Table 2
Example outputs showing threshold Price of an Intervention (2019 $USD per year) by Scenario. Shading indicates whether the value is positive (green) or negative (red) with a darker shade indicating distance from zero.

		Animal productivity intervention impact				
Human AMR prevalence impact	**LIC**	**Falls 2%**	**Falls 1%**	**Constant**	**Rises 1%**	**Rises 2%**
	Falls 2.5%	144m	162m	180m	198m	216m
	Falls 5%	258m	276m	295m	313m	331m
	Falls 10%	487m	505m	523m	541m	559m
	Falls 16%	762m	780m	799m	817m	835m
	MIC	**Falls 2%**	**Falls 1%**	**Constant**	**Rises 1%**	**Rises 2%**
	Falls 2.5%	340m	405m	470m	534m	599m
	Falls 5%	731m	796m	861m	926m	991m
	Falls 10%	1.51bn	1.58bn	1.64bn	1.71bn	1.77bn
	Falls 16%	2.45bn	2.52bn	2.58bn	2.65bn	2.71bn
	HIC	**Falls 2%**	**Falls 1%**	**Constant**	**Rises 1%**	**Rises 2%**
	Falls 2.5%	-110m	64m	238m	412m	587m
	Falls 5%	15m	189m	364m	538m	712m
	Falls 10%	266m	440m	615m	789m	963m
	Falls 16%	567m	741m	916m	1.09bn	1.26bn

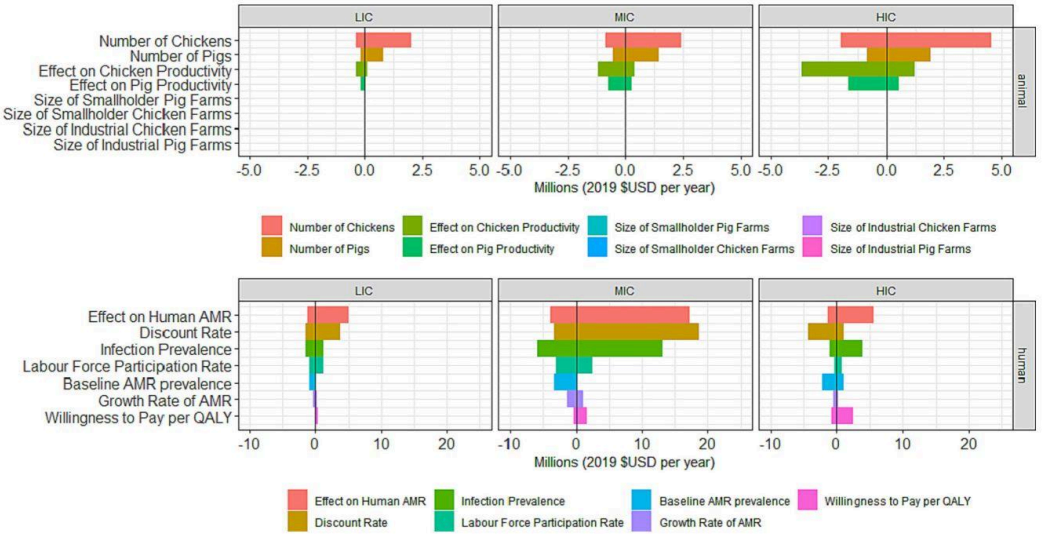

Fig. 3. Example outputs showing tornado plots showing univariate sensitivity of threshold prices to key animal (top) and human (bottom) parameters

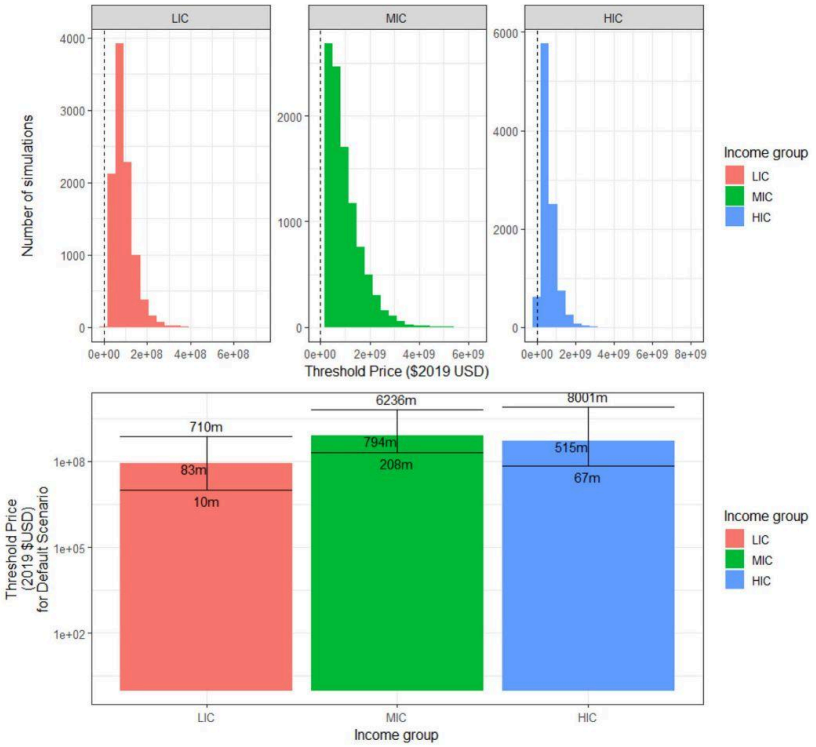

Fig. 4. Example outputs showing distribution of Threshold Price (2019 $USD per year) after Monte Carlo Simulation.
The full distribution for 10,000 model simulations is shown for low-income (red), middle-income (green) and high-income (blue) countries, with the median and range on a log *scale. Each simulation used a different parameter combination to estimate the threshold price.*

By disaggregating the intervention impact by sector, AHHME is also able to consider distributional concerns. For example, it may reveal that the societal benefit of an intervention is likely to be large and positive, but that it will likely affect the food animal sector negatively. This can reveal the need for compensation or insurance, and can give insight into the political feasibility of interventions.

By including detailed options for scenario, sensitivity, and robustness analysis, the model also allows users to explore uncertainty and to have a more realistic impression of the potential impacts of interventions, and of which values need to be parameterised with greater certainty.

4.2. Limitations

Because it is a model, AHHME is by definition a simplification of a complex process. A key limitation to the explanatory power of the model is that it does not mechanistically model the link between antibiotic use and either farm outcomes or population-level resistance prevalence. This shortcoming is not the result of intentional oversimplification but an acknowledgment of a lack of knowledge of, and great contextual variation in, these relationships [8].

A range of other outcomes could not be included in the model. For instance, it does not capture the spillover benefits of AMR reduction for neighbouring countries, or the effect of AMU reduction on the stochastic emergence of new resistant strains, which may be even more important than the effect on the prevalence of existing resistant strains(30,31). We were also unable to model the effect of AMR prevalence on the safety of treatments such as invasive surgery and chemotherapy for cancer[7]: this relationship has not yet been estimated at the population level and would require a separate and novel investigation beyond the scope of this paper.

We express human health, healthcare sector cost, food animal productivity and labour productivity outcomes in like (monetary) terms. While evaluated QALYs are compared directly to healthcare costs according to health economic evaluation standard practice(32), expansion of this to other economic outcomes (farmers' incomes, labour productivity loss) implies that these can also be compared directly to human life years, an idea which can be challenged on ethical grounds.

Finally, because the model relies on willingness-to-pay thresholds which are specific to a given country and healthcare system context, the results of AHHME can only be used to inform resource allocation within a given country. Comparing results across countries and using this information to inform resource allocation among countries would necessarily involve a differential valuation of human life across countries, which by definition would be racist and unethical.

[7] Because people undergoing invasive surgeries and chemotherapy for cancer are at risk of bacterial infections, and typically require antibiotics. A high level of AMR may make these antibiotics less effective and may increase the risk of these procedures.

4.3. Future research

In order to get the greatest use out of the AHHME model, further research should be done: a) on the effect of AMR-related interventions on farm outcomes, using system dynamic models, intervention trials and farm survey data, and b) on the ecological relationship between AMU and AMR using panel data regression on public health surveillance data. Doing this will allow two key model parameters (the intervention impact on farm productivity and on human AMR prevalence) to be more accurately parameterised, increasing the potential value of AHHME. Our current and upcoming research as part of the SEFASI consortium(33) aims to do just that. In addition, our consortium is in the process of developing a new model, named AHHME-B, which uses a similar modelling structure to estimate the societal burden of AMR, considering both the attributable and associated burden.

Above all, we encourage researchers and policymakers to use our open-source code and free interactive app to explore, design, model, and rank AMS interventions in their own contexts. We also encourage researchers to adapt and improve our code, applying it to interventions in other One Health contexts such as human and environmental health.

5. Conclusions

Our AHHME model allows for the cross-sectoral integration that is vitally needed to support intervention analysis and decision-making for the public health priority that is AMR. Our model allows insight into the potential value of AMU reduction interventions in food animals to our society as a whole, and this holistic insight can lead to better-informed intervention design and selection. Future work should tailor this model to specific settings, using local data and considering the policy context and local priorities. This will be best supported by more comprehensive farm-level trials, and use of big data to model the population-level determinants of AMR.

Author contributions

Conceptualisation: ETE, JW, GMK, NRN; data curation: ETE, SDX, TTHL, NRN; formal analysis: ETE, NRN; funding acquisition: ETE, JW, GMK, NRN; investigation: SDX, TTHL; methodology: ETE, GMK, NRN; project administration: JW, GMK, NRN; resources: SDX, TTHL; software: ETE, NRN, GMK; supervision: JW, GMK, NRN; validation: GMK, NRN; visualisation: ETE, GMK, NRN; writing - original draft: ETE; writing - review and editing: ETE, SDX, TTHL, JW, GMK, NRN.

Ethical approval

No ethical approval was sought as this project did not involve human or animal subjects or the collection of new data

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Declaration of Competing Interest

The authors declare no conflicts of interest

Data availability

Data are available on GitHub and linked in the manuscript

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.onehlt.2023.100629.

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2.1.3 Implications

Briefly, the paper had several key implications as is relevant to my overarching research questions. For one, it highlights that traditional cost-utility and cost-benefit analysis fall short when looking at pan-sectoral problems like agricultural AMR. Those methods are standard practice in health economics(149–151) and involve comparing the implementation cost of an intervention to the direct monetary benefit or the (quality-adjusted) life years saved. This may be appropriate for comparing (for example) two surgical techniques with differing costs and survival rates, but national-level agricultural AMR interventions can have major impacts on agricultural productivity, on (paid and unpaid) labour productivity, and can affect the number of people living with lifelong sequelae at the population level. In fact, when running the AHHME model across different representative parameter sets, we saw that the value of QALYs saved was not the sole (or even the main) contributor to the overall cost-effectiveness of the interventions being modelled, especially when looking twenty years into the future with predictions for demographic change and growing agricultural production.

AHHME provides a practical alternative to healthcare perspective models, and can be used in health-economic modelling outside of AMR as well due to its flexibility and modularity. Unlike other frameworks for holistic OH health-economic evaluation of AMR, this paper parameterises the model with real data and demonstrates how to run it. By including these outcomes (in like terms), we approach a more complete picture of the true societal impact of AMR interventions. This is not to downplay the importance of human health outcomes, but rather to show that, when including a range of other outcomes, AMR interventions may be even more valuable than previously thought, and that this value does not have to remain nebulous. It also allows us to see distributional effects of interventions more clearly, giving an idea of (for example) how much farmers would have to be compensated in order to make an intervention a Pareto improvement(152) and acceptable to all parties.

The paper also highlights the importance of methodological assumptions and uncertainty. Parameters such as the willingness to pay (WTP) for a QALY, or the discount rate used, are often assigned using rough rules of thumb like “use a discount rate of 4% for middle-income countries”, “use a WTP threshold of 80% of nominal GDP per capita”(151,153). When I performed sensitivity analysis on the AHHME results, variation in these parameters was often much more influential on final cost-effectiveness results than medically important parameters like the rate of AMR. This highlights firstly that determining those parameters using rules of thumb is potentially dangerous, and that those assumptions should be interrogated when interpreting outputs. It also underlines that, as health-economic models become more complex, the effect of parameter uncertainty on final outputs is compounded: models which provide very narrow confidence intervals may be making too many simplifying assumptions about very complex systems. This is not to undermine the power of modelling, but to remind us as modellers that modelling outputs can not inform policy decision-making on their own, and should instead be used to aid conversations involving stakeholder consultation and other more qualitative methods of decision-making.

2.1.4 Applications

Since the publication of this paper, the model has been shared, adapted and applied in a range of contexts. When participating in the JPIAMR *New Perspectives on Bacterial Drug*

Resistance workshop in June 2022, I saw Dr. Chantal Morel (who is a co-supervisor of my PhD) present her extensive framework for bottom-up estimation of the holistic OH burden of AMR at the national level(56). I was excited by the framework but saw that applying and parameterising it would require very extensive data that would be very difficult to find. I therefore presented a framework for how an AHHME-like model structure could be used to estimate this burden in a top-down way with much lighter data requirements. She subsequently hired me as part of the SNAP-ONE consortium(154) to produce a model which does this, and I thus created the AHHME-B (AHHME-Burden) model (also presented in paper 1). We are working together as part of that consortium to apply the model to Zambia and Malawi, estimating the societal burden of AMR.

I created GitHub repositories for both models(155,156), which include guidelines on how to use the models as well as on how to apply them to one's own country context, and how to adapt them to model different intervention types, production systems, etc. These GitHub repositories include links to the ShinyApp web apps that I have created for the two models(157,158). These apps allow people to manually edit the model parameters and to see how model outputs change in response, allowing for a more exploratory analysis. This was intended to make the models more accessible to policymakers and stakeholders who are not necessarily modellers or coders themselves, and to explore potential interventions prior to doing more in-depth modelling. I am currently working with consortium members Dr. Derek Chan and Dr. Michel Dione to apply AHHME to prospective interventions in Senegal (more on this in section 3.3).

I have presented the AHHME and AHHME-B models at several international conferences, including: the OHARP 2023 workshop in Singapore (where I stayed after the workshop to teach members of the National University of Singapore School of Public Health how to use the models), IDDCONF 2023 in Ambleside, ICOHAR 2023 in Copenhagen, and the World One Health Congress 2024 in Cape Town. I have also worked with colleagues at the SEFASI consortium to run workshops in Dakar and London, where I presented these models to stakeholders and elicited feedback on the model design and applications. I am now working with collaborators within the consortium to apply the model to Senegal, and we are using the outputs of our other papers to estimate the impact of a combined AMS / biosecurity intervention in livestock production, then using AHHME to evaluate the holistic health-economic consequences of that intervention. I am also working with a collaborator in Cameroon, aiming to analyse existing surveillance and survey data and to feed results into AHHME to simulate agricultural AMS interventions there.

For me, these collaborations, presentations and applications represent the main goal of the AHHME model family. Namely, to offer policymakers and researchers around the world an accessible open-source tool for modelling the holistic societal-level One Health impact of AMR and AMR interventions. This carries with it the goal of responding to the shortfalls in the health-economic methods currently used in the AMR space, and offering a feasible alternative that can be parameterised with data available in most countries.

2.1.5 Limitations

That being said, there are notable limitations to the AHHME model family, and limitations with the paper that I present here. Originally, I had created the AHHME model with the aim of

evaluating agricultural AMS interventions in Vietnam, in collaboration with Hanoi-based partners at ILRI. The paper would introduce the AHHME model, then simulate the national-level rollout of an AMS intervention in pig and poultry production and evaluate its health-economic significance. Using some data from farm-level trials of antimicrobial replacement interventions, I did do this, but eventually elected not to include the case study because:

a) It was difficult to use the results of the trials to estimate the effect of an intervention on farm-level outcomes, because the sample sizes were small and the results were not presented in a format which could easily be plugged into AHHME
b) It was difficult to estimate the impact of a given fall in agricultural AMU on the incidence of resistant infections in humans at the national level, given the lack of available literature on the topic
c) It was difficult to estimate the cost of the intervention implementation, and after consulting with stakeholders it seemed that national-level rollout of such an intervention would be impractical

Therefore instead of running a case study, I decided to choose a range of possible outcomes of an intervention (on farm productivity and on the prevalence of AMR in human infections), and to evaluate the health-economic impact of interventions in representative settings of different income levels under those different scenarios. While this was useful in all of the ways detailed above, a major reason for writing this paper was that many frameworks for holistic OH health-economic evaluation of AMR have not been applied concretely, and in a sense I continued this trend.

A main take-away from the writing process, therefore, was the need for more studies investigating the effect of AMS interventions on farm-level outcomes, and investigating the ecological relationship between animal AMU and human AMR. Having a more concrete knowledge of both of these relationships could produce results which can feed into AHHME, and make the concrete health-economic analysis that I talk about here more feasible, with useful implications for policy design and decision-making. This became the main motivation for the subsequent papers presented in this thesis, which respectively estimate those two relationships. The end goal of that process was to take those results and feed them into AHHME, something which I am currently doing for Senegal along with other members of the SEFASI consortium.

Another goal which I had to drop in the writing process was to demonstrate that the AHHME model can be applied to health-economic problems outside of agriculture and AMR. The modular nature of the model means that it can evaluate the health-economic impact of any intervention as long as the intervention impact can be expressed in terms of the model's ninety-odd parameters. In fact, when teaching faculty members of the School of Public Health at NUS how to use the model, we talked at length about how it could be used to simulate wastewater treatment interventions in Singapore, a country where domestic livestock production is much less important than in the UK, Denmark or Senegal. However, in order to keep the paper publishable and digestible, I had to maintain a focused scope and concentrate on the applications to agricultural AMS.

In terms of the model itself, there are several key limitations. For one, AHHME does not mechanistically model the effect of interventions on farm-level outcomes or human AMR.

While this was the original goal of the model, I decided not to do this and to keep the model focused on health-economic evaluation. This decision emerged largely from the fact that these two key relationships are not well-known in the literature, and I did not feel that I could confidently model them.

Another limitation is that, given the large number of parameters and the complexity of the model, results have a wide range of uncertainty and small changes in mechanical parameters or methodological assumptions can alter the results by millions of dollars. This, I feel, is not an inherent weakness of the AHHME model, but rather an honest admission of the limitations of modelling when applied to complex issues, especially at the ecological level. The model presents cost-effectiveness estimates in a technical way, but in reality AMR policy decisions must be made in a political and social context, which is why I emphasise that AHHME should only be used to guide and inform a policy decision making process which involves diverse stakeholders and consideration of political economy.

Related to this, while the model is powerful and unique in that it compares a wide range of outcomes in like (dollar) terms, which is very useful for designing and selecting policies, there are ethical considerations in doing so. Can human life years really be compared with loss of agricultural productivity? If an intervention saves lives but the loss of agricultural output and healthcare costs is greater than the value of the QALYs saved, is it really not worth implementing? While a loss of agricultural output can cause food insecurity and harm the livelihoods of precarious farmers, gains to agricultural productivity may (especially in the context of capitalism) simply be appropriated by landowners and wealthy farm owners in the capitalist class - is this really comparable to the value of human life? Cost-utility analysis does make some sense in a healthcare context where resources saved (by the healthcare sector) are used to save lives, but farm profits are not directly used for this purpose in the same way. In many ways, it would make more sense to directly model the impact of agricultural productivity losses on mortality and quality-of-life arising from hunger, but this again is an ecological relationship which is not well-understood or quantified.

Finally, although AHHME is a One Health model, the environmental compartment is not explicitly modelled. I considered trying to do this, but decided not to. The reason for this was that, while the environment is an important reservoir for the emergence and dissemination of AMR, the harm caused by AMR itself (as opposed to the harm caused by antibiotic residues and other contaminants in the environment) is felt in terms of its impact on human and animal health. Thus, environmental transmission and emergence of resistance is implied by the model but, not being a transmission model, it is not explicitly modelled.

2.1.6 Where does this leave us?

AHHME (and AHHME-B) are useful and valuable models with the potential to run health-economic analysis of AMR policies in a way which more completely reflects the true societal impact of AMR. However, confidently applying them to real-world policy questions will require a greater knowledge of two key relationships. Namely, the effect of AMS intervention packages on farm-level outcomes (theme 1), and the ecological relationship between agricultural AMU and human AMR (theme 3). For this reason, after creating these models, I focused my time on trying to elucidate those two relationships, with the eventual goal of improving our understanding of the impact of agricultural AMR policy using the

AHHME modelling framework. This began with analysis of farm-level survey data from the AMUSE studies, discussed in section 2.2 (below).

2.2 AMUSE papers: investigating the effect of AMU and farm practices with farm-level survey data

2.2.1 Introducing the papers

In 2022, a member of the SEFASI consortium, Dr. Michel Dione (supervisor), let me know that he and his colleagues at ILRI had access to farm-level survey datasets collected using the AMUSE tool(159). AMUSE is a survey tool designed to standardise and harmonise data collection on AMR knowledge, attitudes and practices (KAP) in livestock production. It has been applied to small and semi-intensive livestock producers in a range of countries, including Senegal, Uganda, Burkina Faso, the three countries covered in the papers I discuss in this section. Previous papers published using the AMUSE datasets focused on characterising KAPs(21,33,40).

Because the datasets included information on farm-level outcomes (such as animal productivity, morbidity and mortality) as well as on AMU and on other relevant factors (such as vaccination, biosecurity, and access to public vets), I felt that they could be repurposed to answer the questions which had made an AHHME case study difficult. Specifically, I saw that I could use statistical regression to measure the relationship between farm outcomes and both AMU and other factors. This could help to get a better idea of the likely impact of prospective stewardship interventions (including combined interventions) on farm outcomes, in the absence of targeted farm-level trials.

For one, it is important to know the extent to which nontherapeutic AMU, which is often thought of as unnecessary and irrational(47), is important to maintaining animal productivity and health in smallholder livestock farms. If that AMU does play an important role, then we cannot target its elimination without other (complementary) measures in place to make that reduction safer for farmers' incomes and animal health.

A second consideration is that, even if certain types of AMU are not essential for animal health and productivity, farmers may still be unwilling to reduce it due to risk aversion. Antibiotics are relatively cheap, and farmers may be unwilling to remove a key method of safeguarding against potential outbreaks(6). In fact, banning or restricting agricultural AMU outright may be counterproductive, leading to farmers using counterfeit or inappropriate antibiotics and worsening the potential to drive AMR(53).

It therefore makes sense to look at factors which are associated with better stewardship outcomes. That is, which potential interventions could be put in place which would make farmers feel safer reducing their antibiotic use, and could encourage better stewardship in a way which does not strip precarious farmers of their agency.

Investigating all of these outcomes would help to answer the questions:

a) Is nontherapeutic AMU, and AMU generally, important for animal health and productivity on smallholder livestock farms? Or, can it safely be targeted for elimination, as is implied in much of the policy discourse?
b) Can other interventions (e.g. biosecurity, vaccination) substitute AMU in promoting animal health and productivity? Can they be combined with stewardship interventions to make reductions in AMU safer for farmers and for wider food security?

c) What interventions can we implement which would make livestock farmers more likely to improve their antibiotic stewardship? These interventions can potentially be combined with restrictions on AMU

From there, we can try to answer the more concrete question: *Can we safely reduce nontherapeutic AMU on smallholder livestock farms, and what combined intervention packages should we recommend which will encourage stewardship and make reductions in AMU safer for animal health and productivity?* This is really the crux of what I wanted to investigate in these papers, as it is most directly relevant for guiding agricultural AMR policy

Ideally, questions like this would be investigated using intervention trials on farms, an evidence gap that became noticeable when writing the AHHME paper. However, I had to adapt to the data available to me, which came in the form of survey data. These data were collected with the purpose of characterising AMR KAPs: they reflected a single point in time, the outcomes measured (while extensive) were not recorded with this type of study in mind, nor were power calculations done for this type of analysis.

I decided to use regression analysis to look at the links discussed above. For example, expressing animal morbidity as a function of nontherapeutic AMU and biosecurity practices, while controlling for the number of type of animal on a farm. I did this for three reasons. Firstly, because regression results can (theoretically) tell us the likely change in our outcome variable following a change in our independent variable. This would give an idea of the impact of particular interventions on farm outcomes, and could be fed into models like AHHME to run HEA of prospective interventions. Secondly, it would allow me to look at interactions between different covariates. For example, regressing animal morbidity against both AMU and biosecurity (with an interaction term) could give a result like *AMU has a benefit for animal health, but this benefit becomes less important if biosecurity is better. Therefore, reducing AMU while improving biosecurity could help to safely implement stewardship interventions*. Thirdly, regression analysis would allow me to control for factors like farm size, animal type, and other potential confounders.

I wrote three papers using this approach, each focusing on a dataset collected from smallholder livestock farms in a different country (Senegal, Uganda and Burkina Faso, respectively) using the AMUSE survey. For each of these papers, I took the raw AMUSE results datasets, cleaned and transformed them, designed and ran a series of tests and regressions, and wrote three papers with supervisory and proofreading input from coauthors.

The papers themselves are presented below. I present them all together as I found it made more sense to discuss their results as an ensemble. I went through the LSHTM ethical approval process for paper 2 (Senegal), but was told that I did not need to do so for papers 3 and 4 because they were written using secondary datasets and because I had included the ethical approval given for the initial data collection.

2.2.2 Papers 2-4

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	2204500	**Title**	Miss
First Name(s)	Eve		
Surname/Family Name	Emes		
Thesis Title	Revisiting key assumptions about animal antibiotic use and human health from a One Health perspective		
Primary Supervisor	Gwen Knight		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Antibiotics		
When was the work published?	February 2023		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	I am enrolled in the PhD by Prior Publication programme, so the papers that form part of this portfolio were already published at the time of registration		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	The dataset used in this analysis was collected by colleagues at ILRI using the AMUSE survey tool. I created the design for this study, and cleaned and prepared the dataset to be used here. I analysed the data in R, and wrote the paper with supervisory input from coauthors.

SECTION E

Student Signature	Eve Tresco Emes
Date	22 October 2024

Supervisor Signature	Gwen Knight
Date	22 October 2024

antibiotics

MDPI

Article

Drivers of Antibiotic Use in Semi-Intensive Poultry Farms: Evidence from a Survey in Senegal

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Abstract: Antimicrobial resistance (AMR), the capacity of microbial pathogens to survive in the presence of antimicrobials, is considered one of the greatest threats to human health worldwide and is growing rapidly in importance. AMR is thought to be driven in part by the use of antimicrobials (AMU) in livestock production. AMU reduction in agriculture is therefore important, but doing so may endanger farmers' livelihoods and hamper broader food security. Understanding the drivers for farmers' antibiotics use is essential for designing interventions which avoid harming agricultural output and to safeguard farmers' economic security. In this study, we analyse AMUSE survey data from poultry farmers in Senegal to explore the effects of vaccination, attitudes towards AMR, and biosecurity practices on: AMU, animal mortality, and farm productivity. We found that farmers with more "AMR-aware" attitudes may be less likely to use antibiotics in healthy birds. Stronger on-farm biosecurity was associated with less use of antibiotics in healthy birds, and in some specifications was linked to higher broiler productivity. Vaccination and AMU were both higher in farms with a higher disease prevalence, and both factors appeared conducive to higher broiler productivity. Overall, there is evidence that awareness raising and biosecurity improvements could encourage prudent use of antibiotics, and that biosecurity and vaccination could to some extent replace antibiotic use as productivity-enhancing and disease management tools in broiler farms. Finally, issues of farm antimicrobial stewardship must be considered at the structural level, with farm behaviours contingent on interaction with state and private stakeholders.

Keywords: antimicrobial resistance; antimicrobial stewardship; One Health; agriculture; biosecurity

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1. Introduction

Antimicrobial resistance (AMR), the capacity of microbial pathogens to survive in the presence of antimicrobials, is considered one of the greatest threats to human health worldwide and is growing rapidly in importance [1,2]. Although AMR has always existed, its increasing prevalence is driven largely by the use of antimicrobials (AMU) by humans [3]. In particular, use of antibiotics in livestock animal production is one of the biggest contributors to total AMU, and reducing its use has been identified as a policy priority [4–7]. As a middle-income country with a high rate of economic growth, Senegal is identified as suffering from the 'double-burden' of rising antibiotic availability and meat

consumption, combined with rates of bacterial infections that remain high in the global context [1].

Senegal's most recent National Action Plan on AMR involved the animal health and food safety sectors [8], and aims to balance rational use of antibiotics and awareness raising on AMR with infection control across all One Health sectors. These findings, and others, will contribute to the evidence base which feeds into the upcoming 2023–2027 plan.

Much antibiotic use globally is deemed to be unnecessary or irrational: for example, antibiotics are commonly used as agricultural growth promotors, or are used purely prophylactically (preventatively) rather than therapeutically, and may often be used without a prescription [9]. However, antibiotics can play a therapeutic role in livestock production, and even sub-inhibitory and non-therapeutic use can play a role in animal productivity, and may thus be important to farmers' income security [9]. Therefore, reducing AMU in livestock production, especially in small-scale and semi-intensive farms, may harm farmers' livelihoods and economic security, and may contribute to food insecurity at the population level if it negatively affects farm productivity. Achieving a reduction in farm AMU will not be realistic or safe if farmers do not feel secure in doing so. It is therefore important to understand which interventions can be paired with AMU reduction that can prevent any associated loss in farm productivity, and can make farmers feel more comfortable withdrawing or replacing antibiotics.

We investigated this question using the case study of semi-intensive peri-urban poultry farms in Dakar and Thiès, in Senegal. The domestic poultry industry in Senegal is rapidly growing, and is a key user of antibiotics [10,11]. Semi-intensive farms were selected because they comprise a very large portion of agricultural production in Senegal and many other middle-income countries, the group of countries which is most vulnerable to the effects of AMR [12,13]. In other countries, the shift from backyard farming to small- and medium-sized semi-intensive farms in recent decades has been associated with a range of novel and diverse farming practices [14]; in some cases meaning more indiscriminate antibiotic use [15,16], with medium-sized farms especially likely to misuse antibiotics [17]. Semi-intensive farms are also more economically vulnerable than larger-scale farms, and may have a precarious relationship to creditors and suppliers [16], making them a key target for this investigation. In Senegal, while many studies have been carried out on AMU in poultry farms, these studies tend to be descriptive and focus on mapping out knowledge, attitudes, and practices (KAP). This is the first study of this kind pointing to evidence on interventions to reduce AMU in Senegal.

We aimed to investigate factors which could induce farmers to reduce antibiotic use, guide more prudent use, or guard against productivity losses in the event of an antibiotic use reduction intervention. We identified three such factors to investigate, namely: (1) vaccination of chickens; (2) farmers' attitudes to, and awareness of, AMR; and (3) on-farm biosecurity measures. We hypothesised that all three could lead to lower and better-informed AMU and/or could enhance productivity, reducing the need for antibiotics as growth promotion and disease management tools.

Using survey data collected with a modified AMUSE survey tool [18] from 222 farms in Dakar and Thiès, we investigated:

1. Whether better biosecurity, vaccination, and awareness of AMR lead to lower or more selective use of antibiotics (e.g., limiting use to therapeutic use, or avoiding use of antibiotics intended for use in humans) in poultry farms.
2. What effect these three factors, as well as antibiotic use (defined by expenditure on antibiotics), have on farm profitability and disease incidence.

Following our main results, we also investigate how these factors interact with each other, and explored additional specifications.

2. Results

2.1. Descriptive Statistics

Of the 222 farms in our dataset, 124 had broilers only and 97 had layers only, with one farm having both.

Table 1 (below) shows the distribution of categorical variables, and Figure 1 shows the distribution of continuous variables. Correlations (Pearson's correlation coefficient) between key variables are displayed in Appendix F.

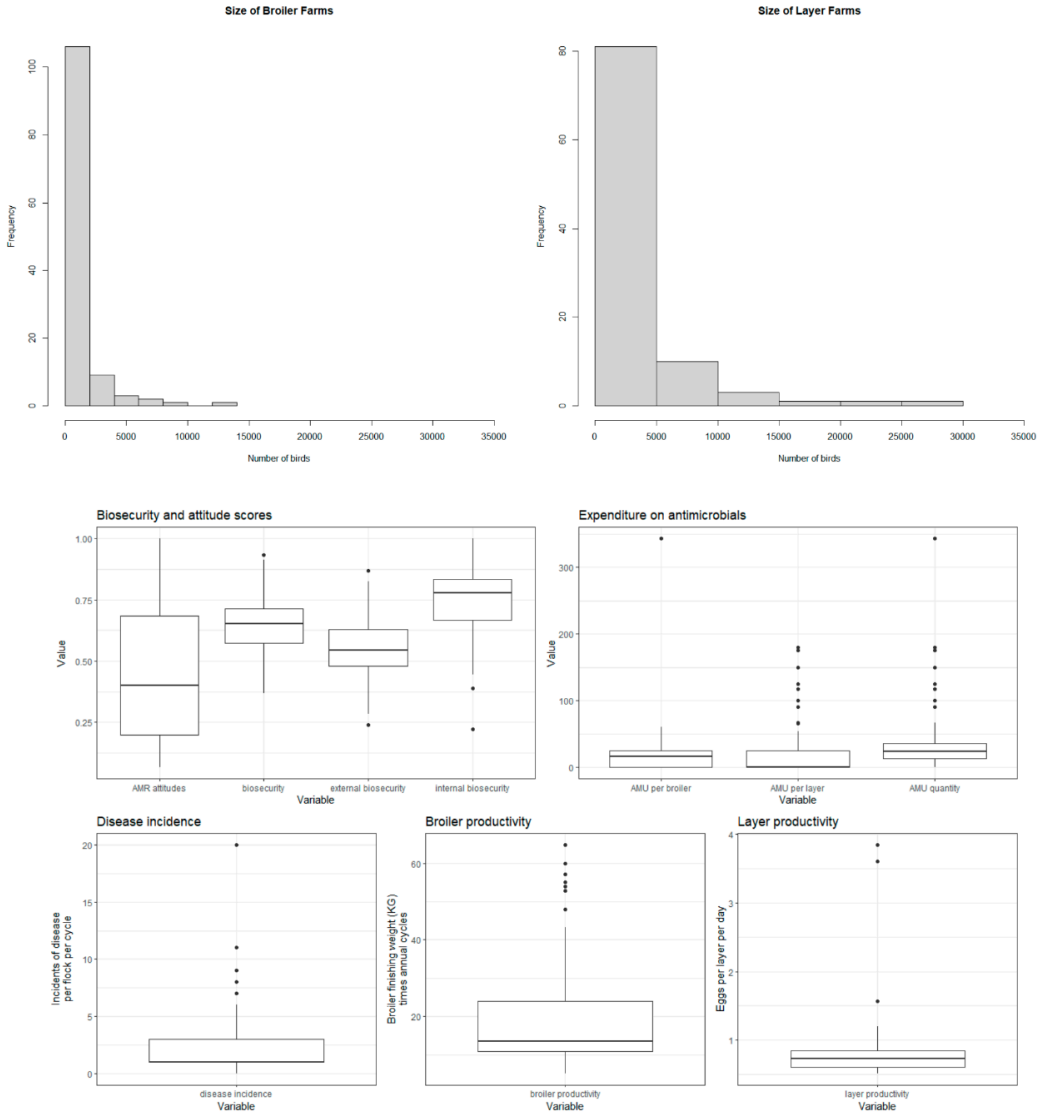

Figure 1. Distribution of continuous variables.

Table 1. Summary statistics of categorical variables.

Variable	Description
"Vaccination"	no protocol (15/222) protocol in place but not always adhered to (6/222) protocol in place and always adhered to (201/222)
"Other species on farm"	no species present other than chickens (193/222) other species present (29/222)
"AMU in healthy birds"	did not use antibiotics in healthy birds (216/222) used antibiotics in healthy birds (6/222)
"Portion broilers"	Broilers only: 124/222 Layers only: 97/222 53% broilers and 47% layers: 1/222

Summary statistics of categorical variables used.

Histograms of the size of broiler and layer farms, and box-and-whisker plots showing the distribution of key variables used.

2.2. *Main Results*

Tables 2–6 (below) shows the results of our main regressions, where we look at the effect of our three main covariates ("biosecurity", "AMR attitudes", and "Vaccination") on the quantity of AMU ("AMU quantity") (Table 2); the likelihood of using antibiotics on healthy birds ("AMU in healthy birds") (Table 3); animal morbidity ("Disease incidence") (Table 4); and farm productivity ("broiler productivity" and "layer productivity") (Tables 5 and 6).

Table 2. Determinants of AMU quantity.

	Dependent Variable			
	"AMU quantity"			
	(1)	(2)	(3)	(4)
vaccination	4.130			5.545
	(5.925)			(6.254)
biosecurity		−10.110		−10.815
		(33.572)		(36.783)
"AMR attitudes"			−8.173	−9.224
			(12.762)	(13.718)
"farm size"	−0.003 **	−0.003 **	−0.003 **	−0.003 **
	(0.001)	(0.001)	(0.001)	(0.001)
"other species on farm"	−3.767	−3.100	−3.585	−3.981
	(9.838)	(9.860)	(9.829)	(9.934)
"portion broilers"	−17.822 **	−18.575 **	−18.197 **	−18.156 **
	(7.439)	(7.552)	(7.424)	(7.593)
Constant	41.024 ***	55.206 **	52.623 ***	49.912 **
	(12.857)	(22.799)	(9.176)	(23.493)
Observations	134	134	134	134
R^2	0.071	0.068	0.070	0.076
Adjusted R^2	0.042	0.039	0.042	0.033
Residual Std. Error	39.553 (df = 129)	39.614 (df = 129)	39.565 (df = 129)	39.751 (df = 127)
F Statistic	2.464 ** (df = 4; 129)	2.358 * (df = 4; 129)	2.444 ** (df = 4; 129)	1.746 (df = 6; 127)

Note: * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$; (1) Effect of vaccination on AMU; (2) effect of biosecurity on AMU; (3) effect of attitudes on AMU; and (4) effect of all three on AMU (standard errors in parentheses).

Table 3. Determinants of antibiotic use in healthy birds.

	Dependent Variable			
	"AMU in healthy birds"			
	(1)	(2)	(3)	(4)
vaccination	0.077			0.137
	(0.290)			(0.300)
biosecurity		−0.326		0.163
		(1.520)		(1.602)
"AMR attitudes"			−0.846	−0.896
			(0.543)	(0.565)
"farm size"	−0.00005	−0.00005	−0.00004	−0.00005
	(0.0001)	(0.0001)	(0.0001)	(0.0001)
"other species on farm"	0.009	0.019	0.017	0.005
	(0.443)	(0.443)	(0.446)	(0.447)
"portion broilers"	1.606 ***	1.582 ***	1.600 ***	1.621 ***
	(0.314)	(0.322)	(0.315)	(0.327)
Constant	−0.655	−0.298	−0.117	−0.456
	(0.606)	(1.039)	(0.372)	(1.089)
Observations	220	220	220	220
Log Likelihood	−132.635	−132.647	−131.451	−131.329
Akaike Inf. Crit.	275.271	275.294	272.902	276.659

Note: *** $p < 0.01$; (1) Effect of vaccination on antibiotic use in healthy birds; (2) effect of biosecurity on antibiotic use in healthy birds; (3) effect of attitudes on antibiotic use in healthy birds; and (4) effect of all three on antibiotic use in healthy birds (standard errors in parentheses).

Table 4. Determinants of disease incidence.

	Dependent Variable			
	"disease incidence"			
	(1)	(2)	(3)	(4)
vaccination	0.409			0.515
	(0.327)			(0.344)
biosecurity		−0.251		−0.199
		(1.858)		(2.016)
"AMR attitudes"			−0.794	−1.000
			(0.705)	(0.753)
"AMU quantity"	0.011 **	0.012 **	0.012 **	0.011 **
	(0.005)	(0.005)	(0.005)	(0.005)
"farm size"	−0.00003	−0.00003	−0.00002	−0.00002
	(0.0001)	(0.0001)	(0.0001)	(0.0001)
"other species on farm"	−0.167	−0.116	−0.148	−0.208
	(0.542)	(0.546)	(0.542)	(0.545)
"portion broilers"	−0.564	−0.603	−0.600	−0.575
	(0.419)	(0.427)	(0.419)	(0.425)
Constant	1.481 **	2.381 *	2.618 ***	1.923
	(0.736)	(1.290)	(0.567)	(1.310)
Observations	134	134	134	134
R^2	0.084	0.073	0.082	0.098
Adjusted R^2	0.048	0.036	0.046	0.048
Residual Std. Error	2.179 (df = 128)	2.192 (df = 128)	2.181 (df = 128)	2.178 (df = 126)
F Statistic	2.337 ** (df = 5; 128)	2.004 * (df = 5; 128)	2.274 * (df = 5; 128)	1.959 * (df = 7; 126)

Note: * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$; (1) Effect of vaccination on disease incidence; (2) effect of biosecurity on disease incidence; (3) effect of attitudes on disease incidence; and (4) effect of all three on disease incidence (standard errors in parentheses).

Table 5. Determinants of productivity (broilers).

	Dependent Variable			
	"broiler productivity"			
	(1)	(2)	(3)	(4)
vaccination	2.477			0.847
	(2.450)			(2.573)
biosecurity		28.393 **		24.638
		(13.198)		(15.179)
"AMR attitudes"			7.423	2.330
			(5.815)	(6.458)
"AMU quantity"	0.121 ***	0.121 ***	0.126 ***	0.120 ***
	(0.041)	(0.040)	(0.040)	(0.040)
"farm size"	0.004 ***	0.004 ***	0.005 ***	0.004 ***
	(0.001)	(0.001)	(0.001)	(0.001)
"other species on farm"	2.364	2.174	3.491	2.388
	(4.151)	(4.056)	(4.173)	(4.196)
Constant	8.087 *	−4.919	8.048 **	−5.264
	(4.628)	(8.247)	(3.995)	(8.484)
Observations	84	84	84	84
R^2	0.214	0.248	0.220	0.251
Adjusted R^2	0.174	0.210	0.180	0.192
Residual Std. Error	13.641 (df = 79)	13.344 (df = 79)	13.590 (df = 79)	13.492 (df = 77)
F Statistic	5.378 *** (df = 4; 79)	6.511 *** (df = 4; 79)	5.569 *** (df = 4; 79)	4.292 *** (df = 6; 77)

Note: * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$; (1) Effect of vaccination on broiler productivity; (2) effect of biosecurity on broiler productivity; (3) effect of attitudes on broiler productivity; and (4) effect of all three on broiler productivity (standard errors in parentheses).

Table 6. Determinants of productivity (layers).

	Dependent Variable			
	"layer productivity"			
	(1)	(2)	(3)	(4)
vaccination	−0.072			−0.082
	(0.062)			(0.064)
biosecurity		−0.357		−0.335
		(0.417)		(0.460)
"AMR attitudes"			−0.106	−0.076
			(0.084)	(0.092)
"AMU quantity"	−0.001	−0.001	−0.001	−0.001
	(0.001)	(0.001)	(0.001)	(0.001)
"farm size"	−0.00000	0.00000	−0.00000	0.00000
	(0.00000)	(0.00001)	(0.00000)	(0.00001)
"other species on farm"	0.115	0.119	0.096	0.112
	(0.069)	(0.071)	(0.070)	(0.072)
Constant	0.876 ***	0.956 ***	0.797 ***	1.149 ***
	(0.127)	(0.263)	(0.062)	(0.326)
Observations	26	26	26	26
R^2	0.189	0.166	0.198	0.268
Adjusted R^2	0.035	0.007	0.045	0.036
Residual Std. Error	0.112 (df = 21)	0.113 (df = 21)	0.111 (df = 21)	0.112 (df = 19)
F Statistic	1.226 (df = 4; 21)	1.043 (df = 4; 21)	1.295 (df = 4; 21)	1.157 (df = 6; 19)

Note: *** $p < 0.01$; (1) Effect of vaccination on layer productivity; (2) effect of biosecurity on layer productivity; (3) effect of attitudes on layer productivity; and (4) effect of all three on layer productivity (standard errors in parentheses).

None of our covariates of interest significantly affected the quantity of AMU, regardless of whether they were included together or separately (Table 2). In fact, farm size and production type were the only variables that significantly influenced this, with larger farms consistently using fewer antibiotics per bird (perhaps due to economies of scale) and broiler farms using less per cycle (although production cycles were much shorter).

In univariate specifications (Appendix B), farmers with more 'AMR-aware' attitudes, and those with better biosecurity, appeared less likely to use antibiotics on healthy birds. However, there is little evidence to support the link with biosecurity in our main specifica-

tions (Table 3). Here, AMR-aware attitudes remained negatively associated with antibiotics use in healthy birds, but this relationship was not quite statistically significant ($p = 0.113$ and $p = 0.120$). Broiler farms were consistently more likely to use antibiotics in healthy birds, perhaps due to growth-promotion use.

Antibiotic use was consistently associated with a higher incidence of disease (Table 4), as was our index of vaccination (in the univariate specification only). We speculate that this reflects endogeneity in two ways: (1) that vaccination and antibiotics may be used in response to disease outbreaks; and (2) that farmers who are more aware of animal health are both more likely to report disease incidence and also more likely to vaccinate.

A larger farm size, greater use of antibiotics, and better biosecurity were associated with more productive broilers (Table 5). In the univariate specifications (Appendix B), better vaccination was also associated with higher broiler productivity. Although antibiotics seemed to increase broiler productivity, so did vaccination and biosecurity. Therefore, a reduction in AMU with a simultaneous improvement in biosecurity (and vaccination) could improve antibiotic stewardship on broiler farms without harming productivity. This does not seem to be the case for layer farms, where none of our covariates significantly predicted productivity (Table 6).

2.3. Robustness

Following our main results, we regressed the quantity of AMU against each of the biosecurity measures individually, as opposed to the biosecurity index ("Biosecurity") used elsewhere. Only four individual measures appeared to be significant, but they did not remain significant after adjusting for the false discovery rate or the family-wise error rate.

We also investigated the effect of having a relevant professional (veterinarian, paravet-erinarian, or livestock helper) advise on antimicrobial use, on the quantity of AMU and the likelihood of using antimicrobials in healthy birds (Appendix G). However, this did not significantly affect either outcome.

After this, we used Heckman selection [19] to take account of farms which did not use antibiotics. Our covariates of interest had no significant effect, which is unsurprising given that only 13 farms (9.7%) out of 134 with data on antibiotic expenditure reported zero expenditure.

Finally, we examined three sub-hypotheses using interaction terms, all with disease incidence and productivity as our outcomes of interest (Appendix C). (1) We interacted AMU with biosecurity to see if better biosecurity reduced the need for antibiotics in improving farm outcomes. (2) We interacted vaccination and biosecurity to see if these two measures are substitutes in terms of disease management. (3) We interacted AMR attitudes with AMU to see if better awareness of AMR increased the effectiveness of antibiotics as a disease management tool (following our original assumption that AMU would have a negative effect on disease incidence). However, none of the interaction terms were statistically significant.

3. Discussion

3.1. Overview of Findings

The characteristics and production type of farms were shown to be just as important to antibiotic use practices and farm outcomes, as were our covariates of interest (biosecurity, vaccination, and AMR attitudes). Larger farms consistently used fewer antibiotics per bird, and had more productive broilers. Broiler farms also seemed more likely to use antibiotics on healthy birds. This could be explained by the fact that broiler production cycles are short with farmers desiring quick turn over, as farmers may wish to speed up production cycles using antibiotic growth promotors. Antibiotic use did seem to be associated with a greater productivity in broilers, but not in layers, suggesting a possible growth-promoting role.

Farmers with more 'AMR-aware' attitudes were less likely to use antibiotics on healthy birds in some specifications, which can be seen as indicative of more prudent AMU.

Vaccination was associated with more productive broilers in some specifications, and may be endogenous with disease incidence. Of our three covariates of interest, vaccination likely requires further investigation the most, due to the low variation in vaccination practices among the farms surveyed. This also means that vaccination may have effects that we were not able to capture in this study.

Biosecurity, as measured by an index of various farm practices, was associated with more productive broilers. In univariate specifications, it was also associated with a lower likelihood of using antibiotics in healthy birds.

3.2. Comparison with Previous Work

Previous studies using the AMUSE tool have focused on characterising farm KAP. Our addition of questions concerning productivity, biosecurity, vaccination, and attitudes and knowledge of AMR greatly enhance the tool. This version of the survey (Appendix A) can also be used in other contexts, and a replication of our results in other contexts would yield very useful comparisons.

While the effectiveness of antibiotic growth promoters is controversial, there are reasons to believe that low (sub-inhibitory) doses can promote livestock productivity [9]. Our findings suggest that this may be the case, at least for semi-intensive broiler farms. This reaffirms the necessity of finding interventions which make antibiotic use reduction safer for farmers.

Weaker biosecurity infrastructure has also been associated with worse disease outcomes in other contexts [20]. We did not replicate this result, but we did find a link to broiler productivity.

Lastly, vaccination of poultry is potentially a very effective tool for productivity enhancement and disease management [21]. We found some suggestion of a productivity benefit for broilers, but did not replicate this finding consistently, likely reflecting the small sample size and very low variation in vaccination practices observed.

3.3. Meaning of Results and Implications for Future Research

Overall, there is some evidence that our three factors of interest (biosecurity, vaccination, and AMR attitudes) could be used to reduce AMU in poultry production, either by modulating AMU behaviours or by mitigating the potential productivity lost due to antibiotic withdrawal. Specifically, biosecurity may lower the incidence of disease and reduce the need for therapeutic antibiotic use, and biosecurity and vaccination may offset any productivity loss associated with antibiotic use reduction. In addition, awareness raising and biosecurity improvements may reduce the use of antibiotics in healthy birds and improve prudence to antibiotic use.

The findings aim to inform key interventions of the next multisectoral AMR monitoring action plan for Senegal (2023–2027). The previous plan lasted 5 years and ended in 2022. The overall objective of the plan is to provide an effective response, through an integrated "One Health" approach, to the growing threat of antimicrobial resistance. Specific objectives of the plan which these results can inform include ensuring rational management and use of antimicrobials; informing and raising awareness on the issue of antimicrobial resistance; and the rational use of antimicrobials in animal health.

3.4. Limitations

Using observational survey data such as these poses a few difficulties. For one, there was considerable endogeneity between antibiotic use, vaccination, and disease prevalence, which made causality difficult to disentangle. We recommend the use of larger datasets and annual follow-up to improve the statistical power of this type of study, as well as the use of instrumental variable techniques to mitigate this endogeneity. In particular, more data on the effectiveness of animal vaccination in semi-intensive poultry farms is necessary. Beyond this, a key step to follow should be to test these observational findings in the context of farm-level trials. Antibiotic use reduction (or replacement by non-antimicrobial feed additives)

should be trialled alone, as well as in combination with interventions related to vaccination, biosecurity, and awareness raising. Outcomes measured should include the incidence of disease, farm productivity, the use of antibiotics, the level of resistance in livestock animals, and the extent to which farmers feel safe and willing to withdraw antibiotics.

The relative homogeneity of farms in terms of practices (for example, near-universal antibiotic use and consistent vaccine coverage) not only contrasted stylised facts about the diversity and inconsistency of semi-intensive poultry farming practices [14], but also made statistical inference more difficult. This reaffirms the potential use of farm-level trials, in which these variables are intentionally altered, in future research. We were also not able to obtain enough detail about the different types of vaccines used to investigate this as a factor at this sample size. Since the types of vaccines used will vary among farms, it would be important to understand the differential effect of each vaccine on animal health and antibiotic usage when informing policy.

There was also a very low R^2 value across all regression specifications, likely reflecting the omission of key variables. A more detailed understanding of the relevant production system, for example using system dynamic models informed and parameterised in consultation with stakeholders [22], could help to collect more relevant data and to build more relevant models. Along with colleagues, we have recently submitted a paper which uses stakeholder elicitation to build a system dynamic model of this production system, which investigates the relative importance of potential interventions targeting AMU and profitability.

While we investigated the effect of awareness and attitudes from a statistical perspective, this is not a substitute for an in-depth investigation of these attitudes using mixed-methods research. Other upcoming research using this modified survey tool aims to answer this question in greater detail.

A further limitation is that we were not able to collect data on the actual quantity of antibiotics used, e.g., in defined daily doses, as these data were not collected by farmers, and instead we had to use expenditure on antibiotics as a proxy. This may have introduced bias due to the different prices of various antibiotic types, meaning that these results are harder to compare directly with those from other contexts (or to other metrics such as the global average annual consumption of antibiotics).

Finally, it must be noted that these findings alone may not be sufficient to facilitate changes to farming practices. The adoption of better biosecurity and vaccination practices are not a matter of individual 'smart choices', but are structural and nationwide issues that are heavily dependent on infrastructure and state support, being more effective when rolled out nationally [20,21]; attitudes towards AMR can be thought of in the same way. Farmers moving towards more intensified production systems are exposed to novel challenges and require appropriate state support [14]. Semi-intensive farmers often exist in a state of financial precarity and may require systems of financial support, such as insurance, in order to feel safe altering their practices. Small- and medium-scale farmers have complex upstream and downstream relationships with actors, such as suppliers and creditors [16]. Farmers must be seen as a part of this network, rather than as individual actors, and stakeholders from across this system must be meaningfully consulted in the formulation of future research and interventions.

4. Materials and Methods

4.1. Study Aims, Data Collection Methods, and Setting

The data used in this study came from a modified version of the AMUSE survey tool, which is used to explore farm characteristics and AMR KAP in livestock farms [18]. The original AMUSE tool has been used for descriptive purposes in Senegal as well as in other country settings, and our adapted version was expanded to include more measures of farm productivity, antibiotic use quantity, antibiotic use prudence, vaccination of livestock, AMR knowledge and attitudes, and on-farm biosecurity practices. 'Prudence' in this study refers to the use/non-use of antibiotics in healthy birds. Also of relevance is the effect that

these variables have on farm productivity and disease incidence in chickens. Data were cleaned and answers from sets of questions were compiled into metrics and indices for easier analysis (Table 7).

Table 7. Variable glossary.

Varname	Meaning	Units
"Vaccination"	A score for having (and adhering to) a vaccination protocol for birds	0 = no protocol 1 = protocol in place but not always adhered to 2 = protocol in place and always adhered to
"Internal biosecurity"	A score for internal biosecurity measures on the farm, based on categorical responses to several questions about biosecurity procedures. As with other scores in this dataset, each question about internal biosecurity gave a number of points (1 for the 'best' answer and 0 for the 'worst' answer, with fractions for answers in between). The internal biosecurity score is then calculated as the mean of the scores attained on all questions about internal biosecurity	Continuous, ranging between 0 (met none of the standards) and 1 (met every standard)
"External biosecurity"	A score for external biosecurity measures on the farm, based on categorical responses to several questions about biosecurity procedures	Continuous, ranging between 0 (met none of the standards) and 1 (met every standard)
"Biosecurity"	The mean of the internal and external biosecurity scores	Continuous, ranging between 0 (met none of the standards) and 1 (met every standard)
"AMR attitudes"	A score for attitudes about antimicrobial resistance and stewardship, based on categorical responses to several questions	Continuous, ranging between 0 (met none of the standards) and 1 (met every standard)
"Farm size"	The number of chickens on the farm	Chickens
"Other species on farm"	The presence of animal species other than chickens on the farm	Binary 0 = no other species present 1 = other species present
"AMU quantity"	The quantity of antibiotics used in chicken production. "AMU per broiler" and "AMU per layer" disaggregate this figure by production type	FCFA (Franc de la Communauté Financière Africaine, or West African Franc) spent on antibiotics per bird per production cycle
"AMU in healthy birds"	The use of antibiotics in healthy birds (for whatever reason)	Binary 0 = did not use antibiotics in healthy birds 1 = used antibiotics in healthy birds
"Disease incidence"	Amount of disease occurring in the flock	Number of individual disease incidents recorded in the flock during a production cycle
"Broiler productivity"	Productivity of broilers	Average finishing weight of a broiler, multiplied by the number of production cycles per year
"Layer productivity"	Productivity of layers	Average number of eggs laid per layer per day
"Portion broilers"	Portion of chickens on the farm which are broilers	Portion

The locations of the farms surveyed are detailed in Figure 2 (below). Data collection took place from February to September 2022. A snowball sampling method was used to select farms. This method was chosen because a national database of poultry producers has not yet been compiled, making other sampling methods prohibitively difficult. A representative from each farm was interviewed for an average of one hour per farm. Four people in total were responsible for data collection, divided into two pairs, each composed of a veterinary doctoral student and a member of the Veterinary Service Division (DSV) of Dakar or Thiès, sometimes with the addition of a livestock technician to act as a guide and interlocutor. Data were collected electronically on smartphones using the Open Data Kit (ODK) platform.

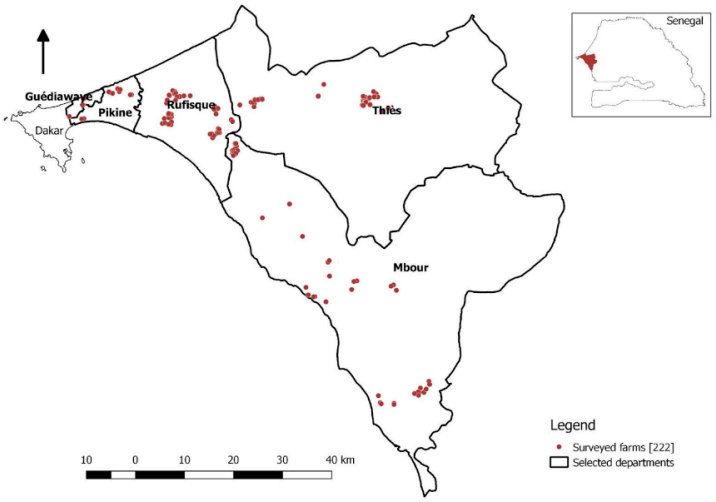

Figure 2. Map of the farms surveyed and the selected area.

The map above covers the six departments in which surveyed farms were located, with location within Senegal indicated in the top-right corner. Each red point represents the location of one of the 222 farms which were surveyed for the purposes of this study.

The full set of survey questions used can be found in Appendix A. Ethical approval can be found in Appendix D and a translated copy of the informed consent form used for the study can be found in Appendix E. Being an observational study, this paper conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist [23].

4.2. Variables Used

We first present descriptive statistics, and then use regression analysis to look at the association between our three variables of interest on the following outcomes (both univariate and controlling for farm characteristics): quantity of AMU (measured by expenditure per bird), the use of antibiotics on healthy birds, farm productivity (meat and egg production), and the incidence of disease. Table 3 (below) details the variable names used throughout this paper, and outlines how variables were derived where relevant.

Farm characteristics that were controlled for included the ratio of broilers to layers, farm size, and the presence or absence of livestock species other than chickens. This is because broiler and layer farms have different production stages and may use antibiotics in different ways; farm size may influence access to resources and economies of scale, and the presence of other species raises additional concerns of cross-contamination and may affect the efficacy of vaccination [21].

4.3. Main Statistical Methods

All statistical analyses were carried out using R version 4.1.2 [24] via RStudio build 554 [25]. Key packages used include Stargazer [26], Tidyverse [27], ggplot2 [28], Corrplot [29], and dplyr [30]. Model specifications were not chosen based on explanatory power (e.g., AIC or BIC) but were pre-specified in the pre-analysis plan based on theory. This is because we wanted to test specific hypotheses about our chosen variables rather than simply finding the model with the greatest explanatory power. Alternative specifications were explored during robustness testing.

First, we regressed the quantity of antibiotics used ("AMU quantity") against each of the three main covariates using ordinary least squares (OLS) (models (1)–(3)), and then against all three main covariates together (model (4)). We adjusted for key farm characteristics of farm size, presence of other species, and the ratio of broilers to layers. We then did this for other outcomes, namely disease incidence and productivity ("broiler productivity" and "layer productivity").

$$Y_t = \beta_0 + \beta_1 * vaccination + \beta_2 * farm\ size + \beta_3 * other\ species + \beta_4 * portion\ broilers + \varepsilon \quad (1)$$

$$Y_t = \beta_0 + \beta_1 * biosecurity + \beta_2 * farm\ size + \beta_3 * other\ species + \beta_4 * portion\ broilers + \varepsilon \quad (2)$$

$$Y_t = \beta_0 + \beta_1 * AMR\ attitudes + \beta_2 * farm\ size + \beta_3 * other\ species + \beta_4 * portion\ broilers + \varepsilon \quad (3)$$

$$Y_t = \beta_0 + \beta_1 * vaccination + \beta_2 * biosecurity + \beta_3 * AMR\ attitudes + \beta_4 * farm\ size + \beta_5 * other\ species + \beta_6 * portion\ broilers + \varepsilon \quad (4)$$

where $i \in \{AMU\ quantity,\ disease\ incidence,\ broiler\ productivity,\ layer\ productivity\}$.

Aside from wanting to investigate the determinants of AMU, we also looked at disease incidence and productivity to see if the three measures of interest (vaccination, biosecurity, and awareness raising) incur any trade-offs in terms of profitability. Ultimately, if we recommend these measures as means of encouraging farmers to reduce or modulate AMU, then we should be confident that this will not endanger their economic security or broader food security at the population level.

Following this, we regressed use of antibiotics on healthy birds against each of the three main categories of covariates using a logistic regression (logit). These logistic regressions were performed in order to see if any of the three measures being investigated improved prudent use of antibiotics.

$$p = \left(1 + e^{-xb}\right)^{-1} \quad (5)$$

where p is the probability of using antibiotics in healthy birds; x is a vector of the covariates used in models (1) through (4); and b is a vector of parameters (odds ratio).

4.4. Robustness and Further Specifications

We first tested the association between AMU and a large number of individual biosecurity measures, as opposed to the biosecurity index ("biosecurity") used elsewhere. We accounted for multiple hypothesis testing using family-wise error rate (using Bonferroni correction [31]) and the false discovery rate (using the Benjamini-Hochberg step-up procedure [32]).

After this, we looked at the effect of our three main covariates on AMU using Heckman selection [19], with a selection function using variables that were seen to affect AMU in other specifications. This was done to take better account of farms which did not use antibiotics.

Finally, we looked at a number of interactions between key covariates to test more specific hypotheses. All of these interactions looked at productivity and animal mortality as outcomes. The hypotheses are described below.

Interacting AMU with biosecurity to see if better biosecurity reduced the need for antibiotics in improving farm outcomes, i.e.,

$$broiler\ productivity = \beta_0 + \beta_1 * biosecurity + \beta_2 * AMU\ quantity + \beta_3 * biosecurity * AMU\ quantity + \beta_4 * farm\ size + \beta_5 * other\ species + \varepsilon \quad (6)$$

$$layer\ productivity = \beta_0 + \beta_1 * biosecurity + \beta_2 * AMU\ quantity + \beta_3 * biosecurity * AMU\ quantity + \beta_4 * farm\ size + \beta_5 * other\ species + \varepsilon \quad (7)$$

$$disease\ incidence = \beta_0 + \beta_1 * biosecurity + \beta_2 * AMU\ quantity + \beta_3 * biosecurity * AMU\ quantity + \beta_4 * farm\ size + \beta_5 * other\ species + \beta_5 * portion\ broilers + \varepsilon \quad (8)$$

Interacting vaccination and biosecurity to see if these two measures are substitutes in terms of disease management, i.e.,

$$broiler\ productivity = \beta_0 + \beta_1 * biosecurity + \beta_2 * vaccination + \beta_3 * biosecurity * vaccination + \beta_4 * farm\ size + \beta_5 * other\ species + \varepsilon \quad (9)$$

$$layer\ productivity = \beta_0 + \beta_1 * biosecurity + \beta_2 * vaccination + \beta_3 * biosecurity * vaccination + \beta_4 * farm\ size + \beta_5 * other\ species + \varepsilon \quad (10)$$

$$disease\ incidence = \beta_0 + \beta_1 * biosecurity + \beta_2 * vaccination + \beta_3 * biosecurity * vaccination + \beta_4 * farm\ size + \beta_5 * other\ species + \beta_5 * portion\ broilers + \varepsilon \quad (11)$$

Interacting AMR attitudes with AMU to see if better awareness of AMR increased the effectiveness of antibiotics as a disease management tool (following the hypothesis that AMU will be negatively associated with disease incidence), i.e.,

$$broiler\ productivity = \beta_0 + \beta_1 * AMR\ attitudes + \beta_2 * AMU\ quantity + \beta_3 * AMR\ attitudes * AMU\ quantity + \beta_4 * farm\ size + \beta_5 * other\ species + \varepsilon \quad (12)$$

$$layer\ productivity = \beta_0 + \beta_1 * AMR\ attitudes + \beta_2 * AMU\ quantity + \beta_3 * AMR\ attitudes * AMU\ quantity + \beta_4 * farm\ size + \beta_5 * other\ species + \varepsilon \quad (13)$$

$$disease\ incidence = \beta_0 + \beta_1 * AMR\ attitudes + \beta_2 * AMU\ quantity + \beta_3 * AMR\ attitudes * AMU\ quantity + \beta_4 * farm\ size + \beta_5 * other\ species + \beta_5 * portion\ broilers + \varepsilon \quad (14)$$

5. Conclusions

We did not find consistent evidence that biosecurity, vaccination, and attitudes towards AMR reduce the overall quantity of AMU or the use of antimicrobials in healthy birds, although better biosecurity and "AMR-aware" attitudes were associated with less use in healthy birds in some specifications. However, we did find evidence that biosecurity, and potentially vaccination, could mitigate the risks of antibiotic withdrawal in broiler farms by improving productivity.

These findings should be explored further using annual follow-up, larger sample sizes, and farm-level trials which combine antibiotic withdrawal and replacement with interventions in these three areas. Finally, these findings alone may not be sufficient to catalyse change in agricultural stewardship of antimicrobials. AMR in agriculture must always be seen as a structural rather than an individual issue, with stakeholders from across the One Health spectrum meaningfully consulted as part of research and policymaking.

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Institutional Review Board Statement: This study was approved by the Ethics Committee of the London School of Hygiene and Tropical Medicine (protocol code 28216/RR/29425, date of approval 5 September 2022). The original data collection project received ethical and scientific approval from the Ministry of Health and Social Care of The Republic of Senegal (protocol reference SEN22/73, date of approval 31 August 2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data used in this study, as well as the code used for data cleaning and analysis, are available in anonymised form on GitHub at https://github.com/Trescovia/AMUSE-

SEFASI-Sharing (accessed on 23 February 2023). The repository is password-protected, and will be made available upon request to those who email the corresponding author and provide a reason for their desire to access it.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A. Full Set of Survey Questions Used

The questionnaire used (translated into English) can be found in PDF form at https://drive.google.com/file/d/1idDpjdFhoyDgox659YFv2PVhFAHRnRfg/view (accessed on 23 February 2023).

Appendix B. Univariate Specifications

(Standard errors in parentheses)

	Dependent Variable					
	"AMU quantity"			"AMU in healthy birds"		
	OLS			*logistic*		
	(1)	(2)	(3)	(4)	(5)	(6)
vaccination	4.787			−0.099		
	(6.036)			(0.265)		
biosecurity		−14.279			−2.904 **	
		(32.062)			(1.323)	
"AMR attitudes"			−10.015			−0.921 *
			(12.978)			(0.501)
Constant	22.955 **	40.783 *	36.558 ***	0.420	2.125 **	0.681 **
	(11.448)	(20.914)	(7.314)	(0.507)	(0.873)	(0.279)
Observations	134	134	134	220	220	220
R^2	0.005	0.002	0.004			
Adjusted R^2	−0.003	−0.006	−0.003			
Log Likelihood				−150.882	−148.460	−149.247
Akaike Inf. Crit.				305.764	300.920	302.494
Residual Std. Error (df = 132)	40.471	40.537	40.476			
F Statistic (df = 1; 132)	0.629	0.198	0.595			
Note: * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$.						

	Dependent Variable					
	"broiler productivity"			"layer productivity"		
	(1)	(2)	(3)	(4)	(5)	(6)
vaccination	3.968 *			0.007		
	(2.063)			(0.285)		
biosecurity		29.245 ***			−0.002	
		(11.110)			(1.204)	
"AMR attitudes"			4.461			−0.088
			(4.614)			(0.301)
Constant	12.400 ***	1.431	17.436 ***	0.869	0.883	0.925 ***
	(3.893)	(6.974)	(2.476)	(0.560)	(0.798)	(0.172)
Observations	121	121	121	50	50	50
R^2	0.030	0.055	0.008	0.00001	0.00000	0.002
Adjusted R^2	0.022	0.047	−0.001	−0.021	−0.021	−0.019
Residual Std. Error	13.342 (df = 119)	13.170 (df = 119)	13.495 (df = 119)	0.625 (df = 48)	0.625 (df = 48)	0.625 (df = 48)
F Statistic	3.700 * (df = 1; 119)	6.929 *** (df = 1; 119)	0.935 (df = 1; 119)	0.001 (df = 1; 48)	0.00000 (df = 1; 48)	0.086 (df = 1; 48)
Note: * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$.						

	Dependent Variable		
		"disease incidence"	
	(1)	(2)	(3)
vaccination	0.477 *		
	(0.265)		
biosecurity		−0.053	
		(1.306)	
"AMR attitudes"			−0.473
			(0.506)
Constant	1.218 **	2.130 **	2.322 ***
	(0.506)	(0.857)	(0.279)
Observations	220	220	220
R^2	0.015	0.00001	0.004
Adjusted R^2	0.010	−0.005	−0.001
Residual Std. Error (df = 218)	2.040	2.055	2.051
F Statistic (df = 1; 218)	3.247 *	0.002	0.874
Note: * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$.			

Appendix C. Specifications with interactions between Our Main Covariates

(Standard errors in parentheses)

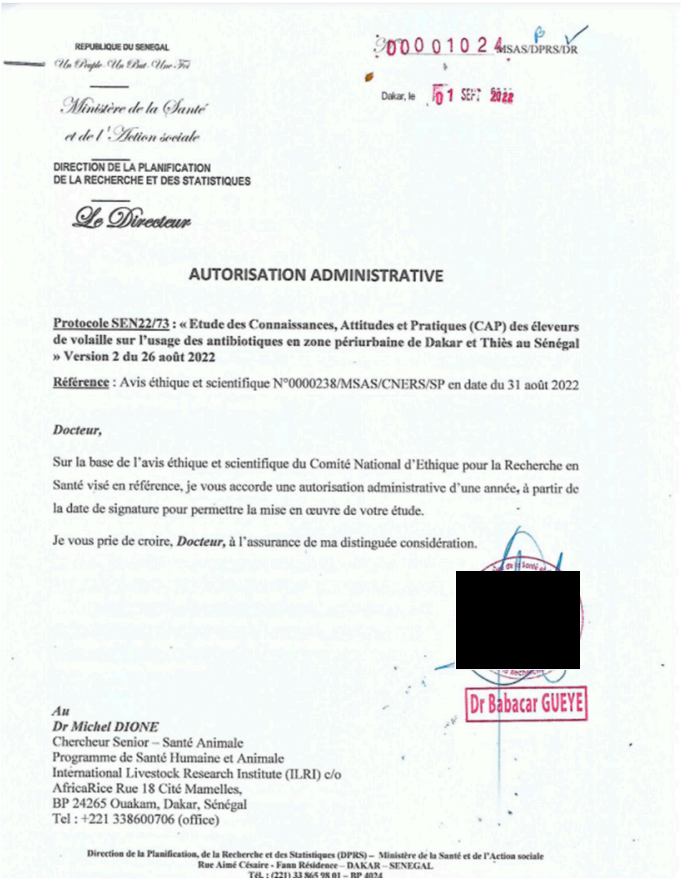
	Dependent Variable		
	broiler_productivity	layer_productivity	disease_incidence
	(1)	(2)	(3)
biosecurity	23.886	−0.503	−3.642
	(29.515)	(0.694)	(2.925)
AMU_quantity	0.103	−0.003	−0.071
	(0.581)	(0.008)	(0.051)
vaccination	0.851	−0.088	0.499
	(2.594)	(0.068)	(0.342)
AMR_attitudes	2.316	−0.087	−1.104
	(6.517)	(0.099)	(0.751)
farm_size	0.004 ***	0.00000	0.00001
	(0.001)	(0.00001)	(0.0001)
other_species_on_farm	2.383	0.109	−0.226
	(4.228)	(0.074)	(0.541)
portion_broilers			−0.589
			(0.423)
biosecurity:AMU_quantity	0.028	0.004	0.132
	(0.942)	(0.012)	(0.081)
Constant	−4.812	1.273 **	4.109 **
	(17.415)	(0.502)	(1.877)
Observations	84	26	134
R^2	0.251	0.272	0.117
Adjusted R^2	0.182	−0.011	0.060
Residual Std. Error	13.580 (df = 76)	0.114 (df = 18)	2.165 (df = 125)
F Statistic	3.631 *** (df = 7; 76)	0.961 (df = 7; 18)	2.063 ** (df = 8; 125)
Note: ** $p < 0.05$; *** $p < 0.01$.			

	Dependent Variable		
	broiler_productivity	layer_productivity	disease_incidence
	(1)	(2)	(3)
biosecurity	11.585	1.719	−7.787
	(48.671)	(16.414)	(5.130)
vaccination	−1.174	0.129	−1.433
	(13.490)	(6.424)	(1.513)
AMR_attitudes	0.773	−0.077	−0.497
	(4.798)	(0.247)	(0.521)
farm_size	0.001	−0.00001	0.00000
	(0.001)	(0.00001)	(0.00004)
other_species_on_farm	2.310	−0.075	0.383
	(3.445)	(0.215)	(0.406)
portion_broilers			−0.771 **
			(0.301)
biosecurity:vaccination	6.352	−0.148	3.406
	(24.938)	(8.130)	(2.614)
Constant	5.433	−0.273	6.284 **
	(25.821)	(12.924)	(2.930)
Observations	120	49	220
R^2	0.086	0.046	0.062
Adjusted R^2	0.037	−0.091	0.031
Residual Std. Error	13.248 (df = 113)	0.473 (df = 42)	2.018 (df = 212)
F Statistic	1.770 (df = 6; 113)	0.335 (df = 6; 42)	2.012 * (df = 7; 212)
Note: * $p < 0.1$; ** $p < 0.05$.			

	Dependent Variable		
	broiler_productivity (1)	layer_productivity (2)	disease_incidence (3)
AMR_attitudes	−1.069	−0.180	0.060
	(11.518)	(0.127)	(1.059)
AMU_quantity	−0.071	−0.001	0.025 *
	(0.233)	(0.001)	(0.014)
farm_size	0.005 ***	0.00000	−0.00002
	(0.001)	(0.00000)	(0.0001)
other_species_on_farm	3.451	0.096	−0.163
	(4.180)	(0.070)	(0.542)
portion_broilers			−0.520
			(0.425)
AMR_attitudes:AMU_quantity	0.362	0.002	−0.030
	(0.423)	(0.002)	(0.028)
Constant	12.802 *	0.832 ***	2.154 ***
	(6.853)	(0.077)	(0.711)
Observations	84	26	134
R^2	0.227	0.222	0.090
Adjusted R^2	0.178	0.027	0.047
Residual Std. Error	13.613 (df = 78)	0.112 (df = 20)	2.180 (df = 127)
F Statistic	4.586 *** (df = 5; 78)	1.138 (df = 5; 20)	2.092 * (df = 6; 127)

Note: * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$.

Appendix D. Ethical and Scientific Approval for Original Data Collection



REPUBLIQUE DU SENEGAL
Un Peuple Un But Une Foi

Ministère de la Santé
et de l'Action sociale

DIRECTION DE LA PLANIFICATION
DE LA RECHERCHE ET DES STATISTIQUES

Le Directeur

0000102 4 MSAS/DPRS/DR

Dakar, le 01 SEPT 2022

AUTORISATION ADMINISTRATIVE

Protocole SEN22/73 : « Etude des Connaissances, Attitudes et Pratiques (CAP) des éleveurs de volaille sur l'usage des antibiotiques en zone périurbaine de Dakar et Thiès au Sénégal » Version 2 du 26 août 2022

Référence : Avis éthique et scientifique N°0000238/MSAS/CNERS/SP en date du 31 août 2022

Docteur,

Sur la base de l'avis éthique et scientifique du Comité National d'Ethique pour la Recherche en Santé visé en référence, je vous accorde une autorisation administrative d'une année, à partir de la date de signature pour permettre la mise en œuvre de votre étude.

Je vous prie de croire, ***Docteur,*** à l'assurance de ma distinguée considération.

[redacted]

Dr Babacar GUEYE

Au
Dr Michel DIONE
Chercheur Senior – Santé Animale
Programme de Santé Humaine et Animale
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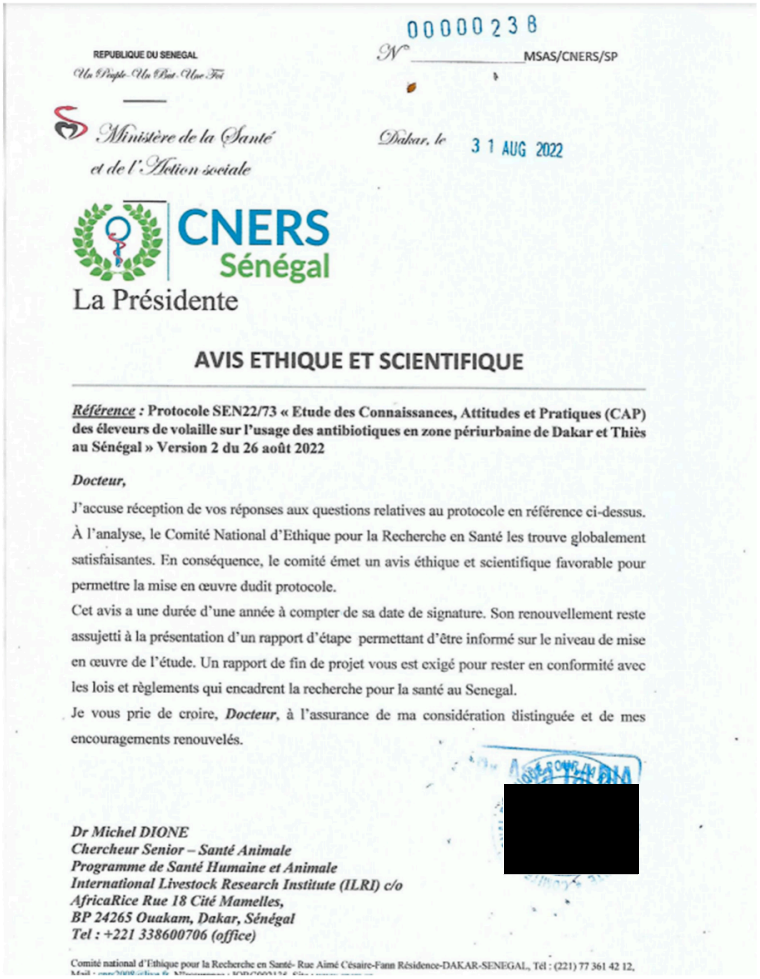

REPUBLIQUE DU SENEGAL
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Ministère de la Santé et de l'Action sociale

00000238
N° _____ MSAS/CNERS/SP

Dakar, le 31 AUG 2022

CNERS Sénégal

La Présidente

AVIS ETHIQUE ET SCIENTIFIQUE

***Référence* : Protocole SEN22/73 « Etude des Connaissances, Attitudes et Pratiques (CAP) des éleveurs de volaille sur l'usage des antibiotiques en zone périurbaine de Dakar et Thiès au Sénégal » Version 2 du 26 août 2022**

Docteur,

J'accuse réception de vos réponses aux questions relatives au protocole en référence ci-dessus. À l'analyse, le Comité National d'Ethique pour la Recherche en Santé les trouve globalement satisfaisantes. En conséquence, le comité émet un avis éthique et scientifique favorable pour permettre la mise en œuvre dudit protocole.

Cet avis a une durée d'une année à compter de sa date de signature. Son renouvellement reste assujetti à la présentation d'un rapport d'étape permettant d'être informé sur le niveau de mise en œuvre de l'étude. Un rapport de fin de projet vous est exigé pour rester en conformité avec les lois et règlements qui encadrent la recherche pour la santé au Senegal.

Je vous prie de croire, ***Docteur***, à l'assurance de ma considération distinguée et de mes encouragements renouvelés.

[redacted]

Dr Michel DIONE
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Appendix E. Copy of the Informed Consent Form (Translated into English)

Informed Consent Form for **AMUSE** survey

1. I (the interviewee) have listened to or read about the study, which I fully understand, and I have been given the opportunity to ask questions, which have been answered to my satisfaction.
2. I understand that participation in this project/interview is entirely voluntary, and I have the right to withdraw at any time.
3. I understand that the activity will not interfere with my usual daily routine work and has no harm to by children.
4. I have been informed that I have the right to not answer specific questions.
5. I understand that any data collected from me and my children will be held as hard copies and/or electric copies. Any personal information will be held securely on protected computers by the investigators
6. I understand that my identity and those of my children will not be disclosed in project reports or any further documents.
7. I have the right to see a final copy of the report from this project.
8. One copy of this form shall be held by me (the interviewee). An additional copy shall be held securely by the lead investigator.
9. I give permission to the researcher to take photographs of me during the research activity and publish them without my name for research purposes only. YES/NO

I have read, understood and agree the terms of consent described above.

Name of the interviewee: _____

Signed: _____ Date: _____

Name of enumerator: _____

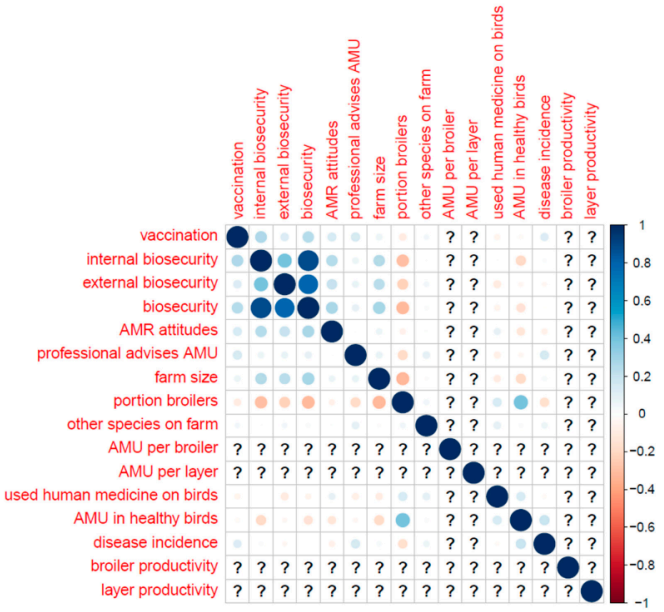
Signed: _____ Date: _____

Contact

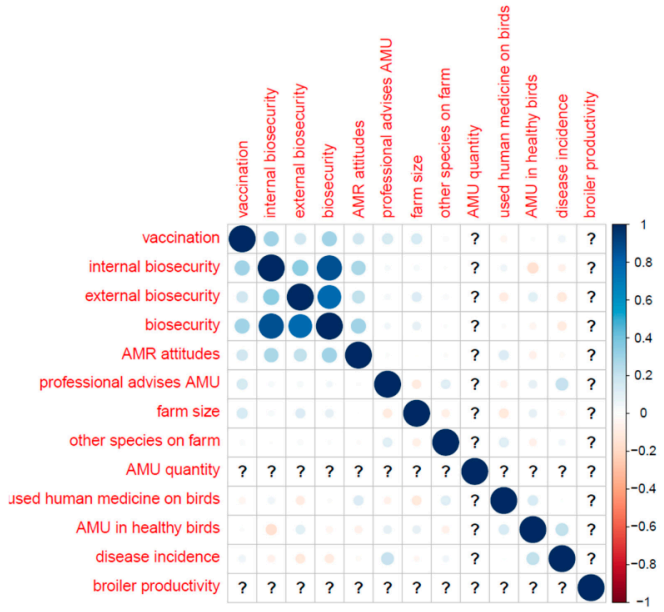
Michel Dione
Tel: 775339670
m.dione@cgiar.org
c/o AfricaRice, Rue 18 Cité Mamelles, BP 24265 Ouakam, Dakar, Senegal

Appendix F. Correlations between Key Variables (Pearson's Correlation Coefficient)

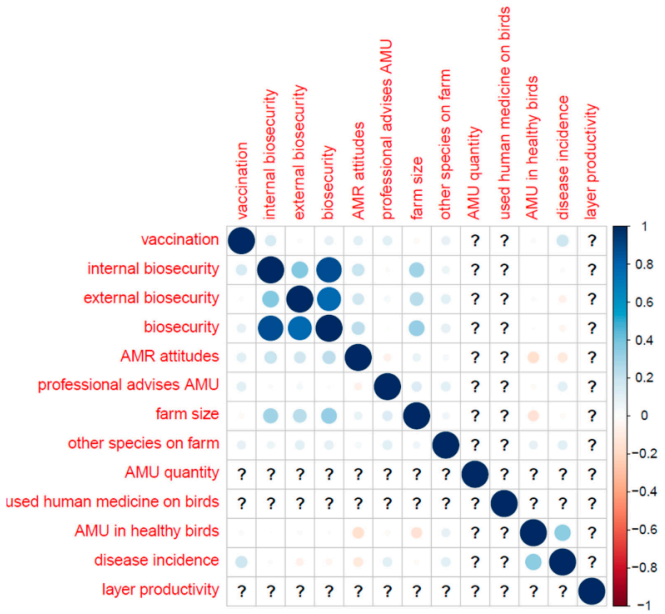
Appendix F.1. The Whole Sample



Appendix F.2. Broilers only



Appendix F.3. Layers only



Appendix G. Effect of Professional Advice on AMU Patterns

	Dependent Variable			
	"AMU quantity" *OLS*		"AMU in healthy birds" *logistic*	
	(1)	(2)	(3)	(4)
"professional advises AMU"	6.673	4.634	0.277	0.244
	(10.034)	(10.404)	(0.414)	(0.422)
vaccination		4.933		0.112
		(6.423)		(0.303)
biosecurity		−11.088		0.176
		(36.905)		(1.604)
"AMR attitudes"		−8.507		−0.884
		(13.855)		(0.566)
"farm size"	−0.003 **	−0.003 **	−0.00005	−0.00005
	(0.001)	(0.001)	(0.0001)	(0.0001)
"other species on farm"	−4.559	−4.745	−0.018	−0.021
	(9.994)	(10.112)	(0.446)	(0.450)
"portion broilers"	−17.031 **	−17.423 **	1.642 ***	1.656 ***
	(7.620)	(7.793)	(0.321)	(0.334)
Constant	42.455 ***	46.570 *	−0.763	−0.643
	(11.506)	(24.733)	(0.465)	(1.138)
Observations	134	134	220	220
R^2	0.071	0.078		
Adjusted R^2	0.042	0.026		
Log Likelihood			−132.447	−131.163
Akaike Inf. Crit.			274.895	278.326
Residual Std. Error	39.560 (df = 129)	39.877 (df = 126)		
F Statistic	2.453 ** (df = 4; 129)	1.516 (df = 7; 126)		

Note: * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	2204500	**Title**	Miss
First Name(s)	Eve		
Surname/Family Name	Emes		
Thesis Title	Revisiting key assumptions about animal antibiotic use and human health from a One Health perspective		
Primary Supervisor	Gwen Knight		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	One Health		
When was the work published?	August 2023		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	I am enrolled in the PhD by Prior Publication programme, so the papers that form part of this portfolio were already published at the time of registration		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	The dataset used in this analysis was collected by colleagues at ILRI using the AMUSE survey tool. I created the design for this study, and cleaned and prepared the dataset to be used here. I analysed the data in R, and wrote the paper with supervisory input from coauthors.

SECTION E

Student Signature	Eve Tresco Emes
Date	22 October 2024

Supervisor Signature	Gwen Knight
Date	22 October 2024

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How farm practices and antibiotic use drive disease incidence in smallholder livestock farms: Evidence from a survey in Uganda

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Biosecurity
Agriculture
Livestock

ABSTRACT

Background: Antimicrobial resistance (AMR) is a growing threat to human and animal health, and the growth in AMR prevalence globally is thought to be partially driven by non-therapeutic antibiotic use in livestock production. However, livestock farms may depend on antibiotics as a prophylactic disease management tool, and reducing antibiotic use in isolation may harm farmers' economic security. In order to help farmers safely reduce their antibiotic use, we must first determine how necessary non-therapeutic antibiotic use is for disease management, and how other farm practices can guard against disease and make antibiotic use reduction safe and feasible.

Methods: Using the *Antimicrobial Use in Livestock Production Settings* (AMUSE) tool, a standardised survey tool for investigating attitudes and practices relating to antibiotic use on farms, we investigated the farming practices and animal disease outcomes of smallholder livestock farms in Uganda. We used logistic regression to investigate the effect of prophylactic antibiotic use; as well as of prophylactic vaccination, non-antimicrobial medicines, and on-farm biosecurity measures; on the likelihood of disease outbreaks.

Findings: We found that prophylactic antibiotic use did indeed seem to guard against disease outbreaks, underlining the rationality of non-therapeutic antibiotic use in smallholder livestock farms and the need to pair antibiotic use reduction with other interventions in order to mitigate risk. The most effective intervention pairing varied by species, with expanded access to animal health services and the use of prophylactic vaccination demonstrating the greatest potential overall.

Implications: These findings echo earlier results generated using the AMUSE survey tool. They should be followed by participatory research in which farmers are consulted to explore intervention options, and subsequently by farm-level intervention trials of combined antimicrobial stewardship interventions to verify their effectiveness.

1. Introduction

Antimicrobial resistance (AMR), the capacity of microbial pathogens to survive in the presence of antimicrobials, is an increasingly prominent threat to human and animal health and the focus of much global health policy discourse [1,2]. In particular, the growing resistance of bacterial pathogens to antibiotics threatens a future in which a large portion of bacterial infections become difficult or impossible to treat, and in which procedures such as invasive surgery or chemotherapy for cancer become much riskier and less viable. While AMR exists in nature, the present growth of AMR is driven mainly by the use of antimicrobials [3].

Use of antibiotics in livestock animal production can be for the purposes of treatment, prophylaxis, metaphylaxis or growth promotion; and is one of the most prevalent forms of antimicrobial use (AMU) globally. For this reason, antimicrobial stewardship (AMS) initiatives often aim to reduce the quantity of antibiotics used in livestock production, placing particular emphasis on forms of AMU deemed 'irrational' (e.g. growth-promotion and prophylaxis) and on classes of antibiotics of critical importance to human health [4–6].

However, even non-therapeutic use of antibiotics can improve

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livestock productivity and avert animal disease, and has therefore been important to farmers' livelihoods and to general food security [7]. Where water, sanitation and hygiene (WASH) and biosecurity infrastructure is unaffordable or unavailable, antibiotics may be used to compensate. This question is particularly relevant also to low- and middle-income countries (LMICs), which bear a disproportionate burden of AMR and where lower levels of food security make agricultural productivity particularly important [1]. In addition, simply placing legal restrictions on the use of antibiotics in livestock production may not be politically acceptable, compliance may be difficult to monitor and enforce, and doing so may cause farmers to switch to illegal or counterfeit antibiotics which may worsen the situation.

For these reasons, it is necessary to design interventions which allow farmers to reduce their antibiotic use safely and without concern for increased incidence of animal disease. It is also important to determine how important non-therapeutic antibiotic use is as a disease management tool. We therefore aimed to investigate the determinants of animal disease outbreaks in smallholder livestock farms targeting pigs, small ruminants (sheep and goats) cattle and poultry, using on-farm survey data from Uganda.

We frame AMR here as a One Health issue, in which human health outcomes form part of a network involving food production systems and animal health. Rather than viewing animal antibiotic use as an issue of veterinary medicine alone, we want to see how it interacts with other agricultural practices and animal health infrastructure, allowing us to make recommendations from a cross-sectoral policy lens.

This study forms part of a body of literature using the *Antimicrobial Use in Livestock Production Settings* (AMUSE) survey tool, and aims to add to a body of literature collected using the tool in different contexts. It is closely linked to those previous studies, allowing comparison across settings. To our knowledge, it is first the study to investigate how antibiotic use and other farm practices influence animal disease outcomes in Uganda's smallholder livestock farms.

2. Methods

2.1. Survey tool

We gathered data using the (AMUSE) survey tool [8], which is designed to collect information about on-farm practices and attitudes relating to antimicrobial stewardship (AMS). This tool has been applied to other settings in a range of countries (Uganda [9], Ethiopia [10], Burkina Faso [11] and Senegal [12]), generating useful insights into the drivers of knowledge, attitudes and practices relating to AMR.

2.2. Setting

The study was conducted in Mukono and Lira districts in Uganda. Mukono district is in central Uganda, 40 km from the capital of Kampala, with a population of 596,804 people; among these, 59% are involved in agriculture [13]. Because of the proximity to Kampala, livestock farmers are assumed to have good access to veterinary drugs and other animal health inputs. Lira District is in Northern Uganda, about 300 km from Kampala with an estimated human population of 377,800 in 2010. The economy of the district is mainly based on agriculture, with 81% of the population engaged in subsistence farming, with cattle being the main source of wealth and bulls and oxen being a major source of traction [14]. Piggery has increasingly become an important enterprise with 40% of sub-counties having piggery as a priority enterprise [15]. Due to the scope of the survey, questions on disease occurrence focused on symptoms rather than pathogen species. Animal disease incidence was higher in rural Lira than in peri-urban Mukono, with respiratory complaints being common in the former and digestive issues being common in both settings.

2.3. Data collection process

Data collection was led by a research technician and veterinarian, heading a team of eight enumerators who each visited one village and interviewed farmers there. Enumerators were trained on data collection to ensure accurate interpretation of responses, and data were collected on tablets using Open Data Kit (ODK) software between 13 August and 10 September 2018.

Further details on the data collection process can be found in Nohrborg et al. [9], the first study to use this dataset.

2.4. Ethical approval

The study was approved by the Uganda National Council for Science and Technology under reference A 583 of 18 June 2018. Informed consent was obtained from all respondents that participated in the study. The full survey tool used, and a copy of the ethical approval given, can be found in the appendix.

2.5. Statistical methods

We first present summary statistics of our main variables of interest (Table 1). These are: the use of on-farm biosecurity measures, whether or not a flock or herd experienced a disease outbreak in the two weeks prior to the visit, average annual per-animal expenditure on antibiotics, vaccination and other medicines, access to animal health services, prophylactic antimicrobial use, prophylactic vaccination, and farm size. Here, 'other medicines' refers to vitamins, dewormers and acaricides. Biosecurity measures include fencing, not allowing herds and flocks to mix with each other, avoiding grazing in the morning, maintaining animal hygiene, regular animal health checkups, restricting visitors,

Table 1
Summary Statistics.

	Cattle	Pigs	Small ruminants	Poultry
Number of farms with this species (out of 482 farms in the survey)	216	465	247	326
Portion of farms using biosecurity measures for the species in question	49/216 (22.7%)	168/465 (36.1%)	45/247 (18.2%)	38/326 (11.7%)
Portion of flocks or herds experiencing disease in the last 2 weeks	47/216 (21.8%)	92/465 (19.8%)	52/247 (21.1%)	44/326 (13.5%)
Average annual expenditure on AB per animal in UGX (USD values in brackets[a])	10,730 ($3.10)	3387 ($0.98)	3369 ($0.97)	162 ($0.05)
Average annual expenditure on vaccines per animal in UGX (USD values in brackets)	2589 ($0.75)	1235 ($0.36)	498 ($0.14)	282 ($0.08)
Average annual expenditure on other medicines per animal in UGX (USD values in brackets)	20,228 ($5.85)	11,174 ($3.23)	5713 ($1.65)	216 ($0.06)
Average flock or herd size (range)	3.31 (1–14)	4.92 (1–55)	4.65 (1–39)	25.75 (1–700)
Portion of farms with access to animal health services	371/482 (77.0%)			
Portion of farms using AMU prophylactically	164/482 (34.0%)			
Portion of farms using vaccination prophylactically[b]	427/482 (88.6%)			

[a] The data were collected in 2018. To obtain present-day USD values, the UGX values are converted to USD using the 2018 exchange rate, then inflated to present day using the US GDP deflator

[b] While the majority of vaccination use was prophylactic, we make this distinction because some farmers reported using vaccines to cure existing diseases and for growth promotion

buying only healthy animals, spraying animals, and confinement of sick animals.

Our main outcome of interest was the probability of disease occurring in the herd / flock. This was a binary variable for whether or not a farmer reported animals in a herd / flock having displayed symptoms of disease in the last two weeks. Disease outcomes were self-reported, and covered respiratory, digestive, dermal and reproductive complaints, as well as parasites, neurological concerns, and mastitis. We investigated which variables were correlated with likelihood of disease for each livestock species using Pearson's correlation coefficient (Table 2).

We then investigated the effect of several farming practices on likelihood of disease using logistic regression (logit), as shown in Table 3. These practices were: prophylactic antimicrobial use, prophylactic vaccination, use of on-farm biosecurity measures, and access to animal health services. All farm practice variables were binary (i.e. whether or not the practice was implemented), as was the variable for accessing animal health services (See Table 3).

Results were first disaggregated by species, and then aggregated across all farm types. When looking at all animal species together, flocks and herds of different species located on the same farm were treated as a separate unit of analysis. All of our regression specifications also controlled for the number of animals in the flock or herd.

Following this, we regressed the likelihood of disease incidence against expenditure on antibiotics, vaccination and other medicines per animal during the past year (in Ugandan Shillings (UGX), omitting extreme outliers (5 SD above the mean[1]). We acknowledge that there may be endogeneity between the outcome and covariates, as farmers may use these medicines in response to disease outbreaks, obscuring any preventative effect that they may have. However, this endogeneity can be minimised by the fact that our covariates concerned average expenditure over the past year, whereas our outcome looked only at disease in the two weeks prior to the survey.

While data were collected from two regions of the country, we did not stratify regressions by region due to small sample size and statistical power concerns, a limitation of this study.

3. Results

Each of the four animal species in the sample was present in at least 45% of farms, with most farms having animals of multiple species (Table 1). Most farms had access to animal health services and used prophylactic vaccination, whereas most farms did not use antimicrobials prophylactically and did not implement on-farm biosecurity measures. Average flock and herd size was small, and expenditure on medicines varied greatly between species and medicine type. Farmers generally spent the most per animal on other medicines (acaricides, vitamins and dewormers), followed by antibiotics and then by vaccines.

Using Pearson's correlation coefficient, having a larger flock or herd size was unsurprisingly positively associated with a higher likelihood of disease across all animal species and for the sample as a whole. Expenditure on vaccination was associated with a lower likelihood of disease for the sample as a whole. However, expenditure on vaccination was not associated with likelihood of disease for any individual species, likely due to a smaller sample size when looking at individual species. Prophylactic use of antimicrobials and access to animal health services were both associated with a lower likelihood of disease in pigs and for the sample as a whole, and prophylactic vaccination was associated with a lower likelihood of disease in chickens. None of the practices presented in Table 2 were significantly associated with disease incidence for either small ruminants or cattle.

Having more animals on the farm was associated with a higher likelihood of experiencing disease across all animals considered, with an additional animal increasing the odds of disease by 0.4% (chickens) to 18.9% (ruminants). For cattle and ruminants, none of the farm practices investigated were significantly associated with odds of disease. For pigs, prophylactic use of antimicrobials reduced the odds of disease by 39.3% and access to animal health services reduced the odds of disease by 69%. For chickens, prophylactic use of vaccination reduced the odds of disease by 59.6%. Across all species, prophylactic use of antimicrobials reduced the odds of disease by 33.3%, access to animal health services reduced the odds of disease by 40.7%, and the presence of an additional animal increased the odds of disease by 0.3%.

For cattle, pigs and chickens, expenditure on any kind of medicines (vaccinations, antibiotics and other medicines) was not significantly related to the odds of disease (see Table 4). For ruminants, spending an additional 1000 UGX ($0.29 USD) on non-vaccine and non-antimicrobial medicines per animal per year (including vitamins, acaricides, and dewormer) was associated with a 2.6% *higher* odds of disease. Across all animal species, spending an additional 1000 UGX per animal per year on vaccination was associated with 12.2% lower odds of disease and the same additional spending on other medicines was associated with a 0.8% higher odds of disease. As in the previous specifications, an additional animal was associated with higher odds of disease between 0.4% (chickens) and 21.4% (ruminants).

4. Discussion

4.1. Findings

Prophylactic AMU, despite often being considered 'irrational', does seem to convey a benefit to smallholder farms, in accordance with studies from other settings using this survey tool [12,16] and with the wider literature [7]. This reaffirms that antibiotic withdrawal must be coupled with other interventions to help mitigate the potential negative effect on animal health; especially in pigs, where prophylactic AMU appeared to be the most effective at preventing disease. This 'intervention pairing' approach has already been successful in medium-sized farms in other contexts [17,18].

Different farm practices were effective in different species, demonstrating the need for a tailored approach when designing interventions to complement AMU reduction. Specifically, animal health services were of the most benefit to pig farms, and prophylactic vaccination was of the greatest benefit to chickens. Surprisingly, on-farm biosecurity did not seem to influence the likelihood of disease; and expenditure on acaricides, vitamins and dewormers seemed positively correlated with the likelihood of disease. However, the level of statistical significance of the latter finding was low, and that result may be due to the modality of these drugs' use (e.g. if acaricides and dewormers are more likely to be used in response to disease rather than prophylactically, which would create endogeneity). There are a number of possible explanations for biosecurity not being associated with the likelihood of disease. In particular, the biosecurity variable that we used covered a broad range of practices, and did not distinguish between farms based on either the number of measures used or by the comprehensiveness of those measures. While expenditure on vaccination was associated with a lower disease incidence overall, we did not see this result when looking at each species individually, likely due to the smaller sample size.

The logistic regressions used here are especially useful because they can provide us with a set of odds ratios with a cardinal real-world interpretation. Looking at our results, we can see that some of the measures considered had a very large impact on the likelihood of disease.

[1] Although a standard approach is often to remove results 3 standard deviations from the mean, upon inspecting the data we realised that this would mean removing a relatively large number of observations from a small dataset. Because there were many observations only marginally closer to the mean than this, it would also involve removing some data points but keeping nearby data points. Thus, the decision to use a five standard deviation cutoff reflects the underlying variation in expenditure across farms, and only removing results which were truly outliers.

Table 2
Correlates of Disease Likelihood by Species (Pearson's correlation coefficient).

Correlates of Disease Likelihood by Species					
	Cattle	Pigs	Small ruminants	Chickens	Whole sample
Prophylactic AMU	-0.07	-0.098*	-0.1	-0.013	-0.076**
Prophylactic vaccination	0.066	0.016	0.012	-0.111*	-0.005
Expenditure on antibiotics	-0.015	-0.055	0.061	0.035	0.005
Expenditure on vaccination	-0.064	-0.09	-0.052	-0.05	-0.061*
Expenditure on other medicines	0.046	-0.069	0.094	-0.002	0.023
Use of on-farm biosecurity practices	0.072	-0.038	0.011	0.059	0.020
Number of animals	0.189**	0.114*	0.266***	0.177**	0.072*
Access to animal health services	-0.107	-0.204***	0.01	0.013	-0.094***

Pearson's correlation coefficient
*Note: *p < 0.1, **p < 0.05, ***p < 0.01*

Table 3
Effect of Practices on Disease Likelihood (Odds Ratio).

	Dependent variable:				
	disease				
	Cattle	Pigs	Small Ruminants	Chickens	Whole Sample
	(1)	(2)	(3)	(4)	(5)
Prophylactic AMU	0.681	0.607	0.532	0.991	0.667
	$t = -0.965$	$t = -1.787$*	$t = -1.588$	$t = -0.025$	$t = -2.426$**
Prophylactic Vaccination	1.508	0.904	1.105	0.404	0.912
	$t = 0.622$	$t = -0.262$	$t = 0.197$	$t = -2.105$**	$t = -0.409$
Access to Animal Health Services	0.558	0.310	1.136	1.051	0.593
	$t = -1.516$	$t = -4.324$***	$t = 0.333$	$t = 0.123$	$t = -3.174$***
On-Farm Biosecurity Measures	1.823	0.911	1.229	0.867	1.223
	$t = 1.476$	$t = -0.338$	$t = 0.495$	$t = -0.259$	$t = 1.157$
Number of Animals in Flock / Herd	1.173	1.058	1.189	1.004	1.003
	$t = 2.511$**	$t = 3.171$***	$t = 3.498$***	$t = 2.226$**	$t = 1.922$*
Constant	0.157	0.549	0.105	0.293	0.382
	$t = -2.597$***	$t = -1.462$	$t = -3.559$***	$t = -2.420$**	$t = -3.917$***
Observations	216	465	247	326	1254
Log Likelihood	−107.278	−215.918	−117.455	−124.705	−594.432
Akaike Inf. Crit.	226.556	443.835	246.910	261.409	1200.865
Note:	*p < 0.1; **p < 0.05; ***p < 0.01				

t is the test statistic - a greater size represents a greater degree of statistical significance.

4.2. Limitations

While in this paper we investigated the effect of having some sort of on-farm biosecurity measure(s) in place, future research could consider in more detail the effects of different biosecurity strategies individually as well as combinations of different measures. In addition, the apparent lack of impact of biosecurity measures may be due to the extensiveness or quality of the measures in use on the farms in our sample - it is possible that interventions which use different or more extensive biosecurity measures may yet improve animal health outcomes. In addition, all farms in the sample used antibiotics, and it is possible that biosecurity measures would indeed be effective disease management tools in a context with less antibiotic use.

In terms of assessing the impact of vaccination expenditures, the recorded expenditure only covers vaccines bought by the farmers out of pocket, and not those which were provided by animal health services. Frequency of vaccination may be a more useful indicator to use in future studies, although information on this was not available in this dataset. In addition, the effect of access to animal health services on disease outcomes may thus be partially mediated by vaccination.

When interpreting the results of this paper, we must keep in mind that smallholder farmers exist as part of a complex economic network which includes vets, consumers, drug sellers, creditors, marketeers, landlords, suppliers and others [19]. Interventions targeting AMU in smallholder farms must thus involve the entire network and cannot target farmers in isolation [12,16]. While statistical analyses such as this

Table 4
Effect of Expenditures on Disease Likelihood (odds ratio for additional 1000 UGX / 0.29 USD per animal per year).

	Dependent variable:				
	disease				
	Cattle	Pigs	Small Ruminants	Chickens	Whole Sample
	(1)	(2)	(3)	(4)	(5)
Annual Expenditure on Antibiotics per Animal	1.005	0.996	1.021	1.292	1.006
	$t = 0.410$	$t = -0.235$	$t = 0.885$	$t = 0.705$	$t = 0.679$
Annual Expenditure on Vaccination per Animal	0.894	0.872	0.880	0.835	0.878
	$t = -1.502$	$t = -1.366$	$t = -1.020$	$t = -0.844$	$t = -2.519^{**}$
Annual Expenditure on Other Medicines per Animal	1.009	0.994	1.026	0.884	1.008
	$t = 1.584$	$t = -0.589$	$t = 1.921^{*}$	$t = -0.291$	$t = 1.892^{*}$
Number of Animals in Flock / Herd	1.194	1.036	1.214	1.004	1.004
	$t = 2.779^{***}$	$t = 2.147^{**}$	$t = 3.771^{***}$	$t = 2.580^{***}$	$t = 2.289^{**}$
Constant	0.132	0.231	0.086	0.140	0.219
	$t = -6.176^{***}$	$t = -8.836^{***}$	$t = -7.206^{***}$	$t = -9.992^{***}$	$t = -18.565^{***}$
Observations	213	461	244	322	1240
Log Likelihood	−105.450	−224.541	−114.855	−122.624	−590.060
Akaike Inf. Crit.	220.899	459.081	239.711	255.248	1190.119
Note:	$^{*}p < 0.1$; $^{**}p < 0.05$; $^{***}p < 0.01$				

t is the test statistic - a greater size represents a greater degree of statistical significance.

are useful, they must be coupled with in-depth discussions with farmers about their knowledge, attitudes and practices in order to gain an understanding of what interventions might help them to feel safe in reducing their AMU.

While data were collected from two regions of the country, we did not stratify regressions by region due to small sample size and statistical power concerns, a limitation of this study. While we focused on the influence of farm practices here, we acknowledge that the efficacy of these practices could be modulated by farmers' attitudes and knowledge. As many of our variables were binary, we could not investigate the severity of disease or the quality of veterinary care in detail. Finally, animal disease data captured only a snapshot, and a longer cohort study could have controlled for the disease history on each farm.

4.3. Future research and links to other research

Application of the AMUSE survey tool to semi-intensive poultry farms in Dakar and Thiès, Senegal, found that stronger biosecurity aided broiler productivity, as might vaccination (although neither directly influenced disease incidence). The findings of this paper reaffirm the previous finding that smallholder livestock farms have a good rationale for using antibiotics, underscoring the importance of holistic AMS interventions.

The next step should be context-specific in-depth qualitative research in collaboration with smallholder farmers to determine useful interventions to safeguard incomes and facilitate AMU reduction. Subsequently, interventions should be trialled which pair AMU reduction with other interventions in the areas investigated in this paper (especially relating to vaccination and access to animal health services).

4.4. Implications

Our findings challenge the conceptualisation of non-curative antibiotic use as irrational, and the idea that antibiotic stewardship efforts should focus on encouraging or requiring individual farmers to reduce or modulate their antibiotic use unilaterally. Smallholder livestock farmers exist as part of a complex network of stakeholders across the One Health spectrum [19], and we draw focus towards creating an environment in which farmers can safely improve stewardship on their own terms without risking incomes and food security. Intervention pairing can facilitate this, and we provide some insights into the best intervention pairings for this context. More broadly, involvement of farmers alongside creditors, suppliers, veterinarians, the public sector and other stakeholders can target stewardship through a whole-system framework [12,16].

5. Conclusions

We found that prophylactic AMU was often effective as a disease management tool for smallholder livestock farmers. While there are strong arguments against non-curative antibiotic use in livestock, our findings suggest that it is not always irrational. This highlights the need to combine AMU reduction with other interventions to mitigate any potential loss to animal health and farmers' incomes: prophylactic vaccination and expanded access to animal health services are suitable candidates for this.

These results should be followed by participatory research involving farmers to explore intervention options, followed by trials of combined AMS interventions. Smallholder farms exist as part of an interdependent economic network, and any intervention aiming to reduce AMU in these farms should work across the supply chain.

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Institutional review board statement

The study was approved by the Uganda National Council for Science and Technology under reference A 583 of 18 June 2018. Informed consent was obtained from all respondents that participated in the study. The full survey tool used, and a copy of the ethical approval given, can be found in the appendix.

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

CRediT authorship contribution statement

Eve Emes: Conceptualization, Methodology, Software, Validation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization, Funding acquisition. **Barbara Wieland:** Writing – review & editing. **Ulf Magnusson:** Writing – review & editing. **Michel Dione:** Conceptualization, Investigation, Data curation, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Appendices

Survey questions.
To access the full set of survey questions used, please follow this link.
Ethical approval for the original data collection.

Data availability

Data will be made available on request.

Acknowledgments

The authors express their gratitude towards the farmers who participated in this survey.

Uganda National Council for Science and Technology

(Established by Act of Parliament of the Republic of Uganda)

Our Ref: A 583 26th June 2018

Dr. Michel Mainack Dione
Principal Investigator
International Livestock Research Institute/Biodiversity International
Kampala

Dear Dr. Dione,

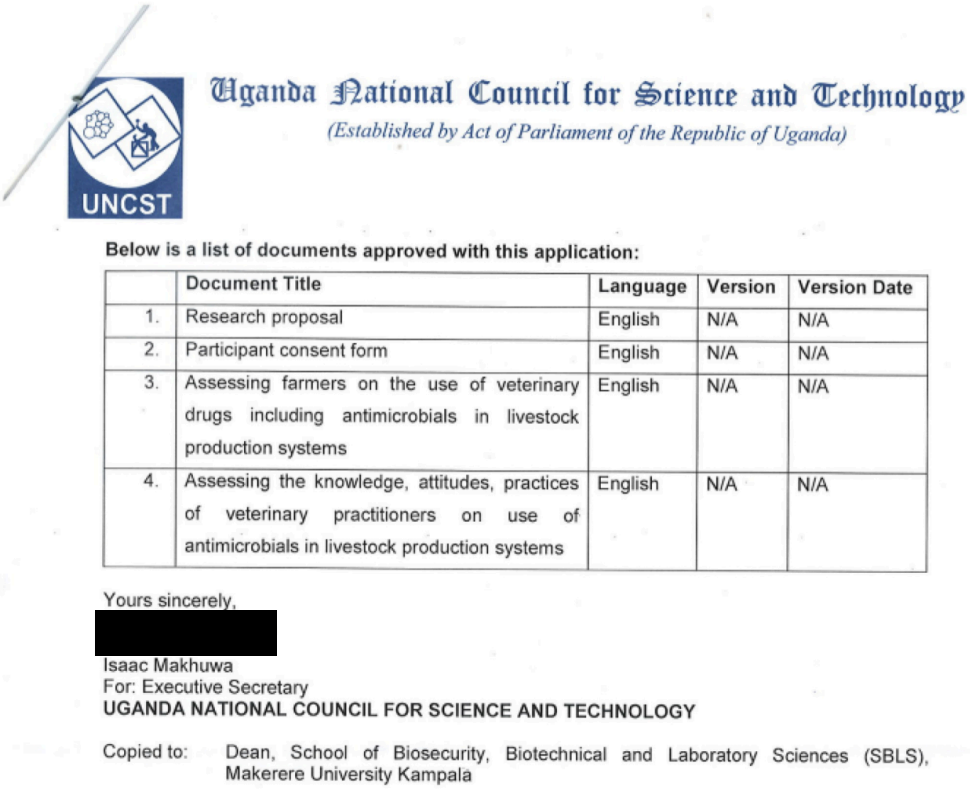
Re: Research Approval: Measuring the Quality and Impacts of Antimicrobial Agents in Pigs Systems in Uganda

I am pleased to inform you that on **18/06/2018**, the Uganda National Council for Science and Technology (UNCST) approved the above referenced research project. The Approval of the research project is for the period of **18/06/2018** to **18/06/2021**.

Your research registration number with the UNCST is **A 583**. Please, cite this number in all your future correspondences with UNCST in respect of the above research project.

As Principal Investigator of the research project, you are responsible for fulfilling the following requirements of approval:

1. All co-investigators must be kept informed of the status of the research.
2. Changes, amendments, and addenda to the research protocol or the consent form (where applicable) must be submitted to the designated Research Ethics Committee (REC) or Lead Agency for re-review and approval **prior** to the activation of the changes. UNCST must be notified of the approved changes within five working days.
3. For clinical trials, all serious adverse events must be reported promptly to the designated local IRC for review with copies to the National Drug Authority.
4. Unanticipated problems involving risks to research subjects/participants or other must be reported promptly to the UNCST. New information that becomes available which could change the risk/benefit ratio must be submitted promptly for UNCST review.
5. Only approved study procedures are to be implemented. The UNCST may conduct impromptu audits of all study records.
6. An annual progress report and approval letter of continuation from the REC must be submitted electronically to UNCST. Failure to do so may result in termination of the research project.



Uganda National Council for Science and Technology

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UNCST

Below is a list of documents approved with this application:

	Document Title	Language	Version	Version Date
1.	Research proposal	English	N/A	N/A
2.	Participant consent form	English	N/A	N/A
3.	Assessing farmers on the use of veterinary drugs including antimicrobials in livestock production systems	English	N/A	N/A
4.	Assessing the knowledge, attitudes, practices of veterinary practitioners on use of antimicrobials in livestock production systems	English	N/A	N/A

Yours sincerely,

[redacted]

Isaac Makhuwa
For: Executive Secretary
UGANDA NATIONAL COUNCIL FOR SCIENCE AND TECHNOLOGY

Copied to: Dean, School of Biosecurity, Biotechnical and Laboratory Sciences (SBLS), Makerere University Kampala

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Student ID Number	2204500	**Title**	Miss
First Name(s)	Eve		
Surname/Family Name	Emes		
Thesis Title	Revisiting key assumptions about animal antibiotic use and human health from a One Health perspective		
Primary Supervisor	Gwen Knight		

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SECTION B – Paper already published

Where was the work published?	Frontiers in Veterinary Science		
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	The dataset used in this analysis was collected by colleagues at ILRI using the AMUSE survey tool. I created the design for this study, and cleaned and prepared the dataset to be used here. I analysed the data in R, and wrote the paper with supervisory input from coauthors.

SECTION E

Student Signature	Eve Tresco Emes
Date	22 October 2024

Supervisor Signature	Gwen Knight
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Determinants of animal disease and nontherapeutic antibiotic use on smallholder livestock farms

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Introduction: Reducing nontherapeutic antibiotic use (ABU) in livestock animals has been identified as an important way of curbing the growth of antimicrobial resistance (AMR). However, nontherapeutic ABU may be important for managing animal disease. In order to reduce nontherapeutic ABU, farmers may need to implement other complementary interventions to safeguard animal health and minimize risk. We should therefore investigate if nontherapeutic ABU is associated with better animal health outcomes before advocating to reduce it. We should also investigate non-antibiotic factors which protect animal health and can make nontherapeutic use less necessary, as well as factors which can encourage farmers to improve their antibiotic stewardship.

Methods: The study investigated these questions using data from the AMUSE survey, which is designed to evaluate knowledge, attitudes and practices relating to AMR in smallholder livestock farms. The sample included 320 animal herds from 216 smallholder livestock farms in Burkina Faso, with livestock species including poultry, small ruminants, and cattle. The determinants of the occurrence of animal disease and nontherapeutic ABU were investigated using binary logistic regression.

Results: Results revealed that nontherapeutic ABU was positively associated with animal disease, although the potential reverse causality of this relationship should be investigated further. Going primarily to a public veterinarian for animal health services, and having a higher level of formal education, were negatively associated with the occurrence of disease. Going primarily to a community animal health worker was positively associated with using antibiotics nontherapeutically, whereas going primarily to a public veterinarian was negatively associated with this outcome. Having an animal health professional (of any kind) provide diagnosis and treatment was positively associated with nontherapeutic antibiotic use for goats and sheep.

Discussion: These findings support the expansion of education access and public veterinary services as a way to encourage better antibiotic stewardship while guarding against any animal health risks associated with doing so. They also highlight that animal health professionals other than public veterinarians may prioritize animal health outcomes over antibiotic stewardship goals.

KEYWORDS

antimicrobial resistance, livestock, antimicrobial stewardship, One Health, epidemiology, Burkina Faso

1 Introduction

Antimicrobial resistance (AMR), the ability of microbial pathogens to survive in the presence of antimicrobials, is an important and growing danger to human health, environmental health, and food security. The use of antimicrobials (AMU) by humans has resulted in growing rates of AMR (1). The use of antibiotics in livestock animals is one of the biggest forms of AMU, and has been the target of extensive national and international health policy initiatives (2, 3). In particular, international AMR policy targets a reduction in 'irrational' AMU in livestock animals, usually referring to nontherapeutic (metaphylactic, prophylactic and growth-promoting) use (4–6).

However, characterizing these uses as always irrational is neither fair nor constructive. While some work has suggested that reducing nontherapeutic antibiotic use in smallholder livestock farms may not worsen animal health or may improve it (7, 8), there is also good evidence of health and productivity benefit from sub-inhibitory doses of antibiotics in livestock animals (9), and previous work from this consortium has pointed to nontherapeutic antibiotic use averting animal disease in smallholder livestock farms (10). In addition to this, the potential growth-promoting effects of antibiotic use in livestock animals may be important for smallholder farmers' incomes, and for food security generally. This is especially important for countries such as Burkina Faso, which has both a high rate of population growth and a relatively low degree of food security (11, 12). In addition to this, smallholder livestock farmers exist as part of a network of interdependent economic actors which involves marketeers, suppliers, creditors, landlords, pharmaceutical sellers, animal health professionals, and others (13). Simply placing legal restrictions on the use of antibiotics in these farms may not be feasible, and could result in farmers circumventing restrictions by buying substandard or counterfeit antibiotics illegally, which may worsen AMR outcomes.

This gives rise to the problem of how to improve antibiotic stewardship on smallholder livestock farms without potentially endangering animal health or farm productivity, and in a way which farmers are willing to uptake. For this reason, it is important to determine three main things. Firstly, the extent to which nontherapeutic antibiotic use in smallholder livestock farms is important for averting animal disease, assessed here by measuring the association between nontherapeutic AMU and animal disease. Understanding this will help to know if reducing nontherapeutic antibiotic use carries a risk to food security and farmers' incomes, given that animal disease can negatively affect both of these outcomes.

Secondly, which non-antibiotic measures are associated with animal disease. This gives an insight into factors which could potentially guard against disease, and could therefore be paired with antibiotic use reduction to mitigate risks.

And thirdly, which factors are associated with nontherapeutic antibiotic use. This can give insight into factors which could potentially encourage or facilitate improvements in antibiotic stewardship.

In order to address these three points, the study analyzed data collected using the AMUSE survey (14) among smallholder livestock farmers in peri-urban areas of Ouagadougou. AMUSE is a standardized survey developed by the International Livestock Research Institute to assess knowledge, attitudes and practices (KAP) relating to antibiotic use and resistance in smallholder livestock farms (14). The survey has been used in Burkina Faso (15), Ethiopia (16), Senegal (17, 18), and Uganda (10, 19), and adds to a growing bank of knowledge which can inform agricultural AMR policies at the national and international level. The survey allows results to be compared across contexts, and these survey data have been used to write papers similar to this one focusing on Senegal (17) and Uganda (10).

The study uses binary logistic regression to investigate the determinants of animal disease and nontherapeutic antibiotic use in the smallholder livestock farms surveyed. It aims to use these results to provide insight into the role of nontherapeutic antibiotic use in protecting against disease in this context. It also aims to identify non-antibiotic factors which protect animal health and can reduce the need for nontherapeutic antibiotic use, as well as factors which can encourage farmers to improve their antibiotic stewardship.

2 Materials and methods

2.1 Study area

Ouagadougou is the most densely populated city in Burkina Faso, West Africa, with 2.4 million inhabitants. The farms surveyed were located in the peri-urban areas on the outskirts of the city.

2.2 Study population

A total of 216 farms were surveyed as part of the study. All of the farms were smallholder livestock farms located in the peri-urban areas of Ouagadougou (see Figure 1 for a map of the study area). The livestock species found on the farms included poultry, cattle, and small ruminants (sheep and goats). Some farms had multiple flocks / herds of different species, meaning that from the 216 farms there were 320 flocks / herds included in the sample, and each flock / herd was treated as a separate unit of analysis.

2.3 Study design

The study uses data collected using the AMUSE survey tool. It is a retrospective study using data collected by the International Livestock Research Institute (ILRI) as part of a previous study. Survey results were analyzed using both descriptive and inferential statistics (binary logistic regression).

2.4 Method of data collection

The study used secondary data from a survey implemented in Burkina Faso between March and July 2020 that evaluated the knowledge, attitudes and practices of smallholder livestock farmers in the peri-urban areas of Ouagadougou, Burkina Faso, with a focus on antibiotics (15). During and after data collection, authors had access to information (including name and gender) which could identify individual participants. Data were collected using Open Data Kit (ODK), a source-based smartphone platform that can be used to create electronic questionnaire forms for real-time data entry. Enumerators interviewed one representative from each farm,

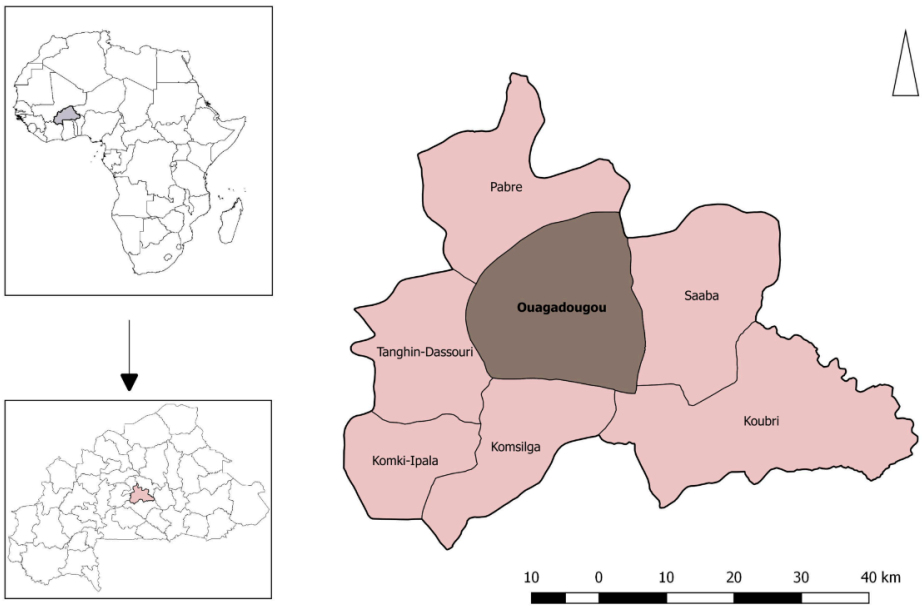

FIGURE 1
Map of the study area.

either in French or Mooré, depending on the languages spoken by the respondent.

2.5 Sampling method and sample size calculation

Farmers were contacted through a directory of farms in Ouagadougou area between March and July 2020. For each farm, the manager (the owner or a designated worker) was contacted and asked to participate in the study. Inclusion criteria were that the farm be a smallholder livestock farm. Farms were excluded if they were large-scale commercial farms or non-livestock farms. The number of farms included in the dataset was determined as part of a previous study (15) for which the data were originally collected, and this study simply made use of that dataset. The sample size of that study was selected to be sufficient to detect differences in the characteristics of farms which did and did not consult a veterinary professional before buying antibiotics, with a risk of error α of 5% and a confidence interval of 95%, assuming that 12.1% of farms did so based on results from a previous study (15, 20).

2.6 Data management and statistical analysis

Statistical analyses were performed with RStudio version 2023.03.01 + 446 (21) using R version 4.1.2 (22).

First, survey responses from each farm were compiled into a cross-sectional dataset.[1] Where farms had multiple flocks and herds of different species, each flock or herd was treated as a separate unit of analysis.

Following cleaning and examining the dataset, two outcomes of interest were selected: the occurrence of disease in the flock or herd in the last 6 months, and the nontherapeutic use of antibiotics (this dataset included data on use for prophylaxis and fattening). Every farm which used antibiotics for fattening also used them for prophylaxis, so we refer to this outcome variable simply as 'nontherapeutic antibiotic use' for clarity.

Binary logistic regression was used to investigate the effect of covariates on the likelihood of these outcomes. For both the bivariate and multivariate models, significance was assessed at the 1% ($p < 0.01$), 5% ($p < 0.05$), and 10% ($p < 0.1$) levels, and results were considered significant if they had a p-value of $p < 0.1$, as has been the case for other regression-based papers written using the AMUSE survey, as well as the original paper written using this dataset from Burkina Faso (10, 15, 17). All specifications controlled for the number of animals in the flock / herd, given that the occurrence of a single incident of disease or nontherapeutic antibiotic use may increase with the number of animals.

Both binary and numeric variables were used as covariates in the logistic regression specifications. Binary variables included:

1 A cross-sectional dataset is one which includes observations from multiple subjects at a single point or period in time.

'uses antibiotics prophylactically,' 'believes that antibiotics can be used for fattening,' 'goes to [particular animal health service provider],' 'professional provides diagnosis and treatment,' and the animal species dummies. Numeric variables included: 'number of animals in flock/herd' and 'formal education level.' For binary variables, the values displayed in the results tables are the adjusted odds ratios (exponentiated logistic regression coefficients) for the variable being 1 relative to the variable being 0. For numeric variables, the values displayed are adjusted odds ratios (exponentiated logistic regression coefficients) for a unit increase in the variable.

In order to determine which covariates to include in the multivariate models, bivariate models were first run in which each outcome variable was regressed against each covariate individually (controlling for the number of animals in the flock or herd). This was done first for each livestock species (cattle, poultry, sheep and goats) individually, and then for the whole sample (including all flocks and herds surveyed). Whole-sample results included species dummies. Multivariate models were then run for each of the two outcome variables (by livestock species and for the whole sample), including the covariates which were significant in the bivariate models. Separate regressions were run for each livestock species to investigate if the determinants of animal disease and nontherapeutic antibiotic use varied by species.

2.7 Ethical approval

The study was approved by the ethical committee of the Ministry of Health, Burkina Faso, with reference number 2020-9-186. Informed (written and signed) consent was obtained from each participant before they were interviewed.

3 Results

Bivariate models were first run to select covariates for the multivariate models. The outputs of the univariate models which produced significant results are available in the Appendix.

In the bivariate models, several factors were significantly associated with the occurrence of animal disease. For goats and sheep, and for cattle, prophylactic antibiotic use was positively associated with animal disease. For the sample as a whole, prophylactic antibiotic use was positively associated with animal disease. Having a higher education level and going primarily to a public veterinarian were negatively associated with the occurrence of disease for the sample as a whole. No factors were significantly associated with the occurrence of disease for chickens alone.

Several factors were also significantly associated with the habitual use of antibiotics for nontherapeutic purposes in the bivariate models. For chickens, going primarily to a community animal health worker was positively associated with nontherapeutic AMU. A professional providing diagnosis and treatment, and primarily going to a public veterinarian, were negatively associated with nontherapeutic AMU for chickens.

For goats and sheep, having a professional provide diagnosis and treatment was positively associated with nontherapeutic AMU. For the sample as a whole, going primarily to a community animal health worker was positively associated with nontherapeutic AMU, whereas going primarily to a public veterinarian was negatively associated with nontherapeutic AMU. No factors were significantly associated with nontherapeutic AMU for cattle alone.

Multivariate models were then run for each of the two outcome variables (Tables 1, 2), including the factors which were significant in the bivariate models.

In the multivariate model (Table 1), habitual prophylactic use of antibiotics remained positively associated with the occurrence of disease for goats and sheep, for cattle, and for the sample as a whole. Primarily going to a public veterinarian, and having a higher level of formal education, were both negatively associated with the occurrence of disease for the sample as a whole.

In the multivariate model (Table 2), primarily going to a community animal health worker remained positively associated with using antibiotics nontherapeutically for poultry and for the sample as a whole. By contrast, primarily going to a public veterinarian remained negatively associated with using antibiotics prophylactically for poultry and for the sample as a whole. Having a professional provide diagnosis and treatment remained positively associated with using antibiotics nontherapeutically for goats and sheep, but was no longer significant for poultry.

4 Discussion

The study found that habitual prophylactic antibiotic use was consistently positively associated with the occurrence of disease on smallholder livestock farms, whereas having a higher level of formal education and primarily accessing public veterinarians for animal health services were negatively associated with disease.

Primarily going to a community animal health worker for animal health services was positively associated with nontherapeutic antibiotic use, whereas primarily going to a public veterinarian was negatively associated with nontherapeutic antibiotic use. For goats and sheep, having an animal health professional (of any kind) providing diagnosis and treatment was positively associated with nontherapeutic antibiotic use.

It is interesting that habitual nontherapeutic antibiotic use was positively associated with animal disease. This finding is consistent with evidence from farm-level trials in other contexts which suggest that nontherapeutic antibiotic use does not improve, or may actively worsen, animal health outcomes in smallholder livestock farms (8). Other trials suggest that antibiotic stewardship improvements on smallholder poultry farms, when combined with biosecurity interventions and non-antimicrobial food additives, can improve animal health outcomes (7).

However, some studies have identified a positive role for nontherapeutic antibiotics. Earlier studies using the AMUSE survey in Uganda suggested that nontherapeutic antibiotic use guarded against disease in smallholder livestock farms (10). Nontherapeutic antibiotic use may also have benefits for livestock productivity, as evidenced in a study using the AMUSE survey tool in Senegal (17), and there is evidence in the literature that sub-therapeutic doses of antibiotics convey a health and productivity benefit to livestock (9). Our finding of a positive association between animal disease and nontherapeutic antibiotic use may also be subject to reverse causality, as having had more animal disease in the last 6 months may have

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TABLE 1 Determinants of animal disease (adjusted odds ratio).

	Occurrence of disease in last 6 months		
	Goats and Sheep	Cattle	Whole sample
	(1)	(2)	(3)
Uses antibiotics prophylactically	17.559***	4.080*	2.044*
	$p = 0.001$	$p = 0.072$	$p = 0.062$
Primarily goes to a public vet			0.532*
			$p = 0.083$
Level of formal education			0.747**
			$p = 0.035$
Number of animals in the flock / herd	1.008	1.098**	1.000
	$p = 0.702$	$p = 0.039$	$p = 0.916$
Cow dummy			0.069***
			$p = 0.00000$
Goats and sheep dummy			0.039***
			$p = 0.000$
Constant	0.056***	0.084***	8.137***
	$p = 0.001$	$p = 0.002$	$p = 0.00003$
N	59	49	312

***Significant at the 1 percent level.
**Significant at the 5 percent level.
*Significant at the 10 percent level.

TABLE 2 Determinants of habitually using antibiotics for nontherapeutic purposes (adjusted odds ratio).

	Using antibiotics nontherapeutically		
	Chickens and other poultry	Goats and Sheep	Whole sample
	(1)	(2)	(3)
Primarily goes to a community animal health worker	7.265***		2.358**
	$p = 0.004$		$p = 0.020$
Primarily goes to a public vet	0.432*		0.512*
	$p = 0.094$		$p = 0.096$
Professional provides diagnosis and treatment	0.438	4.797**	
	$p = 0.114$	$p = 0.020$	
Number of animals in the flock / herd	1.001**	0.983	1.001**
	$p = 0.013$	$p = 0.497$	$p = 0.042$
Cow dummy			0.072***
			$p = 0.00000$
Goats and sheep dummy			0.073***
			$p = 0.000$
Constant	3.664***	0.239**	2.940***
	$p = 0.008$	$p = 0.037$	$p = 0.004$
N	212	59	320

***Significant at the 1 percent level.
**Significant at the 5 percent level.
*Significant at the 10 percent level.

prompted farmers to adopt more cautious antibiotic use protocols which involve greater nontherapeutic use.

That accessing public veterinary services was negatively associated with disease suggests a positive role in managing animal health. This echoes findings from Uganda that accessing animal health services improved disease outcomes in smallholder livestock farms (10). However, it is worth noting that the same relationship was not observed for other providers of animal health services. That accessing private veterinarians, regardless of qualification status, was not associated with better health outcomes raises questions about the potential for perverse incentives in private antibiotic prescribing. For example, there may be an incentive to sell expensive but inappropriate medicines, a concern raised by stakeholders in the SEFASI consortium's 2022 workshop in Dakar (23).

It is interesting to note that going primarily to a community animal health worker was positively associated with nontherapeutic antibiotic use, and that having an animal health professional (of any kind) provide diagnosis and treatment was positively associated with nontherapeutic antibiotic use for goats and sheep. This could suggest that animal health professionals do not, by default, prioritize antibiotic stewardship over animal health. This is consistent with results from consultation with poultry industry stakeholders in the UK, who stressed that humanely safeguarding animal health through antibiotics remains an immediate priority for veterinarians (23). The fact that the opposite was true for public veterinarians could mean that they have been more exposed to government goals as part of the ongoing national action plan on AMR in Burkina Faso: these include a drive to involve veterinary medicine in antibiotic stewardship efforts and to change antibiotic prescribing culture (24). In the case of private veterinarians especially, there may also be an incentive to overprescribe to maximize revenue, or to prescribe excessively broad-spectrum antibiotics to minimize the risk of ineffective treatment, a concern raised in previous consortium workshops (23).

This study aimed to identify factors which are associated with animal disease outcomes and nontherapeutic antibiotic use on smallholder livestock farms in Burkina Faso. This addresses the broader goal of identifying potential interventions to facilitate reductions in nontherapeutic antibiotic use while safeguarding against any animal health risks associated with doing so. The results of this study identify expanded public veterinary access as a potential way of achieving both of these goals, and emphasize that not all providers of animal health services are likely to improve antibiotic stewardship outcomes. Improving farmers' access to education may also help to improve animal health, and therefore to safeguard against health risks associated with reductions in antibiotic use. Studies have emphasized the role of veterinarians' education in improving AMS outcomes (25), and the value of interventions to improve farmers' knowledge about AMS (15–17), but there is little literature on the role of formal education in improving AMS outcomes in smallholder livestock farms in this context.

4.1 Limitations

Difficulties with the dataset limited the scope of specifications which could be performed. For instance, the small number of farms which used antibiotics intended for humans on animals meant that this could not be included as an outcome. The small number of farms which had taken part in awareness and vaccination campaigns also meant that the effect of this could not be investigated as a covariate. Several livestock species (pigs, rabbits, horses, and donkeys) were represented on only a small number of farms and thus could not be included in the analysis.

Data on the use of drugs in animals only covered the last 4 weeks, meaning that the study could not investigate the effect of drug use frequency on the occurrence of disease due to the potential for reverse causality. The survey used is also a snapshot, giving static information about farm practices and outcomes. A longer-term cohort study could capture changes over time and give insight into the role of covariates in improving farm outcomes over time. Similarly, while this study used observational data, an intervention study could give more specific insight into the most useful ways to improve antibiotic stewardship while safeguarding animal health and farm productivity.

Finally, in any research concning antibiotic stewardship, it must be borne in mind that smallholder farmers exist as part of a complex network of actors which includes lenders, landlords, drug sellers, animal health professionals, marketeers and more (13). Any intervention aiming to improve stewardship outcomes must acknowledge and involve this entire network.

5 Conclusion

Using a survey of smallholder livestock farms in Burkina Faso, this study found that there was a greater likelihood of animal diseasrms where habitual prophylactic antibiotic use was observed. This contradicts the authors' original hypothesis that prophylactic antibiotic use may protect against animal disease, although the relationship observed may be subject to reverse causality. It also found that there was a lower likelihood of animal disease when farmers had a higher level of formal education, or went primarily to public veterinarians for animal health services (as opposed to other animal health service providers).

The study also found that primarily going to a community animal health worker was positively associated with using antibiotics nontherapeutically, whereas primarily going to a public veterinarian was negatively associated with that outcome. Having an animal health professional (of any kind) provide diagnosis and treatment was also positively associated with nontherapeutic antibiotic use in goats and sheep.

These findings highlight the potential of expansion of education access and public veterinary services as a way to encourage better antibiotic stewardship while safeguarding against any animal health risks associated with reducing nontherapeutic antibiotic use. They also highlight that some types of animal health professional may prioritize animal health outcomes over antibiotic stewardship goals.

Future research should involve farm-level trials and qualitative studies to examine the relationship between nontherapeutic antibiotic use and animal disease in more detail, to explore the extent to which different animal health service providers face incentives to overprescribe, and to test the effect of expanded public veterinary access on antibiotic stewardship and animal health outcomes.

Finally, smallholder farmers form part of a complex network of actors, and this whole network must be considered when designing and implementing antibiotic stewardship policies.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: anonymised data can be made available upon request. Requests to access these datasets should be directed to eve.emes@lshtm.ac.uk.

Ethics statement

The studies involving humans were approved by the Ethical Committee of the Ministry of Health, Burkina Faso, with reference number 2020-9-186. Informed (written and signed) consent was obtained from each participant before they were interviewed. Consequently, all participants gave their consent to participate in the study. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

EE: Conceptualization, Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. AK: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Writing – review & editing. MD: Writing – review & editing, Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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2.2.3 Implications

The findings of the three papers were, in short, mixed. Due to the outcomes included in each of the datasets used, each paper answered slightly different questions, but it is possible to identify trends and to make general inferences by considering the findings together.

In Senegalese poultry production, the first of the three settings that I looked at, I found that farmers with “AMR-aware attitudes” and better biosecurity practices used fewer nontherapeutic antibiotics. Productivity was higher when farmers vaccinated birds more, used more antibiotics, and (in some specifications) had better biosecurity.

Here, vaccination and AMU were both associated with a higher disease incidence, although the direction of causality is difficult to infer. To elaborate, AMU was measured by the amount spent on antibiotics for a flock during a production cycle, and disease incidence was the number of incidents during a production cycle. Because both variables refer to the same period of time, antibiotics used in response to disease could result in a positive association. The fact that broiler productivity was positively associated with AMU suggests that there was an animal health benefit from AMU, and therefore that the association between AMU and disease may reflect reverse causality rather than AMU causing disease.

In Uganda, across a range of livestock types, I found that prophylactic AMU was associated with a lower likelihood of disease outbreak. A range of other factors also seemed to guard against disease, with vaccination and and accessing animal health services doing so the most consistently. This study looked at disease outcomes only, and did not look at the determinants of productivity because that was not included in the dataset used. Unlike in Senegal, (prophylactic) AMU was negatively associated with disease - this may be because ‘prophylactic AMU’ referred to habitual use of antibiotics for prophylactic purposes whereas disease incidence referred to the occurrence of disease in the last two weeks only. Therefore antibiotics used in response to disease would be less likely to create a false positive association.

In Burkina Faso, across a range of livestock types, I looked at the determinants of both disease and nontherapeutic AMU. Nontherapeutic AMU was associated with a higher likelihood of disease, although there is the potential of reverse causality here. ‘Disease’ referred to the occurrence of disease in the last 6 months, and ‘nontherapeutic AMU’ referred to habitual use of antibiotics for prophylaxis or fattening. Because of the longer timeframe over which the occurrence of disease was measured, there may be a greater likelihood of farmers updating their practices to use more antibiotics in response to the occurrence of disease, and therefore more potential for a false positive association to emerge.

Formal education, and going primarily to a public veterinarian (as opposed to other providers of animal health services) were associated with a lower likelihood of disease. In terms of the determinants of nontherapeutic AMU, going primarily to a community animal health worker was associated with more nontherapeutic AMU and going primarily to a public vet was associated with less nontherapeutic AMU. For some animal species, going to an animal health professional in general was associated with more nontherapeutic AMU.

Taken together, we can say a few things. For one, nontherapeutic AMU in smallholder livestock farms may be important for animal health and productivity, depending on the context and production type. It appeared to improve broiler productivity in one context, and for the dataset with the least likelihood of reverse causality it also seemed to guard against disease.

I identified a range of non-antibiotic factors that could safeguard animal health and productivity, reducing the need for AMU, as well as factors which could encourage better stewardship in their own right. Overall, combining AMU restrictions with biosecurity, vaccination, and expansion of access to public veterinary services appears to be a strong candidate for a combined intervention to safely improve stewardship. In particular, the results from the Burkina Faso paper concerning the effects of different animal health service providers on stewardship outcomes highlight the conflicting incentives that these providers might have, and the desirability of either prioritising public vets as the primary provider of animal health services or bringing other providers onboard with NAPs on AMR. In Burkina Faso, vets are integrated into the NAP on AMR(160). In our 2023 Consortium workshop in London, some of our public health stakeholders from Senegal emphasised that bringing (private) community animal health workers onboard with NAPs on AMR, educating them about stewardship, and standardising and formalising their service provision, was an important goal for OH AMR in many countries where such services are commonplace.

2.2.4 Applications

Other similar datasets to the ones used in these studies are emerging as the AMUSE survey is used in more and more countries (Burkina Faso, Uganda, Senegal, Kenya, Benin, Ethiopia). At the moment, I am planning to do a similar analysis on an AMUSE dataset from Benin. I have also been in touch with a collaborator based in Cameroon, whose team have collected several survey datasets from semi-intensive livestock farms there. We have discussed plans to use similar methods to the ones used here to investigate the effect of potential stewardship interventions. We would also analyse data on antibiotic imports alongside sentinel surveillance from hospitals to characterise the ecological relationship between AMU and AMR (either using statistical or mathematical modelling). These results could then be used as inputs into the AHHME model, parameterising it for a range of hypothetical stewardship interventions.

I am also in the process of working with collaborators from within the SEFASI consortium to use the results of the Senegal AMUSE paper, as well as the results from an ongoing mathematical modelling project on the ecological relationship between AMU and AMR, to parameterise AHHME for Senegal and to simulate (and evaluate) a range of potential interventions. Next year, we at the SEFASI consortium also plan to apply for funding for a three-year project based in Senegal. The project would involve intervention trials and data collection across all three OH compartments, with larger sample sizes than what I have worked with here. It would aim, among other things, to follow up on the findings of these three papers and to reinvestigate those questions using more extensive and purpose-built data as well as targeted trials of actual interventions informed by these results. Eventually, those results (combined with analysis of surveillance data) could be used to parameterise AHHME and to evaluate prospective interventions with much more confidence.

I have also presented the results of these three papers to stakeholders in the SEFASI "Knowledge Hub" workshops, and have formally elicited their feedback on the believability and implications of these results. The Knowledge Hub is a group of stakeholders and experts from across the OH AMR spectrum (including policy, research, agriculture, veterinary and human medicine, etc.), working primarily in the three SEFASI countries (England, Senegal, Denmark), who were recruited using a snowball sampling process. They have been involved in a series of workshops to elicit their views on the findings and research directions of the SEFASI consortium.

Overall, stakeholders were divided on the expected impact of eliminating nontherapeutic AMU on animal infections. Some thought that it would have little effect on infections or would increase them, and some felt that the effect would depend on the optimality of the farm's production system. However, the most common answer was that it would actually reduce the incidence of infections, reflecting the general trend in the AMR discourse of viewing nontherapeutic animal AMU as harmful. That being said, stakeholders did generally feel that this reduction could harm animal productivity.

In terms of interventions which could encourage farmers to use fewer antibiotics, stakeholders commonly answered that awareness campaigns and access to public veterinary services would be helpful, with some mentioning biosecurity, training and vaccination as well.

After presenting the results to stakeholders at the Knowledge Hub workshop in Dakar in 2022, we used the results to inform collaborative systems mapping which fed into the creation of a system dynamics model of AMR in poultry production in Senegal(53). I have also presented the results of these three papers at IDDCONF 2023.

2.2.5 Limitations

There have been, of course, a number of major limitations in designing and writing these three papers. For one, I had recurring problems with statistical power due to the small size of the datasets used, which made it more difficult to include all relevant covariates and meant that some real relationships may not have been statistically significant. It also meant that the results were not precise enough to be used to parameterise AHHME confidently (for example, by saying "a 5% reduction in on-farm AMU was associated with a 2% increase in animal mortality"). However, the results were still able to highlight factors of importance, and can be used as the basis for designing future trials such as the ones proposed above.

The datasets were also designed for evaluating KAP on AMR, and I often had to use the variables available to me which measured something close enough to what I was interested in. The surveys did not model interventions, and only reflect a snapshot at a single point in time. This made it impossible to observe the effect of changing variables on changing outcomes over time, which would have been helpful for identifying the direction of causality. There were also times where it was difficult to disentangle the direction of causality between disease outcomes and AMU, given that I wasn't able to track those outcomes over time. I was able to account for this to some extent where studies had questions about habitual AMU, or where there were separate questions about recent and less recent practices.

Finally, the datasets used focused on farm-level factors, with little information about systems-level factors. We must keep in mind that agricultural AMS is situated in a broader socioeconomic network composed of actors from a range of sectors. Stewardship initiatives have therefore to be targeted at the systems level as well as at the farm level, otherwise they may result in simply targeting farmers in an attempt to fix a systemic problem. Stakeholders at the Knowledge Hub workshops that I co-ran in London and Dakar raised this point emphatically, and there was a lot of discussion about conflicting views on who is ultimately responsible for agricultural antimicrobial stewardship; with vets, pharmacists, farmers, doctors, policymakers, those in agribusiness, and pharmaceutical manufacturers all being involved. As an example of the complicated political economy of agricultural AMU, Masud and colleagues(20) provide a very interesting case study of the poultry sector in Bangladesh. There, smallholder poultry farmers are highly dependent on private poultry dealers, who also function as creditors and determine a large part of their decision-making around farm practices and AMU.

2.2.6 Where does this leave us?

Taking these three papers as a whole, we have interesting results which challenge some of the prevailing assumptions about the role of AMU on farms. The most notable results here are that nontherapeutic AMU may be important for animal health and productivity, and that different animal health providers may have different incentives in terms of antibiotic stewardship.

These results point to combined intervention packages which could be used to encourage better on-farm stewardship while safeguarding animal health and productivity. They highlight the need for more specific and purpose-built farm-level trials of prospective interventions, and provide guidance on what these interventions could look like. Combined with studies on the ecological relationship between animal AMU and human AMR, these results could be used to begin to parameterise the AHHME model and to simulate the holistic impact of prospective agricultural AMS intervention packages.

2.3 Investigating the ecological relationship between animal AMU and human AMR using regression models

2.3.1 Introducing the paper

At this point, I had acknowledged and explored a series of literature gaps limiting our ability to design and evaluate agricultural AMR policy holistically and usefully. I had created an alternative health-economic framework and had applied it to representative data, but applying it more concretely required a more robust understanding of two key relationships. For the first of these, I had explored a series of farm-level survey datasets to understand how on-farm AMU and other practices affect animal health and productivity outcomes. However, applying AHHME confidently still required a more robust quantification of the ecological relationship between (agricultural and human) AMU and human AMR.

Fundamentally, discourse on agricultural AMS rests on the idea that reducing animal AMU helps to curb human AMR. As outlined in chapter 1, there is a scientific basis for expecting this to be the case, but the ecological relationship is seldom quantified and studies that do investigate it provide uncertain or contradictory results. There are also good reasons to expect that reductions in animal AMU may not have a strong impact on human health.

In order to design and prioritise AMR policies, we need to be able to estimate the number of resistant infections averted by a given change in animal AMU. Without this, the health-economic impact of stewardship interventions cannot be estimated. Given this, I wrote a paper in 2022 advocating for ecological panel regression as a means of estimating this relationship and feeding into holistic cost-effectiveness analysis (161). Later that year, I presented a framework for how ecological panel regression, farm-level analysis, and health-economic frameworks like AHHME could be used to facilitate more robust health-economic analysis of AMR interventions, at the JPIAMR *New Perspectives on Bacterial Drug Resistance* workshop.

Through 2023 and 2024, I collaborated with SEFASI partners in the UK and Denmark to apply this regression framework to those two countries.

For the UK, unified data on AMU across livestock species are not available, so I decided to focus the work specifically on the relationship between ABU in poultry production and the rate of resistance in human *Campylobacter* isolates.

I have an honorary contract with the UK Health Security Agency (UKHSA), and so was able to collaborate with the UKHSA surveillance team to obtain human infection and AMU data for the UK. I also collaborated with private poultry producers to obtain data on ABU in poultry production. I designed an initial study, and worked with stakeholders to co-design the final pre-analysis plan through a series of workshops involving the British Poultry Council, the UKHSA, the UK Animal and Plant Health Agency (APHA), the LSHTM, and the Royal Veterinary College (RVC). These stakeholders have also been involved in reviewing drafts of the paper.

In Denmark, my plan was to collaborate with the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DanMap)(162) and VETSTAT(163) to get access to

data and to co-design studies in a similar way. However, the collaborators at those institutions eventually dropped out of contact and did not give me access to the raw data used in DANMAP. While I was granted access to VETSTAT data on animal AMU, I had to extract data on human AMR from what was publicly available on the DanMap website.

We also have plans to run similar analyses for Senegal. Here, we would likely obtain human AMR data by collaborating directly with hospitals to access human infection data, and would estimate animal AMU by using data on antibiotic imports. The very different process of obtaining data and designing studies using surveillance data in different countries, and the lack of straightforwardness even in countries with (theoretically) world-leading open-access surveillance infrastructures, certainly gives pause for thought on the nature of AMR data and the existence of *de facto* data silos.

For both the UK and Denmark papers, I designed the studies, organised collaboration with relevant stakeholders to refine research questions and analysis plans, obtained and cleaned the data, wrote and ran the code, and wrote the resultant papers with supervisory input from coauthors.

I include only the Denmark paper here. For the UK paper, the BPC were only willing to supply annual rather than quarterly data on animal AMU and would only provide data at the level of the UK (rather than at the member nation level). This, combined with other data limitations, meant that I did not have the statistical power needed to run panel regression methods (fixed effects, random effects, difference-in-difference) as in Denmark. I tried to write the paper using pooled ordinary least squares (POLS) regression, and produced a preprint which had some interesting implications. However, upon doing additional robustness tests suggested during peer review, it became clear that POLS was not appropriate or robust. I therefore withdrew the preprint and have removed it from this thesis, keeping a description of the writing process above due to its relevance to the thesis as a whole.

2.3.2 Paper 5

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Student ID Number	2204500	**Title**	Miss
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Primary Supervisor	Gwen Knight		

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SECTION B – Paper already published

Where was the work published?	One Health		
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I created the design of the study with input from coauthors. I liaised with collaborators at VETSTAT and DanMap to gain access to the data used in this study. I cleaned and analysed the data in R, and wrote the paper with supervisory input from coauthors.

SECTION E

Student Signature	Eve Tresco Emes
Date	22 October 2024

Supervisor Signature	Gwen Knight
Date	22 October 2024

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The contribution of animal antibiotic use to antibiotic resistance in human infections: Panel evidence from Denmark

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ABSTRACT

Antibiotic use (ABU) in animals is postulated to be a major contributor to selection of antibiotic resistance (ABR) which subsequently causes infections in human populations. However, there are few quantifications of the size of this association. Denmark, as a country with high levels of pig production and strong ABR surveillance data, is an ideal case study for exploring this association.

This study compiles a dataset on ABU across several animal species and antibiotic classes, and data on the rate of antibiotic resistance (ABR) in humans across key pathogens, in Denmark over time (2010–2020). Panel data regressions (fixed effects, random effects, first difference and pooled ordinary least squares) were used to test the association between the level of ABR in human isolates and the level of ABU in animals.

A positive relationship was identified between ABR in humans and ABU in cattle, with some evidence of a positive relationship for poultry and companion animals, and a negative relationship for fish, although the latter is likely driven by confounding factors. When lagging ABU by one year, the effect of ABU in cattle and companion animals remained similar, the effect of ABU in poultry fell in size, and ABU in fish was no longer significant, perhaps due to differences in life cycle length among animal species. Additional covariates were explored, including pet populations, agricultural production and GDP per capita (at purchasing power parity), but these results were limited by the statistical power of the dataset. Under all models, animal ABU determined only a minority of the change in human ABR levels in this context with adjusted R^2 ranging from 0.19 to 0.44.

This paper supports the role of animal ABU in determining human ABR levels but suggests that, despite comprising a large portion of systemwide ABU, it only explains a minority of the variation. This is likely driven in part by data limitations, and could also be due to a persistence of ABR once resistance has emerged, suggesting a significant role for socioeconomic and transmission factors in bringing ABR down to desirable levels.

1. Introduction

Antibiotic resistance (ABR), the capacity of bacterial pathogens to survive in the presence of antibiotics, is considered a major and growing threat to human health worldwide (1,2). Antibiotic use (ABU) in animals is the largest form of AMU globally (3), and as such there has been international policy focus on reducing and modulating this ABU in order to lower the rate of ABR in human infections and safeguard human and animal health.

Food animals represent the largest destination of global ABU (3), and significant transmission of resistomes between humans and companion animals have made animal ABU in general an important target for interventions, although the latter is less often studied (4). Numerous microbiological and genomic studies (5–7) support the existence of a link between animal ABU and human ABR, and there is a very strong theoretical basis for expecting ABU in animals to generate ABR in humans (8). Despite this, knowledge of the shape and size of this relationship remains limited (8,9), and some microbiological and genomic

Acronyms: ABR, Antibiotic resistance; ABU, Antibiotic use; AMR, Antimicrobial resistance; AMS, Antimicrobial stewardship; AMU, Antimicrobial use; DanMap, The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme; OLS, Ordinary least squares regression; One Health, The interplay between human, animal and environmental health; POLS, Pooled OLS; SEFASI, Selecting Efficient Farm-Level Antimicrobial Stewardship Interventions from a One Health Perspective.

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studies fail to find consistent evidence of it (4,8,10–12). This has complicated implications for AMR policy decision-making in the One Health space, where policymakers need to know the likely effect of AMS interventions on the number of resistant infections in humans and animals in order to estimate the intervention benefit. Panel regression can give specific quantitative insight into this outcome, and can feed more directly into intervention design and prioritisation at the population level.

This study uses panel data regression (13), which the authors identify as a powerful tool for investigating the relationship between ABU and ABR at the ecological level, and which has not yet been applied to Denmark specifically (9). Using these methods, Rahman and Hollis (14) found that, across a panel of European countries, ABU in food animals and in humans were independently and causally related to the rate of ABR in both humans and animals. Adda (15) found that, in the United States, ABU in humans and animals both contributed to the rate of ABR in human infections, with human ABU being a greater contributor and with more recently-introduced antibiotics having a greater effect. More recently, Allel et al. (16) found that, across a range of countries, ABU in animals and humans contributed to the rate of ABR in infections by critical priority pathogens in humans. Zhang et al. (17) found a positive relationship between human ABU and the rate of fluoroquinolone resistance in *E. coli* and *P. aeruginosa* in Europe, and a negative relationship between animal ABU and fluoroquinolone resistance in *P. aeruginosa*.

Studies have also used panel regression methods to investigate the role of non-ABU factors, including socioeconomic variables and medical staffing, in determining ABR rates in humans. Collignon et al. (18) found that, across a range of countries and for a set of key drug-pathogen combinations, indices of infrastructure and governance were inversely related to the rate of ABR in human infections, even when human ABU was not. Zhang et al. (17) found that medical and veterinary staffing numbers were negatively related to the rate of fluoroquinolone resistance in *E. coli* and *P. aeruginosa* across European countries. Allel et al. (16) also found links between socioeconomic, demographic, political and environmental factors and human ABR across a range of countries. ABR can therefore be seen not as a purely biological problem but as a public health phenomenon which is jointly determined by biological and socioeconomic factors.

This study considers phenotypic resistance (the susceptibility of bacterial assays to antibiotics), rather than genotypic resistance (the presence of genes conferring resistance), as this is how resistance is recorded in the datasets used.

Denmark is a strong case study to investigate the relationship between animal ABU and human ABR due to the comprehensiveness of its ABR surveillance infrastructure across the One Health space, with the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) (19) and VetStat (20,21) tracking ABU and ABR in humans and animals. The human ABR data available through DanMap also focuses on *Campylobacter* and *Salmonella* species, which are key foodborne pathogens of relevance to human health (22). Because these pathogens are often transferred from food animals (19,23,24), they are also more likely candidates to give insight into the relationship between animal ABU and human ABR.

Denmark is considered a world leader in preventing and managing ABR from a One Health perspective: use of antibiotics in animal health has been low and consistent since 2000, and agricultural growth promoters have been phased out since then (25,26).

Denmark is also considered a world leader in agricultural AMS (27): since 1995, a series of policies has been implemented aiming to regulate and limit the use of antibiotics in animals, including bans on agricultural growth promoters from 1998 (28). Animal antibiotics are sold on a prescription basis and veterinarians may not profit from their sale (27). The 2010 Yellow Card Initiative (29) places quantitative restrictions on use of antibiotics in food animal production, and has been adjusted since then to place different weights on various antibiotics depending on AMS priorities. Finally, as a country with a large amount of food animal production, particularly of pork (30), Denmark represents a strong case study for investigating the relationship between ABU in animals and the rate of ABR in human infections.

ABU may also have a delayed effect on the rate of ABR (14), especially in food animal production, where antibiotics used at the beginning of production cycles may take time to pass into the human population. Understanding the role of lagged ABU can help to understand these transmission mechanisms.

Based on these considerations, this paper aims to investigate if ABR in human isolates in Denmark is linked to the quantity of antibiotics used in animals, and to quantify that link. And, if a relationship is observed, to determine whether or not it varies among animal species. After addressing these questions, the study will explore the shape and nonlinearity of that relationship. Finally, it will investigate whether antibiotic use in previous periods is linked to the rate of ABR, and how strong this link is compared with that of same-period ABR, as well as exploring the role of other covariates including GDP per capita and animal populations. These covariates will help to account for changing socioeconomic conditions which could influence the relationship between ABU and ABR, as well as potential relationships between populations of, and therefore use of antibiotics in, different animal types.

2. Materials and methods

2.1. Data

Data on the rate of ABR in humans was sourced from DanMap (19), the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme. DanMap makes publicly available a repository of data on ABR indicators and zoonotic bacteria in humans, livestock and companion animals in Denmark, drawing on routine surveillance across primary and secondary healthcare, veterinary surveillance and prevalence surveys from livestock animals. In humans, data coverage is high - representing a near complete proportion of all microbiological analyses. The source of the bacterial sample depends on the pathogen species, ranging from bloodstream infections to colonisation samples. This study uses the term “human ABR” to mean the proportion of isolates for a certain bacterial species collected by DANMAP in routine surveillance (often only the first isolate from a patient per year) that were tested and found to be resistant to the antibiotic being considered (19).

Data on the use of antibiotics in food and companion animals was sourced from VETSTAT (20), a database which records all prescription drugs sold for animal use in Denmark. In this dataset, ABU refers to the total amount of each antibiotic prescribed for use in each animal type, by kg of active compound, each year.

2.2. Variables

Data were cleaned and compiled into a panel at the {*year*, *drug-pathogen*} level. Drug-pathogen refers to the observed rate of resistance of isolates of a particular bacteria species (pathogen) to a specific class of antibiotic (drug). For example, the rate of resistance of *Salmonella typhimurium* to tetracyclines represents one drug-pathogen pair.

For each year, and each drug-pathogen pair, the dataset therefore covers:

- The portion of human bacterial isolates which were resistant to various antibiotics, from routine healthcare surveillance, from 2010 to 2021.
- The total use of antibiotics in kg in several livestock animal types, and for companion animals, from 2010 to 2020

Antibiotics here were sorted at the class level. While the use of antibiotics was recorded by antibiotic class, the resistance dataset recorded resistance against individual drugs. For this reason, drugs were grouped

into classes (31), and the ABR variable refers to the average rate of resistance against all drugs from each antibiotic class. For more detail on the classification of antibiotics in this study, see Appendix 1. The pathogens covered by the dataset include *Campylobacter coli*, *Campylobacter jejuni*, *Escherichia coli*, *Salmonella derby*, *Salmonella enteritidis*, *Salmonella infantis* and *Salmonella typhimurium*. The classes of antibiotic included in the dataset were: aminoglycosides, amphenicols, carbapenems, cephalosporins, fluoroquinolones, macrolides, penicillins, polymyxins, quinolones, sulfonamides, and tetracyclines.

The animal types included in the study were: cattle, sheep and goats, pigs, poultry, fish, and companion animals.

2.3. Statistical methods

The raw datasets were cleaned by extracting relevant data, standardising the classification of antibiotics across the two datasets, aggregating data into a {*year*, *drug-pathogen*} panel, and merging the two datasets. Data coverage and completeness was then explored across humans and animals and across the different years and drug-pathogen pairs covered.

Summary statistics were generated on the use of antibiotics by animal species and class over time, as well as on the rate of resistance in human isolates over time (by drug-pathogen combination).

The regression analysis used fixed effects, random effects, first difference, and pooled ordinary least squares (POLS) regressions. A Durbin-Wu-Hausman test (32) was used to determine whether or not random effects models should be included.

First, multivariate regression analysis was performed, regressing human ABR against ABU in each animal species together. This gives the main regression models (below).

Fixed effects

$$resistance_{a,b,t} = \beta_0 + \beta_1 * use.cattle_{b,t} + \beta_2 * use.sheep.goats_{b,t} + \beta_3 * use.pigs_{b,t} + \beta_4 * use.poultry_{b,t} + \beta_5 * use.fish_{b,t} + \beta_6 * use.companion.animals_{b,t} + \mu + \nu + \varepsilon_{a,b,t}$$

Random effects and POLS

$$resistance_{a,b,t} = \beta_0 + \beta_1 * use.cattle_{b,t} + \beta_2 * use.sheep.goats_{b,t} + \beta_3 * use.pigs_{b,t} + \beta_4 * use.poultry_{b,t} + \beta_5 * use.fish_{b,t} + \beta_6 * use.companion.animals_{b,t} + \varepsilon_{a,b,t}$$

First difference

$$\Delta resistance_{a,b,t} = \beta_0 + \beta_1 * \Delta use.cattle_{b,t} + \beta_2 * \Delta use.sheep.goats_{b,t} + \beta_3 * \Delta use.pigs_{b,t} + \beta_4 * \Delta use.poultry_{b,t} + \beta_5 * \Delta use.fish_{b,t} + \beta_6 * \Delta use.companion.animals_{b,t} + \Delta\varepsilon_{a,b,t}$$

Where:

- β_0 is the intercept and β_{1-6} are the regression coefficients,
- Δ refers to the change in a variable between year $t-1$ and year t,
- $resistance_{a,b,t}$ is the portion of tested human isolates from pathogen a which were resistant to antibiotic b in year t,
- $use.animal_{b,t}$ is the quantity of antibiotic b used in each given animal type in year t
- μ and ν are the year and drug-pathogen fixed effects (fixed effects model only), and
- $\varepsilon_{a,b,t}$ is the error term

That is, use of antibiotic b in each animal type in year t may affect the rate of resistance of tested human isolates of pathogen a to antibiotic b in year t. Random effects, fixed effects and first difference models allow this relationship to vary among drug-pathogen pairs. A β coefficient of 1 means that an increase in ABU in a given animal type of 1 kg per year is associated with a 1 % point increase in the portion of tested human isolates which were resistant to that antibiotic class.

After this, univariate analyses were performed, regressing human ABR against ABU in each livestock species individually.

Following this, the multivariate specifications were run against ABU lagged by one year. Then, the univariate specifications were run while including a quadratic term, to explore nonlinearities.

Finally, the main univariate and multivariate specifications were run with the addition of key covariates. Namely: GDP per capita (at purchasing power parity), the population of each livestock species, and pet ownership, over time. GDP per capita was included due to the potential role of socioeconomic covariates discussed earlier (16–18). Animal populations were included because populations of each animal may also be related to each other. For example, if cow and sheep meat have a negative cross-elasticity of demand, then an increase in cow production (and therefore an increase in ABU in cows) may engender a fall in the population of (and therefore ABU in) sheep, while simultaneously resulting in an increase in human ABR. This could create the erroneous impression that the fall in ABU in sheep caused a rise in human ABR, creating the appearance of a negative relationship between sheep ABU and human ABR.

Data on GDP per capita (PPP) was sourced from World Bank Open Data (33), and data on animal populations came from Statistics Denmark (34).

3. Results

3.1. Summary statistics

The (combined DanMap - VetStat) dataset had 62 different drug-pathogen combinations across 7 bacterial species and 11 antibiotic classes. Data on ABR covered 2010–2021 and data on ABU covered 2010–2020 (11 years). Seven ABU and ABR variables were used in this investigation (ABR in humans, and ABU in 6 different animal types). Across 7 variables, 7 pathogen types, 11 antibiotic classes, and 11 years, a complete dataset would have 5929 observations across 847 year-drug-pathogen combinations.

The dataset contained:

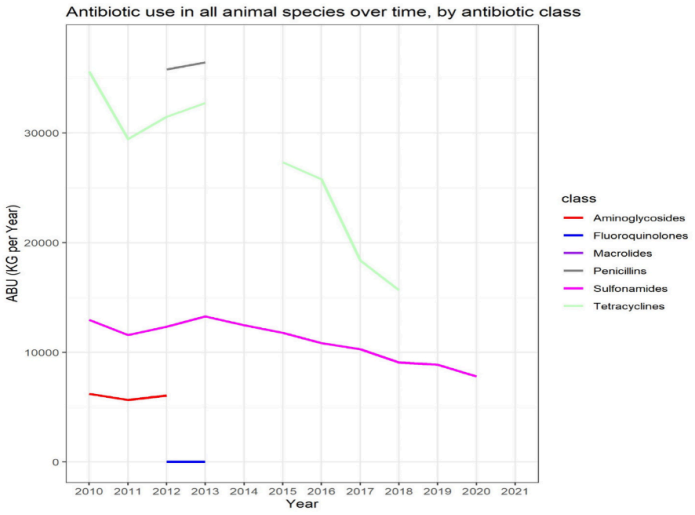

Fig. 1. - Antibiotic use (kg per year) in all animal types over time, by antibiotic class.

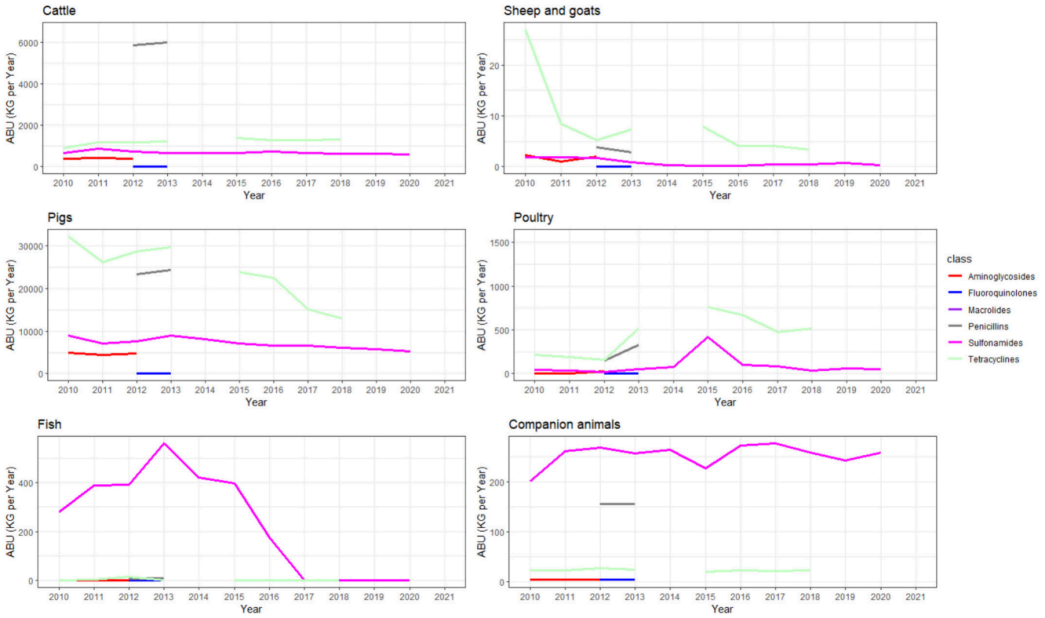

Fig. 2. - Antibiotic use (kg per year) over time in each livestock species, by antibiotic class.

- 893 non-NA observations (15.1% completeness)
- 149 year-drug-pathogen combinations with data on human ABR (17.6% completeness)
- 124 year-drug-pathogen with data on animal ABU (14.6% completeness)
- 48 year-drug-pathogens with data on both human ABR and animal ABU (5.7% completeness)

Thus, while a complete dataset would have had a very large number of datapoints, missingness greatly reduced this study's statistical power. Further, the very low overlap between year-drug-pathogen

(a version of the figure with the full legend is available in Appendix 4)

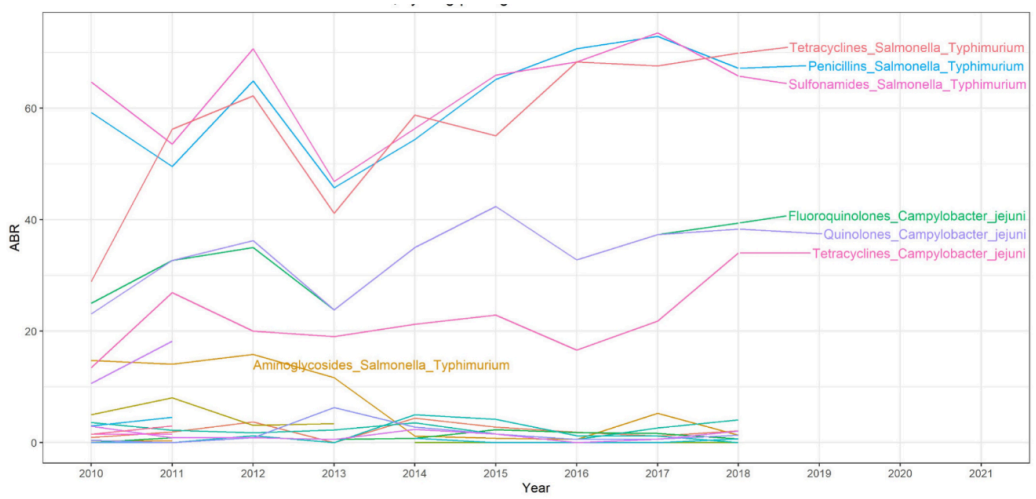

Fig. 3. - Rate of ABR in humans over time in Denmark, by drug-pathogen combination.
(a version of the figure with the full legend is available in Appendix 4)

combinations with data on human ABR and animal ABU meant that the dataset effectively had only 48 observations, creating statistical power issues especially when (year and drug-pathogen) fixed effects or covariates are introduced. Significant results were nevertheless obtained in certain specifications, and the inclusion of different models (fixed effects, random effects, first difference, and POLS) helped to discern relationships.

As can be seen from the summary statistics (Fig. 1), total use of sulfonamides in animals has fallen slowly and consistently over the study period, and use of tetracyclines has fallen considerably. The latter is largely driven by use in pigs (which comprises the bulk of tetracycline use), in which there was a sharp decline from 2015 to 2018, although declines also occurred in poultry and sheep and goats during that time (Fig. 2). There have also been noticeable falls in the use of sulfonamides in fish from 2013 to 2017, and in the use of tetracyclines in sheep and goats from 2010 to 2012 (Fig. 2). By contrast, use of tetracyclines in poultry rose from 2012 to 2015, and use of sulfonamides in poultry spiked in 2015 (Fig. 2). Note that the total quantity of antibiotics used varied considerably by animal type. Pigs accounted for the most by far (78% of all use recorded in the dataset), followed by cattle (7.3%), then poultry (1.4%), then companion animals (0.60%) and fish (0.49%), with sheep and goats (0.022%) accounting for the least total ABU.

The rate of ABR in humans has remained relatively consistent during the study period (Fig. 3), and has risen for some of the drug-pathogen pairs with the highest observed rate of resistance, with resistance of *C. jejuni* and *S. typhimurium* to certain key antibiotics being considerably higher than resistance in other drug-pathogen combinations. In particular, resistance to tetracyclines nearly doubled in these pathogens from 2010 to 2018.

3.2. Multivariate specifications

A Durbin-Wu-Hausman test (32) was run to determine whether random effects should be used. It failed to reject the null hypothesis, indicating that the random effects model was more efficient and no less consistent than fixed effects, and so both fixed and random effects models were included.

After running the multivariate specifications (Table 1), ABU in cattle was positively associated with ABR in humans in the random effects and first difference specifications. ABU in poultry was positively associated with human ABR in the POLS regression. ABU in fish was negatively associated with human ABR in the random effects and first difference specifications, and ABU in companion animals was strongly positively associated with human ABR in the POLS specification only. All of the specifications were jointly significant, except for the fixed effects regression (as measured by the F-statistic). Of the three significant specifications, the adjusted R^2 ranged between 0.188 and 0.443. ABU in pigs was not associated with ABR in humans in any model.

3.3. Univariate specifications

After running the univariate specifications (Table 2), ABU in cattle was positively associated with human ABR in the random effects, first difference, and POLS regressions (Table 2.1). ABU in sheep and goats was negatively associated with human ABR in the fixed effects, random effects and first difference specifications (Table 2.2). ABU in pigs was negatively associated with human ABR in the random effects and first difference specifications (Table 2.3). ABU in poultry was positively associated with human ABR in the random effects and POLS specifications (Table 2.4). ABU in fish was negatively associated with human ABR in the random effects specification, but positively associated with human ABR in the POLS specification (Table 2.5). Finally, ABU in companion animals was positively associated with human ABR in the random effects and POLS specifications.

3.4. Lagged independent variable

When lagging animal ABU by one year (Table 3), ABU in cattle remained positively associated with ABR in humans in the random effects and first difference specifications, with the effect size remaining similar to the same-period model. ABU in poultry remained positively associated with human ABR in the POLS regression, with the effect size

Table 1
- Multivariate specifications.

	Rate of resistance in human infections			
	panel			*OLS*
	linear			
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
Antibiotic use in cattle	0.014	0.009**	0.036*	0.0001
	(0.019)	(0.004)	(0.020)	(0.003)
Antibiotic use in sheep and goats	−0.528	−0.381	−0.160	−0.711
	(0.505)	(0.311)	(0.441)	(0.776)
Antibiotic use in pigs	−0.0003	−0.001	−0.001	0.0003
	(0.001)	(0.0003)	(0.001)	(0.001)
Antibiotic use in poultry	−0.004	0.002	−0.010	0.039**
	(0.023)	(0.008)	(0.018)	(0.017)
Antibiotic use in fish	−0.016	−0.027**	−0.055*	−0.047
	(0.017)	(0.013)	(0.028)	(0.034)
Antibiotic use in companion animals	−0.013	0.067	−0.118	0.205***
	(0.137)	(0.056)	(0.138)	(0.052)
Constant		15.753**	−0.562	9.769*
		(7.259)	(2.237)	(5.543)
N	48	48	35	48
R^2	0.267	0.377	0.332	0.514
Adjusted R^2	−0.640	0.286	0.188	0.443
Residual Std. Error				19.863 (df = 41)
F Statistic	1.275 (df = 6; 21)	29.574***	2.316* (df = 6; 28)	7.220*** (df = 6; 41)

Notes:
***Significant at the 1% level.
**Significant at the 5% level.
*Significant at the 10% level.

falling. ABU in fish was no longer associated with human ABR; and ABU in companion animals remained positively associated with human ABR in the POLS specification, with the effect size remaining similar. ABU in pigs remained without an association.

3.5. Additional specifications

After this, the univariate specifications were rerun with the addition of a quadratic term. However, no consistent trends were identified (Appendix 2).

Finally, the main univariate and multivariate specifications were rerun with the addition of key covariates (GDP per capita at purchasing power parity and animal populations). For the multivariate specification, populations of all animal types were included, while for the univariate specifications only the population of only one animal type at a time was included. With the addition of these covariates, the multivariate models could not be estimated due to a lack of data.

For the univariate models, covariates had to be excluded in some cases due to multicollinearity or a lack of data (especially for fish, where data on fisheries production was only available since 2017) (Appendix 3). Animal populations were never significantly related to human ABR. GDP per capita (PPP) was positively related to human ABR in some specifications, although this may simply be due to the fact that Denmark's per-person income has consistently increased during the study period, with human ABR rising somewhat as well.

Controlling for animal population and GDP per capita (PPP), ABU in companion animals remained positively related to human ABR in the random effects and POLS models, and ABU in cattle was positively related to human ABR in the POLS model (Appendix 3).

4. Discussion

4.1. Findings and interpretation

Across the univariate and multivariate specifications, there was evidence that ABU in cattle, poultry and companion animals was positively associated with human ABR. The evidence for cattle was the most consistent, and the effect size was greatest for companion animals. The effect size varied greatly between animal types, although this may be simply due to great differences in the volume of antibiotics used in each animal type.

ABU in sheep and goats, as well as in pigs, was negatively associated with human ABR in some univariate specifications but not in the multivariate specifications. ABU in fish was negatively associated with human ABR in some multivariate specifications, and had an indeterminate relationship to human ABR in the univariate specifications. However, ABU in fish comprised such a small component of total ABU that this result cannot be used to infer causality. This may instead be due to a fall in the use of sulfonamides in fish during the study period concurrent with stable or increasing overall levels of ABR in humans driven by other factors.

When lagging antibiotic use by one year, the effects identified in the same-period models remained similar for animals with longer life-cycles (companion animals and cattle). For animals with shorter life cycles the effect either fell in size (poultry) or was no longer significant (fish). No consistent trends were identified when rerunning the univariate specifications with the addition of a quadratic term.

While the multivariate models could not be run with the inclusion of additional covariates, running the univariate models while controlling for animal populations and GDP per capita (PPP) revealed a positive relationship between human ABR and ABU in companion animals and, to a lesser extent, in cattle.

In the multivariate specifications which were jointly significant, the adjusted R^2 ranged between 0.188 and 0.443. This suggests that ABU in animal health does explain a significant portion of variation in human ABR but, despite accounting for a large proportion of systemwide ABU (and two thirds of all ABU globally (36)), is not responsible for the majority of this variation. The effect size observed varied considerably between different animal species, though this may partially reflect large differences in total production and total ABU across different animal types.

It is counterintuitive that negative relationships were observed between human ABR and ABU in some animal species. In the case of pigs, sheep and goats, this may be due to a negative cross-elasticity of demand between consumption of cattle and consumption of pork, lamb and mutton. That is to say, if production of (and therefore use of antibiotics in) pigs, sheep and goats is negatively related to production of (and therefore use of antibiotics in) cattle, then the positive relationship between ABU in cattle and human ABR may create the impression of a negative relationship between ABU in pigs, sheep and goats and ABR in humans in the univariate specifications. This would also explain why those negative relationships were not observed in the multivariate specifications.

While ABU in pigs accounted for the considerable majority of animal ABU during the study period, it was not associated with human ABR in any of the multivariate specifications. This runs counter to the hypothesis that total volume of animal ABU correlates to the rate of human ABR.

ABU in fish was negatively associated with human ABR even in the multivariate specifications. However, this may be due to the significant reduction in the use of sulfonamides in fish production during the study period (Fig. 2) concurrent with a generally stable or slightly increasing rate of human ABR (Fig. 3). ABU in fish accounted for such a small portion of total ABU that concurrent trends such as this may drive

Table 2
Univariate specifications for each animal type.

2.1. Univariate regressions (cattle)

	Rate of resistance in human infections			
	panel			*OLS*
	linear			
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
Antibiotic use in cattle	0.017	0.012***	0.029**	0.007***
	(0.011)	(0.004)	(0.013)	(0.003)
Constant		8.105	0.505	24.022***
		(8.150)	(2.005)	(4.520)
N	48	48	35	48
R^2	0.085	0.114	0.134	0.153
Adjusted R^2	−0.655	0.095	0.108	0.135
Residual Std. Error				24.747 (df = 46)
F Statistic	2.407 (df = 1; 26)	8.973***	5.120** (df = 1; 33)	8.323*** (df = 1; 46)

2.2. Univariate regressions (sheep and goats)

	Rate of resistance in human infections			
	panel			*OLS*
	linear			
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
Antibiotic use in sheep and goats	−0.776**	−0.851***	−0.706*	−0.500
	(0.285)	(0.236)	(0.358)	(0.600)
Constant		23.276***	0.831	34.167***
		(7.745)	(2.015)	(4.641)
N	48	48	35	48
R^2	0.222	0.188	0.105	0.015
Adjusted R^2	−0.407	0.170	0.078	−0.007
Residual Std. Error				26.692 (df = 46)
F Statistic	7.401** (df = 1; 26)	13.028***	3.883* (df = 1; 33)	0.693 (df = 1; 46)

2.3. Univariate regressions (pigs)

	Rate of resistance in human infections			
	panel			*OLS*
	linear			
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
Antibiotic use in pigs	−0.001	−0.001***	−0.001**	0.0004
	(0.0004)	(0.0003)	(0.001)	(0.0004)
Constant		31.196***	0.185	26.382***
		(8.501)	(2.089)	(6.240)
N	48	48	35	48
R^2	0.075	0.174	0.125	0.028
Adjusted R^2	−0.673	0.156	0.099	0.006
Residual Std. Error				26.519 (df = 46)
F Statistic	2.095 (df = 1; 26)	11.793***	4.730** (df = 1; 33)	1.306 (df = 1; 46)

2.4. Univariate regressions (poultry)

	Rate of resistance in human infections			
	panel			*OLS*
	linear			
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
Antibiotic use in poultry	0.012	0.015*	−0.003	0.036**
	(0.015)	(0.009)	(0.013)	(0.016)
Constant		18.133**	2.342	24.714***
		(7.405)	(2.027)	(4.896)

(*continued on next page*)

Table 2 (*continued*)

2.4. Univariate regressions (poultry)				
	Rate of resistance in human infections			
	panel			*OLS*
	linear			
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
N	48	48	35	48
R^2	0.025	0.015	0.001	0.100
Adjusted R^2	−0.762	−0.006	−0.029	0.081
Residual Std. Error				25.511 (df = 46)
F Statistic	0.677 (df = 1; 26)	2.917*	0.042 (df = 1; 33)	5.118** (df = 1; 46)

2.5. Univariate regressions (fish)				
	Rate of resistance in human infections			
	panel			*OLS*
	linear			
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
Antibiotic use in fish	−0.004	−0.026*	−0.045	0.050*
	(0.015)	(0.015)	(0.029)	(0.025)
Constant		21.645***	2.072	28.493***
		(7.405)	(1.922)	(4.128)
N	48	48	35	48
R^2	0.003	0.020	0.068	0.079
Adjusted R^2	−0.802	−0.001	0.040	0.059
Residual Std. Error				25.814 (df = 46)
F Statistic	0.081 (df = 1; 26)	2.962*	2.424 (df = 1; 33)	3.922* (df = 1; 46)

2.6. Univariate regressions (companion animals)				
	Rate of resistance in human infections			
	panel			*OLS*
	linear			
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
Antibiotic use in companion animals	−0.086	0.105*	−0.006	0.143***
	(0.104)	(0.061)	(0.112)	(0.032)
Constant		14.360*	2.283	20.920***
		(7.446)	(2.032)	(4.085)
N	48	48	35	48
R^2	0.026	0.007	0.0001	0.302
Adjusted R^2	−0.761	−0.015	−0.030	0.287
Residual Std. Error				22.463 (df = 46)
F Statistic	0.689 (df = 1; 26)	2.974*	0.003 (df = 1; 33)	19.931*** (df = 1; 46)

Notes:
***Significant at the 1% level.
**Significant at the 5% level.
*Significant at the 10% level.

statistical associations more than any underlying causality.

4.2. Limitations

A major limitation of this analysis was the suitability of publicly available open-access data. While considerable data on ABU and ABR were available, the overlap of years and antibiotic classes covered by the ABU and ABR datasets was limited, meaning that statistical power was similarly limited. This prevented more detailed investigations into the shape of the ABU-ABR relationship, into the role of other covariates, or on what relationships could be observed for specific antibiotic classes and specific bacterial pathogens.

The data available to the authors also did not permit human ABU to be included in the regression models. This represents an important missing variable, and could also introduce bias if there are interactions between human and animal ABU. For example, if human and animal ABR are positively associated, then any effect observed here may be partially caused by changes in human ABU.

DanMap draws from routine surveillance data across primary and secondary care, with very high coverage. However, data on human ABR focuses on key foodborne pathogens (*Campylobacter* and *Salmonella* species, and *E. coli*), and samples are drawn from a range of sources

Table 3
- Multivariate specifications (independent variables lagged by one year).

	Rate of resistance in human infections			
	panel			*OLS*
	linear			
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
Lagged antibiotic use in cattle	0.008	0.009**	0.030**	0.0001
	(0.013)	(0.004)	(0.013)	(0.003)
Lagged antibiotic use in sheep and goats	0.635	0.382	0.687	−0.278
	(0.451)	(0.367)	(0.435)	(0.737)
Lagged antibiotic use in pigs	−0.001	−0.0004	−0.0004	0.001
	(0.001)	(0.0004)	(0.001)	(0.001)
Lagged antibiotic use in poultry	0.009	0.003	−0.006	0.019**
	(0.008)	(0.006)	(0.006)	(0.009)
Lagged antibiotic use in fish	−0.006	0.007	0.018	−0.002
	(0.017)	(0.014)	(0.028)	(0.033)
Lagged antibiotic use in companion animals	0.017	0.081	0.076	0.163***
	(0.126)	(0.063)	(0.125)	(0.051)
Constant		10.012	0.684	8.974
		(7.944)	(2.144)	(5.573)
N	45	45	32	45
R^2	0.253	0.148	0.291	0.508
Adjusted R^2	−0.826	0.014	0.121	0.431
Residual Std. Error				19.217 (df = 38)
F Statistic	1.017 (df = 6; 18)	11.799*	1.714 (df = 6; 25)	6.550*** (df = 6; 38)

Notes:
***Significant at the 1% level.
**Significant at the 5% level.
*Significant at the 10% level.

including colonisation and different types of infection. The rate of resistance may therefore not be representative of the resistance rate in any given infection type, or the rate of resistance across all pathogens. While these are key zoonotic pathogens, they may also not be reflective of the total human burden of ABR, and links between animal ABU and human ABR may have been observable for other pathogens had data on those pathogens been available.

There was also relatively little change in the use of certain antibiotics in certain animals during the study period, and even where large relative changes were observed, the starting level of ABU is low compared with other country contexts. Both animal ABU and human ABR in Denmark have been closely managed since some years before this dataset begins (25,26), meaning that these changes may not greatly influence human ABR.

An important limitation with this type of investigation is the notion that, while the use of antibiotics by humans (in both humans and animals) is generally agreed to have created the ongoing ABR pandemic (8), this does not necessarily mean that reductions in ABU will result in contemporaneous reductions in ABR. Allel et al. (16) also emphasise that ABU reduction alone is unlikely to bring down the rate of ABR in human infections significantly. This 'stickiness' of ABR, especially in a context such as Denmark where rates of resistance are already relatively low and stable, means that associations between ABU and ABR may not be statistically significant, or may be obscured by factors such as negative cross-elasticity of demand among meat types. Similarly, in cases such as the use of sulfonamides in fish, large reductions in certain types of ABU combined with stable or increasing rates of human ABR can generate negative statistical associations between ABU and ABR when a causal association may not exist, particularly for animal species which account for only a small portion of total ABU.

Further, the scope of the study was limited to phenotypic resistance rather than genotypic resistance. That is, the results indicate the extent to which use of an antibiotic is related to the susceptibility of bacterial assays to antibiotics, but do not indicate how ABU is related to the presence of genes conferring resistance. This was done because the datasets used recorded phenotypic resistance, and this approach is generally taken by ecological regression studies of the determinants of ABR (14–18) (22).

Finally, while the Durbin-Wu-Hausman test suggested that random effects models were consistent, the test may have failed to reject the null hypothesis in part due to limited statistical power. If the covariates (animal ABU) were indeed determined in large part by time-invariant unobservables, then the results of the random effects models would become inconsistent.

4.3. Implications for research, policy, and practice

This study identified some evidence of animal ABU contributing to human ABR in Denmark, consistent with other ecological regression studies. Allel et al. (16) found this to be the case across a number of countries, for certain drug-pathogen combinations. Rahman and Hollis (14) found more consistent evidence of this across European countries for a range of drug-pathogen combinations.

While there was some evidence of association, animal ABU did not explain the majority of variation in human ABR and results for some livestock species were not consistently significant. This could suggest, as Adda (15) found in the United States, that while animal ABU has some influence on human ABR, and despite animal use accounting for a large portion of total ABU, it is human ABU which is the more important determinant by far. This could also suggest that, in contexts such as Denmark where ABU in animals is limited to the minimum clinically necessary amount (25,26), the link between human ABR and animal ABU may not be pronounced. Given that resistance has plateaued or even risen for some drug-pathogen combinations in Denmark (Fig. 3), this could suggest that, once ABR reaches a certain level, ABU reductions may not be sufficient to reduce ABR in the short-to-medium term. This is consistent with some trends observed in the data used in this study, such as resistance in humans remaining high despite considerable reductions in ABU. Non-ABU factors, including transmission factors and socioeconomic factors, may be more relatively influential, especially in low-ABU contexts such as Denmark. This is consistent with the findings of Zhang et al. (17) and Collignon et al. (18), who respectively identify medical staffing and socioeconomic factors as important determinants of ABR prevalence in human infections at the population level.

Data-sharing initiatives across the One Health space such as those proposed by the Quadripartite (35) will be key to future work in this area. The authors of this study were able to access nationally aggregated longitudinal data from DanMap and VetStat from open access resources. However, there were limitations to this data such as differences in antibiotic class aggregation and missing timepoints that need to be addressed for optimal analysis. Moving forward, for ecological level of associations being hypothesised for ABR and to inform antibiotic stewardship across the One Health spectrum, aggregated, non-identifiable data is vital and could be shared from both human and animal sectors whilst avoiding any confidentiality issues.

Future studies should repeat these models with more comprehensive data, when available. Given the suggestion of this study, as well as of other regression studies, that ABU reductions alone may be insufficient to bring down human ABR in the short term, future studies should investigate non-ABU covariates (socioeconomic and transmission factors) which may influence human ABR and may modulate the effect of ABU on ABR, as well as looking at longer timeframes as more data become available.

5. Conclusions

This study used ecological regression to investigate the relationship between animal ABU and human ABR in Denmark. There was evidence of a positive relationship between ABU in cattle, poultry and companion animals and ABR in humans. A negative relationship between ABU in pigs, sheep and goats and ABR in humans was identified in the univariate specifications, but was not present in the multivariate specifications and may have been due to confounding factors. For animals with longer life cycles, lagged ABU remained related to human ABR. These findings support the idea that animal ABU influences human ABR, but do not indicate that it is the main determinant of human ABR in Denmark. Especially in contexts such as Denmark with extensive antibiotic stewardship and antibiotic use controls, this suggests that ABU reduction alone may not be sufficient to bring down ABR rates, and that transmission-related and socioeconomic factors may play an important role in future research and policy on One Health ABR.

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Institutional review board statement

The study used only anonymised publicly available data, the sources for which were cited in the study, and as such ethical approval was not required.

Informed consent statement

The study used only anonymised publicly available data, and no human or animal subjects were recruited for the study.

CRediT authorship contribution statement

Eve Emes: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Dagim Belay:** Data curation, Funding acquisition, Methodology, Writing – review & editing. **Gwenan M. Knight:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare no conflicts of interest.

Data availability

The data used in the study are publicly available and are cited in the manuscript.

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Appendix A. Appendix

Appendix 1
- classification of antibiotics in this study.

Listed in human resistance dataset	Unified class	Listed in animal use dataset	Unified class
Amikacin	Aminoglycosides	Aminoglycosides	Aminoglycosides
Amoxicillin/Clavulanic acid	Penicillins	Amphenicols	Other
Ampicillin	Penicillins	Cephalosporins	Cephalosporins
Apramycin	Aminoglycosides	Fluoroquinolones	Fluoroquinolones
Azithromycin	Macrolides	Lincosamides	Lincosamides
Cefotaxime	Cephalosporins	Macrolides	Macrolides
Ceftazidime	Cephalosporins	Other	Other
Ceftiofur	Cephalosporins	Penicillins (ext.)	Penicillins
Chloramphenicol	Other	Penicillins (sim.)	Penicillins
Ciprofloxacin	Fluoroquinolones	Quinolones	Quinolones
Colistin	Polymyxins	Sulfonamides/Trimethoprim	Sulfonamides
Ertapenem	Carbapenems	Tetracyclines	Tetracyclines
Erythromycin	Macrolides	Tiamulines	Other
Florfenicol	Amphenicols		
Gentamicin	Aminoglycosides		
Meropenem	Carbapenems		
Nalidixic acid	Quinolones		
Neomycin	Aminoglycosides		
Spectinomycin	Aminoglycosides		
Streptomycin	Aminoglycosides		
Sulfonamide	Sulfonamide		
Tetracycline	Tetracycline		
Tigecycline	Others		
Trimethoprim	Others		

Appendix 2
- Quadratic specifications.

	Rate of resistance in human infections			
	panel			*OLS*
	linear			
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
Antibiotic use in cattle	0.027	0.020*	0.020	0.026**
	(0.021)	(0.011)	(0.022)	(0.010)
I(abu_cattle2)	−0.00000	−0.00000	0.00000	−0.00000*
	(0.00000)	(0.00000)	(0.00000)	(0.00000)
Constant		4.715	0.639	13.108*
		(9.616)	(2.046)	(7.146)
N	48	48	35	48
R^2	0.098	0.121	0.141	0.218
Adjusted R^2	−0.695	0.082	0.087	0.184
Residual Std. Error				24.039 (df = 45)
F Statistic	1.362 (df = 2; 25)	9.292***	2.629* (df = 2; 32)	6.284*** (df = 2; 45)

	Rate of resistance in human infections			
	panel			*OLS*
	linear			
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
Antibiotic use in sheep and goats	−0.692	−2.341*	−0.415	1.646
	(1.877)	(1.339)	(2.105)	(2.040)
I(abu_sheep_and_goats2)	−0.002	0.047	−0.008	−0.082
	(0.055)	(0.042)	(0.060)	(0.075)
Constant		26.182***	0.910	29.843***
		(8.294)	(2.122)	(6.073)
N	48	48	35	48
R^2	0.222	0.215	0.106	0.041
Adjusted R^2	−0.463	0.181	0.050	−0.002
Residual Std. Error				26.631 (df = 45)
F Statistic	3.559** (df = 2; 25)	14.552***	1.894 (df = 2; 32)	0.954 (df = 2; 45)

	Rate of resistance in human infections		
	panel		*OLS*
	linear		
	Fixed effects	First difference	Pooled OLS
	(1)	(2)	(3)
Antibiotic use in pigs	0.002	0.001	0.004***
	(0.002)	(0.003)	(0.001)
I(abu_pigs2)	−0.00000	−0.00000	−0.00000***
	(0.00000)	(0.00000)	(0.00000)
Constant		0.625	9.970
		(2.142)	(8.344)
N	48	35	48
R^2	0.115	0.149	0.168
Adjusted R^2	−0.664	0.096	0.131
Residual Std. Error			24.805 (df = 45)
F Statistic	1.621 (df = 2; 25)	2.811* (df = 2; 32)	4.533** (df = 2; 45)

	Rate of resistance in human infections			
	panel			*OLS*
	linear			
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
Antibiotic use in poultry	0.016	0.025	−0.053	0.091
	(0.035)	(0.034)	(0.036)	(0.056)
I(abu_poultry2)	−0.00000	−0.00001	0.0001	−0.0001
	(0.00004)	(0.00004)	(0.00004)	(0.0001)

(*continued on next page*)

Appendix 2 (*continued*)

	Rate of resistance in human infections			
	panel			*OLS*
	linear			
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
Constant		17.391**	2.479	21.539***
		(7.982)	(1.992)	(5.760)
N	48	48	35	48
R^2	0.026	0.017	0.067	0.121
Adjusted R^2	−0.831	−0.026	0.008	0.082
Residual Std. Error				25.486 (df = 45)
F Statistic	0.331 (df = 2; 25)	2.936	1.143 (df = 2; 32)	3.108* (df = 2; 45)

	Rate of resistance in human infections			
	panel			*OLS*
	linear			
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
Antibiotic use in fish	0.071	0.035	0.068	0.128
	(0.048)	(0.048)	(0.069)	(0.106)
I(abu_fish2)	−0.0001	−0.0001	−0.0002*	−0.0002
	(0.0001)	(0.0001)	(0.0001)	(0.0002)
Constant		20.804***	2.512	27.913***
		(7.400)	(1.875)	(4.215)
N	48	48	35	48
R^2	0.102	0.052	0.155	0.090
Adjusted R^2	−0.688	0.010	0.102	0.050
Residual Std. Error				25.931 (df = 45)
F Statistic	1.424 (df = 2; 25)	4.804*	2.934* (df = 2; 32)	2.238 (df = 2; 45)

	Rate of resistance in human infections			
	panel			*OLS*
	linear			
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
Antibiotic use in companion animals	0.263	0.276	0.746	0.476**
	(0.911)	(0.178)	(1.029)	(0.184)
I(abu_companion_animals2)	−0.001	−0.001	−0.002	−0.001*
	(0.002)	(0.001)	(0.002)	(0.001)
Constant		10.697	2.127	15.763***
		(8.255)	(2.058)	(4.877)
N	48	48	35	48
R^2	0.032	0.019	0.017	0.351
Adjusted R^2	−0.821	−0.024	−0.045	0.322
Residual Std. Error				21.908 (df = 45)
F Statistic	0.408 (df = 2; 25)	4.025	0.272 (df = 2; 32)	12.156*** (df = 2; 45)

Notes: .
***Significant at the 1% level.
**Significant at the 5% level.
*Significant at the 10% level.

Appendix 3
- Specifications with additional covariates.

	Rate of resistance in human infections			
	panel			*OLS*
	linear			
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
Antibiotic use in cattle	−0.001	0.007***	0.002	0.007**
	(0.029)	(0.002)	(0.002)	(0.002)
Cattle population				0.00002
				(0.0002)
GDP per capita, PPP		0.002***		0.002**
		(0.001)		(0.001)
Constant		−67.061**	3.577	−106.690
		(34.165)	(5.595)	(296.557)
N	48	48	39	48
R^2	0.00005	0.270	0.022	0.271
Adjusted R^2	−0.424	0.238	−0.005	0.221
Residual Std. Error				23.484 (df = 44)
F Statistic	0.001 (df = 1; 33)	16.667***	0.814 (df = 1; 37)	5.441*** (df = 3; 44)

	Rate of resistance in human infections			
	panel			*OLS*
	linear			
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
Antibiotic use in sheep and goats	−0.382	−0.026	−0.856	−0.026
	(0.828)	(0.611)	(1.254)	(0.611)
Sheep population		−0.00005		−0.00005
		(0.001)		(0.001)
GDP per capita, PPP		0.002**		0.002**
		(0.001)		(0.001)
Constant		−62.394	5.319	−62.394
		(122.152)	(5.943)	(122.152)
N	48	48	39	48
R^2	0.006	0.149	0.012	0.149
Adjusted R^2	−0.415	0.091	−0.014	0.091
Residual Std. Error				25.368 (df = 44)
F Statistic	0.212 (df = 1; 33)	7.693*	0.465 (df = 1; 37)	2.564* (df = 3; 44)

	Rate of resistance in human infections			
	panel			*OLS*
	linear			
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
Antibiotic use in pigs	−0.0001	0.001	−0.0001	0.001
	(0.001)	(0.0003)	(0.001)	(0.0003)
Pig population				−0.00001
				(0.00001)
GDP per capita, PPP		0.002***		0.002**
		(0.001)		(0.001)
Constant		−84.444**	4.447	66.663
		(36.916)	(6.009)	(157.153)
N	48	48	39	48
R^2	0.0003	0.193	0.001	0.211
Adjusted R^2	−0.424	0.157	−0.026	0.157
Residual Std. Error				24.428 (df = 44)
F Statistic	0.009 (df = 1; 33)	10.776***	0.052 (df = 1; 37)	3.916** (df = 3; 44)

	Rate of resistance in human infections	
	panel	*OLS*
	linear	

(*continued on next page*)

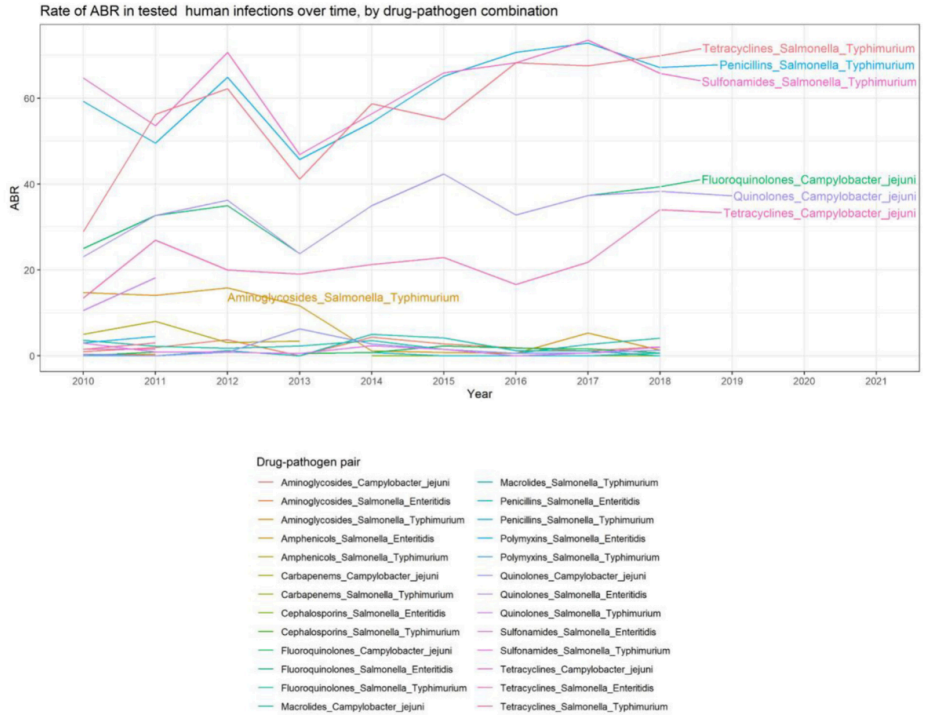
Appendix 3 (*continued*)

	Rate of resistance in human infections			
	panel			*OLS*
	linear			
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
Antibiotic use in poultry	−0.016	0.034**	−0.019	0.017
	(0.039)	(0.016)	(0.026)	(0.017)
Chicken population		−0.00000		−0.00000
		(0.00000)		(0.00000)
GDP per capita, PPP				0.002**
				(0.001)
Constant		29.105***	5.398	−62.130
		(10.290)	(5.925)	(38.891)
N	48	48	39	48
R^2	0.005	0.117	0.014	0.210
Adjusted R^2	−0.417	0.078	−0.012	0.156
Residual Std. Error				24.439 (df = 44)
F Statistic	0.161 (df = 1; 33)	4.553	0.543 (df = 1; 37)	3.900** (df = 3; 44)

	Rate of resistance in human infections			
	panel			*OLS*
	linear			
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
Antibiotic use in fish	−187.655	0.064***	0.624	1.104
	(597.449)	(0.023)	(0.942)	(0.963)
Fisheries production				0.003
				(0.004)
GDP per capita, PPP		0.003***		
		(0.001)		
Constant		−92.557***	9.924	−64.850
		(34.911)	(15.235)	(138.440)
N	9	48	7	9
R^2	0.032	0.275	0.081	0.214
Adjusted R^2	−1.582	0.242	−0.103	−0.049
Residual Std. Error				26.789 (df = 6)
F Statistic	0.099 (df = 1; 3)	17.033***	0.438 (df = 1; 5)	0.814 (df = 2; 6)

	Rate of resistance in human infections			
	panel			*OLS*
	linear			
	Fixed effects	Random effects	First difference	Pooled OLS
	(1)	(2)	(3)	(4)
Antibiotic use in companion animals	0.225	0.156***	0.165***	0.156***
	(0.304)	(0.039)	(0.042)	(0.039)
Pet ownership		−214.733		−214.733
		(257.027)		(257.027)
GDP per capita, PPP		0.004		0.004
		(0.003)		(0.003)
Constant		−72.676*	7.437	−72.676*
		(38.268)	(5.690)	(38.268)
N	31	31	25	31
R^2	0.028	0.497	0.403	0.497
Adjusted R^2	−0.535	0.441	0.377	0.441
Residual Std. Error				21.447 (df = 27)
F Statistic	0.545 (df = 1; 19)	26.662***	15.513*** (df = 1; 23)	8.887*** (df = 3; 27)

Notes
***Significant at the 1% level.
**Significant at the 5% level.
*Significant at the 10% level.



Appendix 4. - Fig. 3 with full legend.

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2.3.3 Implications

In the Denmark analysis, I identified a positive relationship between human AMR and AMU in cattle, with some evidence of a relationship to AMU in poultry and companion animals. This is perhaps surprising, given that the majority of animal AMU in Denmark is concentrated in pig production, suggesting that the causal relationship was not well reflected by this specification. Animal AMU was never a major determinant of human AMR, with R^2 values ranging from 0.19 to 0.44. Exploration of additional covariates was limited by the statistical power of the dataset.

This result runs contrary to the prevailing assumption that reducing animal AMU should significantly reduce the human health burden of AMR (theme 3), but becomes less surprising when looking at the wider literature. It lends credibility to suggestions that animal AMU may be important for the emergence of resistant strains that spread into human populations, but becomes less important once those strains have become widespread(17,114,126). It may also support suggestions that resistant strains have species-specific adaptations, and that pathogens of animal origin may not spread as successfully among human populations(17,126). Or, it may reflect the idea that transmission and selection pathways between OH sectors are complex and poorly understood(17,70,74,75,109,110), and that it may take a long time for changes in animal AMU to significantly affect human health(70). It also lines up with observations that, in many countries, animal AMU has fallen significantly without concurrent falls in human AMR, especially for *Campylobacter*(70,112,113,147). As reviewed in Chapter 1, many statistical modelling studies have found that, even where a link between human AMR and human AMU can be identified clearly, the link to animal AMU is less obvious(111,123). Mathematical modelling has supported this idea, with studies often suggesting that reducing animal AMU alone may not have a significant impact on human AMR, and that targeting transmission (animal-human and human-human) may be more impactful(72,121).

While I encountered limitations with the dataset, the fact that I did not find a consistent link to animal AMU (even when leveraging one of the strongest AMR surveillance infrastructures in the world) is likely indicative of more than a simple lack of statistical power. To me, this is evidence that the presumed relationship between animal AMU and human AMR is not as straightforward as often assumed, and highlights that combating AMR will likely have to go beyond simply reducing AMU, both in animals and in humans.

2.3.4 Applications

In the SEFASI knowledge hub survey in 2023, I asked stakeholders for their thoughts on these findings, in particular asking for their thoughts on the weak link observed between animal AMU and human AMR and on ‘threshold effects’, the idea that the relationship between AMU and AMR may break down once resistant strains become widespread.

Generally, stakeholders felt that some ‘stickiness’ of resistance was believable, and that we may observe threshold effects once resistance has become widespread. They emphasised that this would likely depend on the drug-pathogen combination, and on the fitness cost of resistance, but generally felt that reductions in selective pressure would still reduce AMR over the long term, even if that effect was not observable in the short run. They also noted

that the presence of multidrug resistance (MDR) and accumulation of resistance may mean that resistance to a given drug remains prevalent even when use of that particular drug falls.

In terms of the weak ecological link observed, stakeholders were not generally surprised. They emphasised that animal AMU is likely more important for the initial emergence of resistance and less relevant to subsequent changes. They also emphasised that, while the animal AMU - human AMR link does exist, it is complex and indirect, and that existing studies (including these two) are not designed well enough to be able to characterise and detect it, especially with the very limited data available to us.

In addition to the aforementioned work aiming to combine farm-level survey data and ecological surveillance data to parameterise AHHME to Senegal, I am also working with other SEFASI consortium members to approach the ecological relationship question using mathematical modelling. Led by Dr. Gwen Knight, we are using a modified version of the model proposed by Booton and colleagues and applied to Thailand(121). Parameterising the model to point prevalence data from the three OH compartments in England, Senegal and Denmark, we aim to model the contribution to human AMR of AMU and transmission across sectors. Although this paper has yet to be published, initial results suggest that, for all three countries, changes to animal AMU alone have little impact on human AMR, in line with the results of this ecological regression study. Rather, targeting human AMU, human-human transmission, and animal-human transmission, appear to be more impactful.

2.3.5 Limitations

The most immediately apparent limitation faced with this study (and with the withdrawn UK paper) was with the data available, and my choice of specifications was generally made in response to this. For one, antibiotics were classified differently in different (animal vs. human) datasets, sometimes categorised at the class level and sometimes at the level of the specific drug. These data, even though publicly available, were not coordinated and presented in a way which lent itself to cross-sectoral ecological analysis.

Getting data from (*de facto*) silos was also difficult. In the UK, I was given annual data on poultry ABU, even though human data were available quarterly, and I had to limit the statistical power of the specifications because of that bottleneck. Stakeholders in both countries were often reluctant to give data, even when those data were theoretically open access: I was able to access them due to having connections at the UKHSA, VETSTAT, and the BPC, but was still not able to get access to the DanMap dataset that I wanted to use. While UKHSA data are collected at the member nation (England, Scotland, Wales, N. Ireland) level, the BPC could only give aggregate data from the UK in order to protect the anonymity of individual large producers, there was a mismatch in the datasets used.

In both cases, a complete dataset would have had a very large number of datapoints and would have permitted a high level of statistical power. However, there were many NA observations, and there was limited overlap in drug-pathogen combinations between the human and animal datasets, in addition to differences in the way antibiotics were classified. This means that the final number of timepoints with data on both human AMR and animal AMU for a given drug-pathogen combination was very low (only 5.7% completeness for Denmark). In the UK, this statistical power meant that I had to use pooled ordinary least

squares (POLS) regression, which does not allow for the AMU-AMR relationship to vary among drug-pathogen combinations and was not appropriate for the data, and in Denmark I was not able to include additional covariates in the way I would have liked.

Aside from obvious data limitations, there are general limitations to the approach that I used here. Looking at the contemporaneous relationship between use and resistance for given drug-pathogen combinations may in fact be a case of asking the wrong questions. For one, human health stakeholders at SEFASI knowledge hub workshops emphasised that reducing the portion of human infections which are resistant is not their priority - rather, it is preventing the emergence of new resistant strains and reducing the overall number of infections(144), neither of which is captured in this type of analysis. As reflected both in Chapter 1 and in stakeholder consultations, the process of transmission of resistance between compartments may happen over a longer timeframe than captured here, may occur largely in 'black swan' emergence events, is poorly understood and complex; and is complicated by endemicity thresholds, MDR, and accumulation of resistance. Essentially, the process by which resistance emerges and is transferred between sectors is not well understood and is unlikely to be captured accurately by this type of analysis.

This gives unsatisfying implications for attempting to quantify the ecological relationship between animal AMU and human AMR. To facilitate health-economic analysis to help design and select stewardship policies, we need to know the number of resistant infections averted by a given change in AMU. While I had initially hoped that ecological regression could help to quantify this link, the results of this study do not support that. It is possible that, with access to more extensive and purpose-built data over longer periods of time, these methods could give more insight. For this reason, we plan to apply for funding for a three-year study based in Senegal where we would collect human and animal data simultaneously with the aim of facilitating this kind of analysis. By exploring these questions with better data, ideas like threshold effects and endemicity could be investigated further.

2.3.6 Where does this leave us?

In paper 1, I created a model for estimating the holistic OH health-economic impact of AMR (and AMR interventions) in agriculture. In order to use that model, we need better knowledge of a) the role of AMU and other interventions on farm-level outcomes and b) the ecological relationship between animal AMU and human AMR. In the AMUSE papers, I have gained some insight into the importance of AMU to smallholder livestock farms, and on complementary interventions which can facilitate better stewardship and render reductions in AMU safer and more acceptable for farmers.

I have investigated the ecological relationship between animal AMU and human AMR as well, using regression models. While limited by statistical power, the lack of a strong relationship suggests that using surveillance data to investigate the real-time relationship between animal AMU and human AMR may not be able to capture the complex and poorly-understood process of transmission of resistance between species. At the very least, the results of this paper suggest that reducing animal AMU alone may have little impact on human AMR in the short term. This highlights the importance of alternative methods such as mathematical modelling, and of interventions targeting non-AMU factors such as transmission and socioeconomic welfare.

Chapter 3 - discussion and conclusions

3.1 Overview of the portfolio

AMR is a global problem of growing importance to human, animal, and planetary health. The use of antibiotics in agriculture is a key policy concern, and understanding the role of agricultural antibiotic stewardship is key to designing sustainable OH policy. Throughout this portfolio, I have identified three key assumptions from the discourse on AMR and agriculture. Namely:

1) The tendency to view AMR as primarily a human health concern, and to apply a human health perspective to health-economic evaluations of AMR and related interventions
2) The notion that 'nontherapeutic' AMU in FPAs, particularly in the Global South, is inappropriate and unnecessary
3) The notion that reducing AMU in FPAs is an effective way to bring the human health burden of resistance down to desired levels

In this commentary, I have reviewed the state of our knowledge on those three areas. Namely; on the existing health-economic methods in the AMR field, on the role of AMU and complementary interventions on farm-level outcomes, and on the ecological relationship between animal AMU and human AMR.

Throughout the body of work that I have presented here, I have endeavoured to challenge these assumptions and to begin to bridge these key knowledge gaps, with the ultimate aim of informing holistic OH policy decision-making in the field of agriculture and AMR.

In response to the first assumption, this involved the development of a comprehensive health-economic model, AHHME, which can be used for holistic OH health-economic analysis of interventions in agricultural AMR and beyond.

In response to the second assumption, this involved analysing farm-level survey data from three countries (Senegal, Uganda, and Burkina Faso), to investigate the effect of (nontherapeutic and total) AMU and potential complementary interventions on animal health and productivity, as well as factors which were associated with stronger AMS.

In response to the third question, this involved running regression models on AMR surveillance data from Denmark to quantify the ecological relationship between animal AMU and human AMR.

In this section, I return to these three assumptions, discuss what I am now able to conclude about them after having presented these works, and touch briefly on the value of the research that I have presented here, before reflecting more broadly on the implications of my findings for policy and research.

3.2 Returning to our three assumptions

3.2.1 How should we approach health-economic evaluation of AMR and agriculture?

After creating the AHHME model, and applying it to representative data from settings of different income levels, I have shown that healthcare costs and QALYs (the two components of traditional cost-utility analysis) capture only one part of the societal impact of AMR and AMR interventions. Across scenarios, the effect on agricultural productivity and (paid and unpaid) labour productivity was often at least as significant, notwithstanding factors such as food security which were not included in the model. I have laid out, and demonstrated, a comprehensive framework for capturing these broader societal effects, which also captures the distributional effects of interventions. I have also shown that methodological parameters such as WTP thresholds and discount rates can greatly affect the results of such models, and that relying on rules of thumb to generate these parameters can be dangerous.

That being said, the greater complexity of AHHME (relative to most health-economic methods used in the AMR space) also results in greater uncertainty. This is not a drawback inherent to AHHME, but is a natural consequence of building more complex models to reflect the complexity of OH AMR itself. Applying the AHMHE framework to real-world interventions also requires knowledge of two key relationships (the effect of stewardship interventions on farm-level outcomes, and the ecological relationship between AMU and AMR) of which we have limited knowledge.

Thus, AHHME is not a silver bullet which can give precise answers to AMR policy questions. However, it more honestly and holistically reflects the complexity of the OH AMR system than existing healthcare perspective models, and should be used in concert with mixed-methods approaches to policy design, including stakeholder consultation and consideration of political economy. This is not a bad thing, given that AMR policy (and health policy generally) exists in a social and political context and should not be treated as a purely technocratic issue where modelling outputs can be taken at face value. As an aide in this kind of holistic process, AHHME therefore provides guiding outputs which cannot be produced by other presently available tools.

3.2.2 Is nontherapeutic antibiotic use in livestock unnecessary and irrational?

Through the three AMUSE papers I have shown that, in certain settings and livestock production types, nontherapeutic antibiotic use may be beneficial for animal health and productivity. Returning to different conceptualisations of irrationality, this suggests that, even if medically irrational, such use is not economically irrational. Simply eliminating it may carry a risk to food security, animal health, and farmers' economic security.

I have also highlighted the potential for combined intervention packages where reductions in nontherapeutic antibiotic use are paired with: awareness-raising, involving animal health professionals in stewardship initiatives, improved access to animal vaccination, and support for biosecurity improvements. This approach could encourage and facilitate better agricultural antibiotic stewardship while safeguarding animal health and productivity.

These results should be taken as preliminary, and reflect three very specific geographical contexts. They cannot tell us for certain that nontherapeutic AMU is important to every livestock production system (results varied even among these studies), and do not suggest a

universally applicable intervention package to safely improve on-farm stewardship. However, they provide important findings which challenge the idea that non-curative AMU is irrational and unnecessary, and outline potential interventions which could be incorporated into future stewardship efforts.

3.2.3 Can we expect reductions in animal AMU to produce reductions in human AMR?

Through the ecological regression analysis in Denmark, I have found some evidence of a relationship between human AMR and animal AMU at the ecological level. However, in line with some other studies, this relationship was fairly tenuous and did not explain a large portion of changes in human AMR in the short term.

I had hoped to demonstrate the value of ecological regression as a tool to be applied across settings, to quantify the shape and size of this relationship in a way which can be used to estimate the human health impact of stewardship policies and feed into frameworks like AHHME. The results of this study are, I maintain, more useful than simply assuming a unit elasticity of resistance with respect to systemwide AMU as some studies have done (e.g. the influential 2018 OECD report(13)). However, my results are not sufficiently strong that they could be used in the way that I had hoped.

This will in part be due to data limitations, but also likely reflects that the ecological relationship between animal AMU and human AMR is not satisfactorily captured by comparing those two variables contemporaneously. It also suggests that simply reducing animal AMU is unlikely to be sufficient to reduce human AMR, especially in the short term (theme 3). This highlights the need for continued focus on infection prevention and control, socioeconomic determinants of health, complementary and alternative therapies, and safeguarding new antimicrobials.

3.3 Future research and final reflections

There are several directions for future research that myself and my partners at the SEFASI consortium are already planning to take. I am continuing to work with partners at the JPIAMR SNAP-ONE consortium to apply the AHHME-B model to Zambia and Malawi, aiming to use it to estimate the holistic health-economic burden of AMR in those two countries. Led by Dr. Gwen Knight, we are also working on a study that will use mathematical modelling to estimate the effect of AMU and transmission interventions (across the OH compartments) on human AMR. Building on the system dynamics model(53) developed by Dr. Joshua Aboah following stakeholder consultation at our knowledge hub workshop in Dakar, we are hoping to parameterise that model to real-world data to estimate the effect of stewardship interventions in poultry production, building on the findings of my AMUSE papers.

Led by Drs. Derek Chan and Michel Dione, we are also working to parameterise the AHHME model to Senegal, using the results of the AMUSE papers, the ongoing mathematical modelling work, and potential future ecological regression studies using hospital sentinel surveillance data and antibiotic import data. This will eventually be used to simulate prospective agricultural AMS intervention packages, to estimate their holistic health-economic impact, and to help select optimal interventions as part of the ongoing NAP

on AMR. We are also working with a partner in Cameroon, hoping to use existing and upcoming datasets to perform similar analyses.

We are also planning to apply for funding for a long-term study, based in Senegal, which will involve data collection on AMU and AMR from across the three OH compartments, as well as farm-level trials of stewardship intervention packages. This will learn from the difficulties encountered in the works that I have presented here, and will allow us to collect data in a way which is tailor-made for the kind of analysis that we are proposing and can feed into AHHME. It will also allow us to build on my findings here, exploring interventions which appear promising following the AMUSE papers, and investigating concepts like threshold effects.

As always, the AHHME model family will continue to be available online, as will the associated web apps. I will continue to promote these tools, and to work with researchers and policymakers to help them use these models to answer policy questions in their own contexts. I encourage such people to tailor the models to their own areas of research, to expand and improve them in the spirit of open-source science, and to use these frameworks to inform the creation of new and better tools.

Outside of this, I feel that longer-term and more comprehensive AMR surveillance infrastructures are needed. These data should be truly accessible, coordinating data collection across OH sectors, with regular ecological association studies (both mathematical and statistical) done as part of ongoing surveillance programmes. As longer-term datasets become available, we can use them to begin to pick apart the complex process by which resistance is transferred between animals and humans over time. We should endeavour to include in these models AMR determinants which go beyond changes to AMU, including both transmission factors and socioeconomic determinants of resistance.

We must also continue running large and scalable agricultural AMS intervention studies. They should focus on combined intervention packages to safely improve on-farm stewardship while safeguarding animal health and productivity, and should go beyond the farm level to target actors across the agriculture-AMR nexus.

As more of these results become available, we should feed them into holistic health-economic modelling tools such as AHHME, using them to comprehensively estimate the societal impact of such interventions, and combining this with participatory stakeholder consultation to design and select AMR policies in agriculture and beyond.

It should also be kept in mind that the three main questions of this thesis were explored in different geographical contexts. I looked at the ecological relationship between animal AMU and human AMR within the Imperial Core and found little. Perhaps resistant strains are more endemic there, or perhaps animal AMU has already been reduced so much that small changes no longer make a big difference to the prevalence of human AMR. The relationship may well be different in the Global South, as I hope to explore in Senegal.

The farm-level effect of AMU and farm practices focused on data from the Global South, and found a potential benefit of nontherapeutic animal AMU and a set of potentially effective measures to complement stewardship interventions. The studies reviewed in section 1.3

show examples from the Imperial Core both of productivity losses from AMU reductions and of the beneficial role of farm management interventions when combined with stewardship efforts on farms. Thus, the findings of papers 2-4 no doubt bear some relevance there too, although the most effective intervention packages will doubtless vary by context.

In these papers, I have endeavoured to be as holistic as I could within the constraints of the data and tools available to me, and to take a One Health approach whereby I considered the role and impact of multiple compartments and actors. This, however, like many studies in the One Health space, can be seen as falling short of a truly integrative understanding of health. While beyond the scope of this thesis, understanding that integration and reflecting it in our work is something that I and others should strive for more actively.

Finally, to deviate somewhat, we must be cognizant of the limits of modelling as a decision-making tool. The work I have reviewed and presented here highlights, among other things, that modelling complex systems also introduces great uncertainty, that it is possible for an entire scientific community to have no confident answer to questions of great importance, that even accepted scientific methods can paint but a partial picture, and that prevailing scientific discourse can be misleading.

Liberal science forms part of a colonial epistemology which privileges quantitative and institutionalised ways of knowing, and violently divides systems into discrete parts. But health is not a system of discrete parts - it is a social ecology, and health policy decisions are made in a historically-specific political economic context. Questions of health policy are not distinct from questions of collective liberation, political economy, and material wellbeing. Understanding the economically optimal allocation of resources from a limited pool is of no use if those resources are syphoned off by austerity and colonial extraction.

Modelling, as a tool, has no answer to this complexity, and I do not believe that this contradiction can be resolved through the creation of ever-more-complex models. While we may seek a satisfying technocratic answer to AMR policy questions, to do so is inappropriate and arrogant. The outputs of these modelling exercises can be used to inform the decision-making process, and can be very useful to that end, but they are no more true or real than the testimony of a stakeholder.

This leaves me to reflect on the utility of using what is essentially a liberal rationalist framework, within the institution of The Academy, in my own work. I came into global health from a background of development economics, hoping to put my quantitative skills to good use in a less colonial discipline. Over the years that I have been in Global Health, I no longer see it as less than colonial in any way.

I have tried to do what I can while working within the institutional context of the LSHTM, and hopefully this will have had some positive impact. Policymakers around the globe, coordinated by the Quadripartite, subscribe to the paradigm of producing public health knowledge in the Academy and in multilateral organisations. The position that I occupy within the Academy forms part of that system. By using my existing platform, I hope to challenge some key misconceptions about AMR and agriculture and to provide tools which make the existing framework of analysis slightly more powerful and holistic. I believe that my work is already doing that, but this is not deep systemic change. While describing them here

goes beyond the scope of this project, there are moves to radically decolonise Health, to move towards different ways of knowing, and to dismantle ‘global health’ as an institution. Then, perhaps, we can talk about deep change.

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