Reducing risks of human exposure to antimicrobial resistance originating from livestock supply chains

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Summary

Antimicrobial resistance is one of the biggest health threats for both humans and animals. This justifies the need for a conceptual framework that provides an integrated assessment of the measures and strategies that can be applied within livestock supply chains to reduce the risks of human exposure to resistant pathogens. The aim of this study is therefore to provide a comprehensive supply chain-based conceptualisation that describes the main measures and strategies to reduce the risks of human exposure to resistant pathogens. The conceptual framework presented in this study makes a distinction between on-farm and beyond-farm decision-making contexts. The on-farm decision-making context focuses on the strategies that can reduce antimicrobial use. The beyond-farm decision-making context focuses on the prevalence of (pathogenic) microorganisms. The focus of this framework is on Western European food production systems. A panel consisting of Dutch policy makers on antimicrobial issues assessed various aspects of the framework, including correctness, completeness and consistency. It is concluded that the conceptual framework provides a sound theoretical basis for economic decision-support for policy makers to reduce the risks of human exposure to resistant pathogens originating from livestock supply chains.

Keywords

Antimicrobial resistance – Antimicrobial use – Business economics – Human exposure – Livestock production – Livestock supply chains.

Introduction

Farmers worldwide use antimicrobial agents. Aside from therapeutic treatment of clinically diseased animals, antimicrobial agents are used for prophylactic purposes (i.e. disease prevention), metaphylactic purposes (i.e. administration to clinically healthy animals that belong to the same flock or herd) and growth promotion (1, 2, 3). The World Health Organization (WHO) has published recommendations based on a systematic review of the evidence for a link between antimicrobial use (AMU) in livestock production and the risks of human exposure to resistant pathogens, which poses a threat to continued AMU in veterinary medicine (e.g. 4, 5, 6, 7, 8, 9, 10, 11). This has resulted in various efforts to reduce inappropriate and excessive AMU in livestock production, with the European Union (EU) ban of the use of antimicrobial growth promoters, active since 2006, as the main European measure. Despite the efforts made to combat inappropriate AMU, the overall level of AMU remains relatively high, which provides favourable conditions for the selection, spread and persistence of antimicrobial resistance (AMR). Within the context of

AMU in livestock production in Western Europe, farmers are primarily responsible for the use of antimicrobial agents. However, farmers make such decisions together with or by consulting a veterinarian. Policy, supply chain initiatives and slaughterhouses can set limitations and requirements on AMU (e.g. concepts or brands). Hence, farmers operating within such concepts and brands have to meet these requirements. In that respect, all resources available should be allocated so that both the risks of human exposure to resistant pathogens and the costs of the measures and strategies are minimised.

Previous studies have analysed the problem of AMR. There are studies that have tested associations between veterinary AMU and human exposure by using genomics (12, 13), studies that addressed the occurrence of AMR (14, 15), examined unintended consequences of AMU (3, 16) and assessed the prevention of AMR (17, 18), as well as studies that discussed alternative ways to prevent and combat zoonotic diseases in order to lower AMU (19, 20, 21, 22). In addition, Hudson *et al.* (23) reviewed potential transmission routes of AMR bacteria/genes in agriculture to human infection. From these studies, it can be concluded that AMR is a complex agricultural problem. These types of problem require a conceptual framework to provide an integrated assessment of, in this case, the risks of human exposure to resistant pathogens (24, 25, 26), which can combine both theoretical and empirical findings regarding the problem (27). First, such a framework should provide a systematic overview of the main factors and decision alternatives (i.e. potential measures) that contribute to the problem. Moreover, it should provide a solid basis for the formulation of appropriate policy and analysis questions and clarify the right questions regarding cost and risk trade-offs, all in the appropriate economic decision-making context. Such a framework can support the process of finding and analysing potential measures and strategies for reducing the potential risks of human exposure to resistant pathogens by considering the (farm) economic consequences of applying the measures and strategies (including to whom the additional costs accrue). Such an integrated conceptualisation of the problem of AMR is currently missing.

The aim of this study is to provide a comprehensive supply chain-based conceptualisation that describes the main measures and strategies to reduce both AMU and the prevalence of (pathogenic) microorganisms, and consequently the risks of human exposure to resistant pathogens. The focus of the framework is on pig and poultry production in Western Europe. These supply chains are major contributors to global meat production (1), and pig and poultry meat are major reservoirs of food-borne pathogens and commensal organisms (1, 28, 29, 30).

Conceptual framework

The conceptual framework described in this paper distinguishes the on-farm and the beyond-farm decision-making contexts regarding potential actions to reduce the risks of human exposure to resistant pathogens. The on-farm decision-making context focuses on reducing AMU, whereas the beyond-farm context focuses on reducing the prevalence of (pathogenic) microorganisms, which can be either resistant or non-resistant.

On-farm decision-making context

The on-farm decision-making context is shown in Figure 1, and consists of four different layers: decision-makers, decision areas, treatment decisions and decision objects. The first layer makes a distinction between two types of decision-maker. The first group of decision-makers are the policy makers, including (supra-)national governments and other semi-governmental authorities. These stakeholders have the power to develop, implement and enforce laws, policies, rules and regulations. Hence, they determine the decision space of farmers, who are the other decision-makers included in the on-farm decision-making context. Within this decision space, farmers can apply various measures and strategies to reduce AMU. Various service providers and farm advisors (including veterinarians and feed representatives) can support farmers in making decisions, but the farmer holds the primary responsibility for all on-farm decisions. In that respect, it is important to understand the behaviour of farmers, which is determined by aspects such as: awareness; beliefs and attitudes; knowledge, skills and experience; and objectives. Various economic theories have confirmed the importance of behaviour, e.g. the theory of planned behaviour (31) and the Von Neumann and Morgenstern expected utility theorem (32). In practice, financial motives dominate the decision-making of farmers, as shown by Gocsik *et al.* (33). Therefore, it is assumed that an economically rational farmer aims to maximise their income (34) by minimising the increase in production costs resulting from the applied measures and strategies to reduce AMU (Fig. 1).

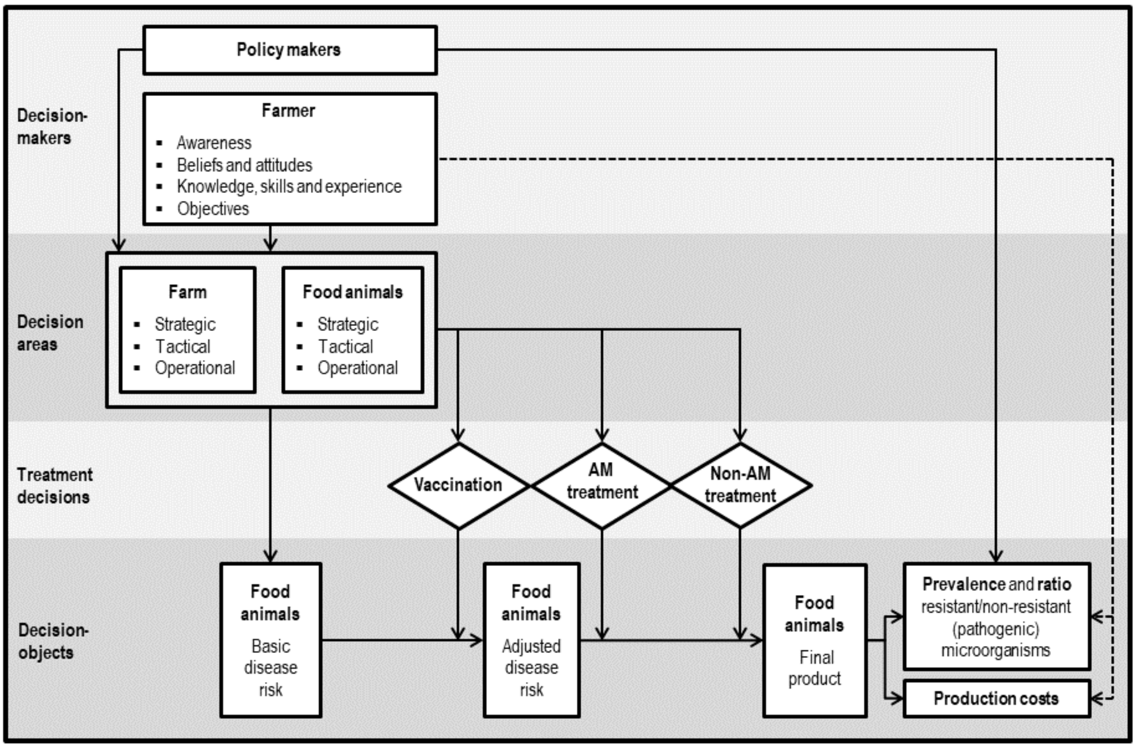

Fig. 1

The on-farm decision-making context

AM: Antimicrobial

The second layer of Figure 1 comprises the decision areas of the farmer. Two decision areas, i.e. the farm and the animals raised for food, and three decision types, i.e. strategic, tactical and operational decisions, are distinguished. Strategic decisions are long-term decisions with a time horizon of 5–10 years that involve relatively large investments, which affect the production costs over several years; these imply long-term and (often) risky financial commitments. Tactical decisions are midterm decisions within a time horizon of a year or a production cycle, and generally involve lower investment costs. Hence, tactical decisions involve fewer financial risks compared with strategic decisions. Operational decisions are day-to-day decisions made by the farmer that fit within the strategic and tactical decision-making context. Table I describes the main economic decision issues related to reducing AMU for both pig production (35, 36, 37) and poultry production (38) by distinguishing the decision area and the type of decision (Table I).

Table I

Catalogue of economic decision issues that can be taken on-farm in order to reduce antimicrobial use

Type of decision	Decision areas	
	Farm	Animal
Strategic	Location of the farm Farm layout Outside (i.e. external biosecurity/keeping diseases outside the farm); Inside (i.e. internal biosecurity/avoiding spread of diseases on-farm) Farm management Production management; Farm management concept	Animal characteristics Animal genetics; Health status (e.g. specific pathogen free animals) Disease management Animal management operations
Tactical	Farm layout Maintenance of buildings; Cleaning and decontamination protocol; Pests and vermin control; Avoiding introduction of diseases on dispatch to the slaughterhouse Farm management Farm visit by consultant; Evaluation of animal health; Monitoring and evaluating nutrition (i.e. quantity, quality and	Animal characteristics Number of animals; Stocking density Disease management Scheduling periodic activities; Individual or group treatment; Use of antimicrobial agents; Use of preventive measures (including vaccination, analgesics, zinc oxide and copper); Use of natural products (including organic acids,

	access); Checking water and water supply system (including quantity, quality and access); Checking the climate control system (including temperature, airflow, humidity and air quality); Checking other factors (including litter quality)	phytogenic substances, natural growth promoters, herbs, probiotics, prebiotics and enzymes); Use of feed additives; Selection of animal breeder; Supply and dispatch frequency (e.g. all-in all-out principle)
Operational	Adaption to and implementation of strategic and tactical decisions	Daily observation, monitoring and treatment

The location of the farm, the farm layout and the farm management are three important issues regarding the decision area of the farm. Decisions regarding the location of the farm are strategic decisions. Several environmental features (including the density and proximity of neighbouring farms, and the type and size of the neighbouring farms) characterise the location of the farm. Those features are important determinants of both the frequency of occurrence and the magnitude of disease outbreaks (39). Therefore, the location of the farm determines the external disease risk. The farm layout consists of the internal and external biosecurity measures, in which the focus is on avoiding the introduction and spread of diseases on the farm. The farmer controls all activities through the farm management.

Within the decision area 'food animals', a distinction is made between animal related decisions (i.e. decisions with respect to the animal itself) and decisions related to disease management.

The third layer of Figure 1 incorporates decisions regarding the treatment of animals. Three treatment possibilities are distinguished: vaccination, therapeutic treatment with antimicrobial agents and non-antimicrobial treatments. Treatment decisions have major impacts on the prevalence of and ratio between resistant and non-resistant (pathogenic) microorganisms. In many cases, veterinarians must decide whether food animals can be treated with an antimicrobial agent and, if so, which antimicrobial agent and by what route of administration (e.g. in feed or in drinking water). The cost of the drug and the severity of the disease often determine the type of antimicrobial agent that is used. It is assumed that non-antimicrobial treatments are beneficial for preventing AMR emergence. However, it is likely that the replacement of AMU with non-antimicrobial treatments will increase production costs, particularly in the short-term, because non-antimicrobial treatments are generally more expensive than antimicrobial agents.

The fourth layer of Figure 1 reflects on the various stages of the decision object, i.e. the food animals. The basic disease risk is determined by the entire complexity and variety of decisions that are taken with respect to the farm and food animals. The disease risk is adjusted when food animals are vaccinated. All measures and strategies, antimicrobial-related or not, have both short-term and long-term effects. The application of those measures and strategies can affect, either directly or indirectly, the technical and economic performance of the farm. In that respect, the application of on-farm measures and strategies can affect both production costs and the risks of human exposure to resistant pathogens.

Beyond-farm decision-making

Livestock supply chains usually consist of the following stages: farm, transport, slaughterhouse, processor, retailer and consumer. Compared with the on-farm decision-making context, more stakeholders are involved in the beyond-farm stage. Asymmetry in costs and benefits among supply chain actors and other stakeholders is quite common in livestock supply chains (40). Moreover, there is a high level of interdependency among the various stakeholders within the supply chain (41).

Figure 2 shows the main stages of a common livestock supply chain. This study is limited to the retail level when discussing potential measures and strategies (i.e. measures and strategies at consumer level are out of scope). Although improper storage and/or improperly prepared food at consumer level add to the level of prevalence (42), there are no policy measures based on the supply chain that can control food preparation by consumers.

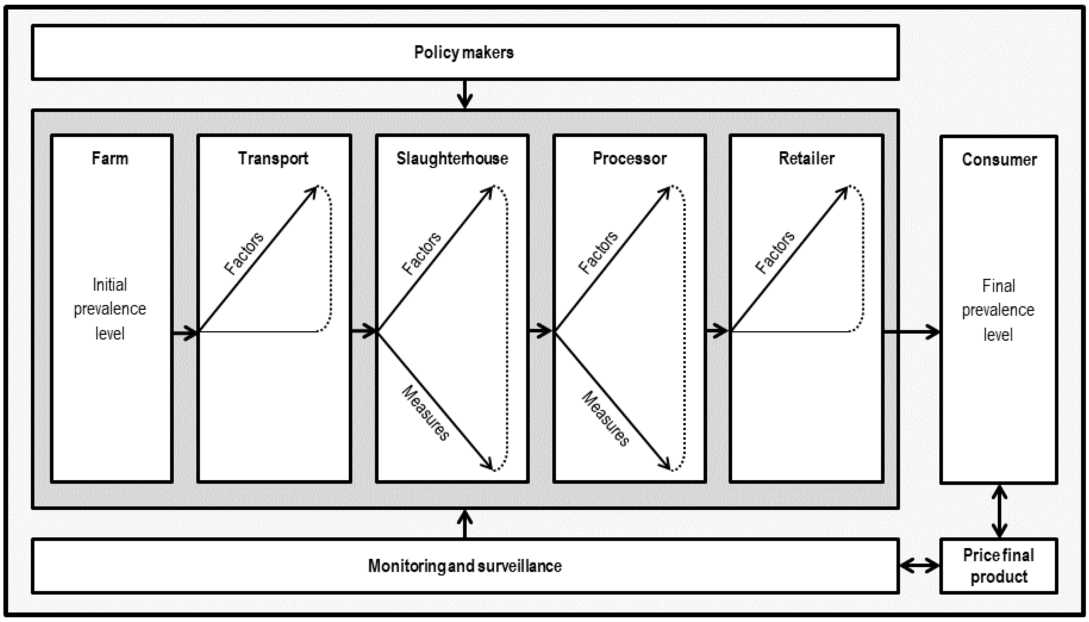

Fig. 2

The beyond-farm decision-making context with factors and measures that can affect the prevalence of (pathogenic) microorganisms

Policy makers, including governments and other (semi-)governmental health authorities, determine the decision space of the supply chain actors. However, actors are free to make their own decisions within those boundaries (Fig. 2).

The flowchart presented in Figure 2 starts with the transport of food animals from farm to slaughterhouse. These food animals, intended for human consumption, leave the farm with a given pathogenic 'load', determined by the prevalence of (pathogenic) microorganisms and the ratio of antimicrobial resistant and non-resistant (pathogenic) microorganisms. The ratio of antimicrobial resistant and non-resistant (pathogenic) microorganisms is assumed to remain unaltered, especially after slaughter. At each stage of the chain, the prevalence of (pathogenic) microorganisms can be affected, either negatively, by factors that increase the prevalence (e.g. cross-contamination), or positively, by measures that decrease the prevalence (e.g. decontamination treatments). An overview of these factors and measures is presented in Table II for both pig and poultry production.

Table II

Factors and measures beyond the farm that can affect the prevalence of (pathogenic) microorganisms in pig and poultry production

Factors and measures	Pig production	Poultry production
Factors influencing prevalence (43)	Transport Stress incidents; Vehicle cleanliness in transit; Crate density and space allowance; Physical hazards during transport; Length of time in transit and number of rest stops; Facilities for in-transit monitoring; Driving and vehicle conditions Slaughterhouse Lairage conditions; Sanitary and hygienic protocols Processor Sanitary and hygienic protocols Retailer Sanitary and hygienic protocols; Storage conditions	Identical to pig production
Measures to counteract (pathogenic) microorganisms (47, 48)	Slaughterhouse/processor Physical decontamination treatments (including scalding and singeing, chilling, water spraying, steam and ultraviolet light); Chemical decontamination treatments (including organic acids and other chemical treatments)	Slaughterhouse/processor Physical decontamination treatments (including water-based treatments, irradiation, ultrasound, air chilling and freezing); Chemical decontamination treatments (including organic acids, chlorine-based treatments, and phosphate-based treatments)

During the transport of food animals from farm to slaughterhouse, various physical, microbial and environmental hazards may adversely affect the quality of the microbial flora in the animals (43). Additionally, the stress level can be increased by adverse transportation conditions; this potentially causes increased pathogen multiplication in carrier animals, as a result of which other animals can be exposed (43). In subsequent stages of the supply chain, the prevalence of (pathogenic) microorganisms can increase through improper storage conditions (44). Contaminated carcasses or food products can contaminate each other via cross-contamination (45). Good sanitary and hygienic processes are the basis for controlling microbial contamination and avoiding cross-contamination (46). However, total prevention of microbial cross-contamination is out of reach under commercial conditions, even when the best hygiene measures are applied (46). Therefore, there is a need for specific targeted measures.

An overview of the intervention possibilities for poultry carcasses beyond the farm was provided by Loretz *et al.* (47). In addition, Loretz *et al.* (48) described the intervention possibilities for pig carcasses. Examples of possible interventions are physical treatments (including hot water spraying, irradiation, steam treatment, ultrasound, ultraviolet light, air chilling or freezing) and chemical interventions (including lactic, acetic and organic acids, and chlorine-based or phosphate-based treatments). These interventions differ in terms of effectiveness and welfare effects. In addition, there may be a legal ban on certain interventions, e.g. the EU ban on the use of organic acids (49). At the retail level, there are no intervention possibilities to reduce the prevalence of (pathogenic) microorganisms. However, inappropriate storage conditions can increase the prevalence (50).

Monitoring and surveillance are possible throughout the supply chain. A generally accepted example of a widely applied monitoring and surveillance approach is the Hazard Analysis and Critical Control Points (HACCP) approach. This preventive approach involves the identification and control of potential food safety hazards.

Compliance, effectivity and governance

The implementation of measures and strategies to reduce the risks of human exposure to resistant pathogens is not straightforward and may come with considerable additional costs, originating from increased production costs, reduced output or a combination of both. This could pose a temptation for stakeholders not to comply with (legal) obligations. Such risks of (partial) non-compliance might reduce the effectiveness of measures and strategies. Various authors have used compliance models that describe the decision-making process within firms (51, 52, 53, 54, 55, 56). According to Rugman and Verbeke (57), and Henson and Caswell (58), responses in terms of compliance depend on the following aspects:

– *Expected economic benefits*. Generally, there will only be a natural tendency to comply with policies when the total costs of compliance are lower than the (commercial) benefits of non-compliance (59).

– *Driver of compliance*. Firms can be stimulated to comply with policies by providing financial incentives (e.g. grants for antibiotic-free meat production), or through sanctions in cases of non-compliance (e.g. financial penalties for using antimicrobial agents that are more likely to cause resistance).

– *Strength of enforcement authorities*. Firms always consider the likelihood of getting caught in cases of non-compliance. In that respect, penalties, monitoring and control could enforce compliance (60).

The development of an appropriate mix of the above-mentioned aspects helps in regulating compliance. Two views of regulation are distinguished: one from the public side and one from the private side (58). On the public side, Henson and Caswell (58) distinguished direct ex-ante regulation (i.e. standards, inspection, product testing and other programmes to ensure good food quality) from product liability (i.e. ex-post regulation, to discourage production of food of insufficient quality). Product liability is not easy to implement owing to existing problems with food traceability (61). On the private side, Henson and Caswell (58) distinguished self-regulation (i.e. internal control systems that assure product quality where the firm sets, monitors and self-certifies control parameters) and certification (i.e. external setting of quality standards). Certification can be attractive, because consumers are willing to pay more for products when food safety is enhanced (62, 63). Governmental authorities can stimulate and facilitate private initiatives of self-regulation and certification by providing (financial) incentives.

Non-compliance is a critical risk factor when the prevailing aim is to reduce the risk of human exposure to resistant pathogens, which can necessitate reduced AMU with coinciding increased food production costs. The risk governance literature has looked at engaging people at different levels (64). However, ensuring accountability, and establishing trust between stakeholders at different levels, is rather complex (65, 66). Hence, minimising non-compliance requires additional costs, e.g. improved governance, monitoring and control; moreover, these costs accrue to different stakeholders. Such additional costs should be included in future quantitative analyses.

Validation of the framework

In addition to literature research, expert knowledge was used to validate the conceptual framework presented in this study. Given the logistical and budgetary constraints, the panel consisted only of Dutch policy makers. The panel included policy makers from the Dutch Product Boards for Livestock, Meat and Eggs, the Dutch Ministry of Economic Affairs, the Dutch Animal Health Service, The Netherlands Food and Consumer Product Safety Authority and the Dutch Agricultural and Horticultural Organisation (one policy maker from each organisation). The panel therefore consisted of policy makers from the main organisations involved in the Dutch food production system. The framework has therefore been validated from the Dutch perspective, but the results can be generalised to other Western European countries because the Dutch food production system is strongly export-oriented, and the Dutch perspective is therefore greatly determined by the approach of customer countries.

The experts were asked to provide feedback on the framework, voluntarily and anonymously, during two organised meetings. First, the panel received the framework electronically. Thereafter, an in-person meeting was organised, which started with a presentation about the framework. Afterwards, the panel assessed the framework on aspects such as correctness and completeness. The outcome of the first meeting was that the figures showing the on-farm and beyond-farm decision-making contexts were too complex. Hence, the figures were adapted after the first meeting. The modified framework was presented during a second in-person meeting. The expert panel addressed minor remarks, including the suggestion of simplifying some elements in Figures 1 and 2. According to the feedback received from the panel, the framework was adapted and finalised after the second meeting.

Conclusions, discussion and future outlook

The aim of this study was to provide a comprehensive supply chain-based conceptualisation that describes the main measures and strategies to reduce AMU, and consequently to reduce the risks of human exposure to resistant pathogens. This paper framed the on-farm and beyond-farm decision-making contexts to assess potential risks of human exposure to resistant pathogens. The conceptual framework as presented is limited to the conditions in Western European food production systems. The possibilities of tackling potential human exposure to resistant pathogens are more complex in middle-income and low-income countries because such countries are likely to have resource issues, lack of governance and different agricultural structures. Measures to reduce both AMU and potential human exposure to resistant pathogens will therefore be different in some respects, at both farm and supply chain levels.

The conceptualisation presented in this study can be used as a qualitative basis for future bio-economic modelling and other quantitative analyses. Specifically, such analyses need to include potential risks and benefits associated with AMU. The need for impact assessments in future research has already been emphasised by Rushton (67), who addressed the fact that such assessment analyses have the ability to identify bottlenecks in the management of AMU and potential impacts in terms of residues or AMR emergence. Assessment analyses therefore must include evaluations of potential interventions for reducing AMU and can reveal potential unintended consequences (67).

The preferred tool for impact assessment analyses is the comparison between the benefits of veterinary AMU on the one hand, and both the financial costs and risks of AMR emergence on the other hand (67). However, there are different categories of costs, i.e. variable and fixed costs. Variable costs differ according to the level of production and are farm-specific (68). Fixed costs are less easily attributed to individual activities and usually involve investments which have been made to last for several production cycles (68). The need to invest in fixed assets to tackle AMR emergence is emphasised by Tisdell (69). In addition, it should be remarked that although veterinary AMU is common, the institutional environments in which antimicrobials are used differ (1), which again affects the efficacy of measures.

Results of future analyses can contribute to the process of developing new policy guidelines to support economic decision-making on reducing AMR to reduce the risks of human exposure to resistant pathogens. The conceptual framework presented in this study is a qualitative basis for such future impact assessment analyses.

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