Tradeoffs between resistance to antimicrobials in public health and their use in agriculture: moving towards sustainability assessment

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Abstract

Antimicrobial use (AMU) in animal agriculture contributes to select resistant bacteria potentially transferred to humans directly or indirectly via the food chain, representing a public health hazard. Yet, a major difference triggering AMU in food animal production is that in addition to therapeutic cure, farmers use antimicrobials to keep their herds healthy and highly productive, while ensuring animal welfare and food safety objectives. As a society, we consequently face difficult tradeoffs, between massive restrictions of AMU, and maintenance of current and potentially non-sustainable consumption levels. Here, we present the different components to be addressed for assessing the sustainability of AMU in animal agriculture. At first, we describe the interests and limits of existing models identified by reviewing the literature, which could potentially be used to assess AMU sustainability, while allowing the reader to capture in a simple and visual manner the complexity of the issue. We address in the following sections the boundaries of the social-ecological system and the indicators that are required for assessment of AMU sustainability. We introduce analytic methods that could be used for assessing the sustainability of antimicrobial use.

Keywords

Antimicrobial use; Antimicrobial resistance; Agriculture; Sustainability assessment; Social-ecological system; Indicators.

1. Introduction

The late twentieth century witnessed incredible improvement in the treatment of bacterial infectious diseases, thanks to discovery of active compounds and affordable access to antimicrobials. Unfortunately, it has become less profitable to develop new antimicrobials compared to drugs for non-communicable diseases, for several reasons, including low likelihood of reaching the market and decreased value when resistance inevitably emerges (Outterson et al., 2007). As the antimicrobial pipeline dries up, the selection of resistant bacteria, unavoidably associated with antimicrobial use (AMU), has led to a situation where the treatment of some infected patients has become difficult, costly or even impossible (Boucher et al., 2013; Carlet et al., 2012; Laxminarayan et al., 2013). The death toll due to antimicrobial resistance (AMR) is estimated at about 50,000 lives a year in the U.S. and E.U. (700,000 globally) (CDC, 2013; ECDC, 2009; O'Neill, 2016), and additional costs to treat a patient infected by resistant bacteria can be up to USD 40,000.

The recent growing awareness regarding AMR as a global public health threat has catalyzed the implementation of regulatory and voluntary public policies aiming at curbing AMU and ensuring antimicrobial stewardship, in order to slow down the erosion of susceptibility or even decrease resistance of bacteria to antimicrobials. A consensus statement has defined antimicrobial stewardship as "coordinated interventions designed to improve and measure the appropriate use of agents by promoting selection of the optimal drug regimen including dosing, duration of therapy, and route of administration" (Society for Healthcare Epidemiology of America; Infectious Diseases Society of America; and the Pediatric Infectious Diseases Society, 2012). Stewardship activities range from individual level (e.g. prescriber) to hospitals and national policies

(Mendelson et al., 2017). These public policies target both human and animal populations, the last representing the major consumption of antimicrobials (Van Boeckel et al., 2014, 2017).

At present, there is much research demonstrating the impact of AMU in animal agriculture on AMR in humans. A recent systematic review and meta-analysis found that interventions to reduce AMU in animal health resulted in decrease in AMR in these animals as well as in human health (Tang et al., 2017). The pooled absolute risk reduction of the prevalence of AMR in animals with interventions that restricted AMU commonly ranged between 10 and 15% (total range 0–39), depending on the antimicrobial class, sample type, and bacteria under assessment. Similarly, in human studies, the pooled prevalence of AMR reported was 24% lower in the intervention groups compared with control groups, with a stronger association seen for humans with direct contact with food-producing animals. Interventions that restrict AMU in food-producing animals are associated with a reduction in the presence of antibiotic-resistant bacteria in these animals. A smaller body of evidence suggests a similar association in the studied human populations, particularly those with direct exposure to food-producing animals. Even if the overall quantitative impact of AMU in animal agriculture on public health remains difficult to assess (Singer and Williams-Nguyen, 2014), the growing magnitude of this public health issue justifies a "One Health" approach towards AMR, addressing health risks at the human–animal-plant-ecosystems interfaces (WHO/FAO/OIE, 2016).

In addition to their therapeutic objective, antimicrobials are used in food animal production to achieve (i) economic objectives, via optimization of farm benefits related to sale of animal derived foodstuffs, (ii) animal welfare objectives, ensuring good health at individual and herd levels, and (iii) public health objectives, via limiting risk of zoonotic diseases (Lhermie et al., 2017). Therefore, in addition to health goals, AMU decision-making relies on an interdependent mix of economic, behavioral, ethical and cultural factors. One way to consider these factors consists of assessing the sustainability of AMU in what has been studied as Social-Ecological Systems (SES), i.e. "complex, nested systems operating at multiple scales" in which human and nature are deeply entangled (McGinnis and Ostrom, 2014). In the case of AMU, SES can be defined as systems in which are intertwined humans (public health, farming economy, and social issues), animals (health and welfare issues), and microorganisms (health and ecosystemic services issues) (Søgaard-Jørgensen et al., 2018).

Notwithstanding its complexity, evaluating AMU sustainability is necessary for advising policy-makers on the potential impact of regulations. In this paper, we set out to determine a conceptual approach for the sustainability assessment of AMU in animal agriculture. A first step consists of a thorough description of the SES, for which we use the Driver-Pressure-State-Impact-Response (DPSIR) framework, which constitutes an excellent communication support system among stakeholders**.** As the DPSIR framework exhibits some limitations for analytic purposes, we adapt an analytic framework for sustainability assessment. We address the boundaries of the social-ecological system and the indicators that are required for assessment of AMU sustainability. We then discuss analytic methods and a framework that could be used for assessing the sustainability of antimicrobial use and for the design of policies for sustainable antimicrobial use.

2. Describing the sustainability challenge in the DPSIR framework

Since its development by the Organization for Economic Cooperation and Development (OECD) two decades ago, the DPSIR framework has been regularly used to understand the cause-effect relationships among the five categories of Drivers, Pressures, Impacts, Responses, and

States constituting the framework, in several areas such as marine resources, biodiversity, coastal management, and energy (Bell, 2012; Brondizio et al., 2016; Gari et al., 2015; Tittensor et al., 2014). Indeed, it allows one to represent the links within a defined SES in a simple, visual and multidimensional manner, and to facilitate communication among stakeholders.

Fig. 1: Drivers-Pressure-State-Impacts-Responses (DPSIR) framework in the context of antimicrobial use (AMU) and resistance in animal agriculture.

2.1 State

Although the DPSIR model lists State as the third component of the approach, we elect to present the state as the first component of addressing AMR, for clarity purposes. According to the European Environment Agency (EEA), the state is described by “the quantity and quality of physical phenomena (such as temperature), biological phenomena (such as fish stocks) and chemical phenomena (such as atmospheric CO_2 concentrations) in a certain area” (European Environment Agency, 2005). Other authors qualify the state by referring to a natural system or a socio-economic system (Elliott, 2011; Giupponi and Vladimirova, 2006). Considering bacteria susceptibility as a natural resource (Fig. 1), states are for AMR the levels of resistance in different pathogens (Wernli et al., 2017). Those states are influenced by drivers, pressures, and responses that occur.

2.2 Drivers

Drivers describe “the social, demographic, and economic developments in societies and the corresponding changes in lifestyles, overall level of consumption and production patterns” (European Environment Agency, 2005). They are mainly constituted by anthropogenic factors; however, according to the Millenium Ecosystem Assessment (MEA), natural factors may also be considered as drivers (Millenium Ecosystem Assessment, 2003). In the case of AMU, disease occurrence (associated with the presence of a pathogen), and the economic benefits of treatments constitute the two upstream drivers. Primary economic drivers consist of management practices. Farmers’ decision making regarding AMU is the result of an analytical process involving farmers’ knowledge regarding diseases and treatments options, and their attitudes and beliefs, as well as the presence of alternatives to antimicrobial treatments (AMT) and diagnostic tools (Lhermie et al., 2017). Additional drivers consist of socio-economic structures and processes, including lifestyle and ideologies, that can impact governance. At the food system scale, the level of integration is highly dependent on the type of production (Sneeringer et al., 2015) and the strength of the sanitary network. At the society level, the consumers' preferences and consumption patterns (e.g. conventional *vs.* organic), their perceptions regarding AMU, and animal welfare are also drivers of AMU in agriculture. Finally, the governance structure, i.e., the presence of animal health organizations, surveillance networks, and the structural and operational capability of governments to enact policies, are important drivers.

2.3 Pressures

The EEA defines pressure as "the ways in which drivers are expressed physically, reflecting the interlinkages between a human activity and the surrounding natural environment" (European Environment Agency, 2005). A basic assumption of the DPSIR framework is that pressures are consequences of human activity. Antimicrobial use constitutes the core pressure for our topic, as it is well established that AMU results in selective pressure which in turn fosters AMR. This generic definition of pressure raises several issues (Maxim et al., 2009). First, the nature of a pressure indicator may be addressed in two different directions: the amount of antimicrobial consumed, or the use of the resource (bacteria susceptibility). The apparent ease of monitoring AMU, and the complexity of meaningfully quantifying AMR, might lead one to consider both indicators in addressing the problem. Second, we should consider the object of change when defining pressure indicators: a marginal change in the state may or may not result from an increase in pressure if there is no overshoot, on the basis of existence of a carrying capacity of the state. Third, the nature of the link between states and the pressure needs to be characterized. Even though some models show correlation between AMU and AMR (Chantziaras et al., 2014; Goossens et al., 2005), it remains difficult to capture underlying complex mechanisms linking

AMU and AMR. Depending on the antimicrobial agent and the bacteria species or even strains, the bacterial response in the presence of antimicrobials varies (Blair et al., 2014). These mechanisms are increasingly characterized, but it remains difficult to draw a general model allowing assessment of the AMU-AMR relationship at a population or meta-population level. Finally, we have to consider the possibility of unknown pressures leading to a decrease in bacteria susceptibility.

2.4 Impacts

Impacts are defined by the EEA as "consequences of changes in the state of the environment for environmental functions". We adopt here a similar position, where impacts result from change in the state (bacteria susceptibility), which affects the SES, in its social, environmental, and economic dimensions. As consequences of this change, impacts are changes in the functions for humans. In its general framework, the MEA proposes to analyze how the consequences of changes in ecosystem services affect human well-being, going beyond how changes in ecosystems affect life on Earth (Millenium Ecosystem Assessment, 2003). This change of perspective will require an adaptation of the DPSIR framework, which represents linear relationships between its different variables, to a more complex system representing interdependencies. Hence, we should define which functions for humans are likely to be affected by a change in the state of susceptibility. This will be addressed in a following section, while defining sustainability indicators.

2.5 Responses

According to the EAA, response indicators refer to responses by individuals and groups in society, as well as government attempts to prevent, compensate, ameliorate or adapt to changes in the state of the environment (European Environment Agency, 2005). Efforts at the global level have been to define the range of possible responses to AMR. In 2016, the World Organization for Animal Health (OIE) released a document, related to World Health Organization (WHO) Global Action Plan, presenting the four objectives of its strategy on AMR and prudent use of antimicrobials: improve awareness and understanding, strengthen knowledge through surveillance and research, support good governance and capacity building, and encourage implementation of international standards (OIE, 2016). Yet, implementing responses to a social-ecological problem such as AMR needs a multilevel governance (Ostrom, 2007), and enactment as well as the measurement of the response remain the responsibility of sovereign nations. To date, some countries have developed a national plan targeting a judicious use of antimicrobials in animal agriculture. Depending on governmental policies, several measures can be implemented to limit AMU to specific indication(s). Indeed, regulators choose to use one or a combination of the following policy instruments: regulations, taxes, and voluntary agreements. Regulations, such as the ban of AMU as growth promoters in the E.U. and the U.S. (European Union, 2003; FDA, 2013), as well as in China for colistin (Walsh and Wu, 2016), comprise the first strategy. The Netherlands and France, are two examples of countries having set additional regulations targeting the use of some antimicrobial classes of critical importance (Speksnijder et al., 2015; Anses, 2018). The major advantage of regulations lies in their ability to reduce quickly AMU. However, it is generally admitted that regulations come with higher costs than other policies (Tietenberg, 2006). Taxes were introduced in 2013 in Denmark, which chose to implement differential taxes by antimicrobials classes. (Høg and Korsgaard, 2017). Conceptually, taxes should be the most efficient policy instrument (Tietenberg, 2006). Yet, this requires good estimates of the social costs of AMR. Voluntary approaches, driven by organizations of farmers or veterinarians, or governments, are initiatives in which participation is not legally binding (Karamanos, 2001), and are also targeted at limiting AMU (Lhermie et al., 2017). As examples, numerous countries, e.g. France, the Netherlands, Sweden, Denmark, U.K, Belgium, and the U.S have developed guidelines reinforcing antimicrobial stewardship (American Association of Bovine Practitioners, 2013, 2017; AMCRA, 2018; Danish Ministry of Food and the Environment, 2018; Dutch Royal Veterinary Association, 2013; French Ministry of Agriculture, 2017; Swedish Dairy Association, 2009; VARSS, 2016). Even though initiatives have been multiplied worldwide, empirical research investigating the benefits of such regulations is still missing, but would help policy-makers and stakeholders to evaluate the relevance of measures potentially enacted at local or national levels. While current effort constitutes a good starting point, we believe that the design and implementation of such policies will benefit from a thorough analysis of the sustainability issues related to AMU, as this would set a common framework enabling us to compare performance of policies. In this regard, responses can be divided regarding the objective fulfilled, and targeted at controlling either drivers (preventive response), pressure (mitigation response), state (restorative response), or impacts (adaptive response) (Spangenberg et al., 2015). Regarding AMR, a general framework distinguishes six strategies of responses: infection control, surveillance, universal access, innovation, and responsible use in human and animal health (Dar et al., 2016). These strategies might target only some categories of people or users, or a larger audience.

3. Assessing sustainability with the tetrahedral DPSIR framework

Notwithstanding the strength of the DPSIR model as a comprehensive tool easy to use and communicate, several authors pointed out its conceptual inability to be an analytical framework (Bell, 2012; Gari et al., 2015; Tscherning et al., 2012). A recent review has identified methods refining the basic framework to improve its analytical power (Gari et al., 2015). Indeed, analyses of sustainability challenges need to address simultaneously the resources, the components of policies, and the responses to the policies (de Olde et al., 2017). The characteristics of a good analytical tool are its simplicity, robustness, and adaptability, with long-term perspectives and potential adjustments of the initial policies (Byrd Jr., 1980). Therefore, we need to implement a slight move from the descriptive model to a model allowing assessment of policies, not only as a snapshot process, but rather as an analysis of a continuum of actions ensuring sustainability in a complex adaptive system. The four spheres for a sustainability framework have been developed by O'Connor as an adaptation of the classic triple bottom line of economic, social, and environmental, in order to facilitate analyses for sustainability (O'Connor, 2006). This requires a better understanding of the interactions and interdependencies among the economic, social and environmental spheres. For example, Maxim et al. have used such a model for analysis of chemical risks for biodiversity (Maxim et al., 2009). The interdependencies among these three spheres may lead to isolated actions (or pressures) on one to the others that can be incompatible, and therefore need to be arbitrated. In this framework, the fourth sphere, namely the political sphere, acts as the regulator organ, providing governance with an aim to satisfy each of the other spheres. This representation allows one to consider the interfaces between the pair of spheres, each interface being related to the action exerted by one sphere on the others. The integrated framework adapted here is represented in a synthetic figure (Fig. 2) and depicted in Table 1.

The economic-social interface illustrates the paradoxical relationship between the economy and communities: the economy provides goods (food commodities) and services (amenities), as well as opportunities of development and employment; conversely, the economy might lead to an erosion of human well-being. In the DPSIR model, the economic and social spheres and their interfaces constitute the drivers of AMU. The environmental-economic interface designates the pressure exerted by the economic sphere (animal farming) on a natural source of capital (antimicrobial susceptibility).

The social-environmental interface designates the "meaning of nature" i.e., the importance that societies give to a natural source of capital. This interface constitutes the theoretical space where the sustainability of AMU can be addressed (*e.g.*, risks of usage, stakeholders' standings, susceptibility conservation, rights of current and future generations regarding bacterial susceptibility, *etc*.). For clarity purposes, we have chosen to represent this interface as the main component of the impacts of the DPSIR model, although we acknowledge that a change in the state will also impact more or less directly every other sphere.

The three other interfaces illustrate the policy domains, the political sphere being the recipient of the claims from each sphere, and sending back economic, social and environmental policies. In the DPSIR model, these interfaces represent the Responses.

Fig. 2: Tetrahedral DPSIR framework (adapted from Maxim et al., 2009) and levels of intervention of available methodologies of interest for antimicrobial use sustainability assessment.

Table 1: Description of the spheres and their interfaces evaluated in the sustainability tetrahedron model.

4. Setting the boundaries of the social-ecological system

According to the Brundtland report, sustainable development implies success in the achievement of 2 major challenges: (i) the challenge of meeting the present needs without compromising the ability of future generations to meet their own needs, and (ii) the challenge of equity in effective citizen participation in decision making (Brundtland, 1987). The concept of sustainable development implies that limitations are imposed on environmental resources by the present technologies and social organizations, and that the system has a certain ability to absorb the impacts of human activities. It also implies that sustainable development can be reached under the constraint of populations' growth. This signifies that sustainable development is a contingent, social-ecological process of change to meet present and future needs. In addition, the Brundtland report states that sustainable development must rest on political will.

Sustainability assessment aims to support policy-makers in their decisions. As for many unsustainable production and consumption practices, the responses to address the challenge caused by the rise of AMR have been formulated *ex post*, and suffer from a lack of consideration of the complexity of the social-ecological system, and therefore the unexpected consequences of potential policies (Merrett et al., 2016). Addressing a complex challenge such as AMR should be based on the continuous interaction between interventions and evaluations, in which assessment and learning is important at each step. Ideally, the decisions should be made prior in the light of information regarding the potential impacts of policies, i.e., *ex ante* assessment. The strength of *ex-ante* assessment lies in its capability to consider a variety of policy situations, the compatibility between policies, and the political agenda. It signifies that sustainability assessment depends not only on the resources, but also on the communities' influences surrounding the decision making process.

Framing sustainability assessment of AMU requires one to (i) set the boundaries of the system in which the assessment is pursued, and (ii) define accurate indicators (Sala et al., 2015). Hence, we will focus on considerations on how to set the boundaries for Sustainability assessment, a necessary step before defining indicators. Indeed boundary Setting is key for understanding any complex SES, yet is particularly challenging (Holland and ebrary, 2012). Boundaries enable one to delimit the resources needed, the actions to be implemented, and the expected outcomes (Murphy and Rhodes, 2013). Once established, the system can be studied either prospectively or retrospectively, for optimization purposes or intervention assessments.

4.1 Moral and ethical concerns

A preliminary step to boundary setting is to understand the challenges associated with moral and ethics considerations, that might lead to study of the SES under several perspectives. Beyond the tragedy of the commons, which represents a first ethical challenge raising directly the question of the existence and the fairness of distribution of potential property rights regarding bacteria susceptibility (or antimicrobial efficacy), AMR is a global challenge presenting significant ethical issues. As AMR progression will potentially make future generations worse off, normative concerns regarding our current choices of food and health consumption arise. In a recent paper, Littman determined five ethical issues, that we develop here with a human and also animal health perspective (Littmann and Viens, 2015). The first one consists of the ethics of drugs and diagnostic tools development addressing that the question of who bears the costs of development. The second one consists of the ethics of antimicrobial stewardship. Many guidelines encourage antimicrobial stewardship; however, the meaning of a “good steward” remains unclear. A dilemma exists between the need for a responsible use of antimicrobials on the one hand, and health workers’ obligations not to compromise the chances of recovery for their patients, whether humans or animals, and their welfare. The third issue consists of the ethics of ignorance and behavior change. It raises the question of awareness towards the risks associated with AMU, and the responsibilities that citizen have to educate themselves. This question is all the more important in animal agriculture, as health workers but also farmers should be considered as professionals with an enhanced comprehension of the consequences of AMU. The fourth issue consists of the ethics of priority setting; for instance the welfare of animals versus humans. The fifth issue consists of the ethics of AMU in animal agriculture. We have already raised animal welfare concerns that might occur in the case of regulations limiting AMU, to fulfill an objective of AMR mitigation. The use of antimicrobials as growth promoters might be seen as unethical, even if it increases food productivity, and since the E.U.'s pioneering of this position in 2006, many countries have banned this form of use (Parsonage et al., 2017). Yet, regardless of the intensification of farming systems, antimicrobials represent a tool that farmers use for economic purposes, enabling them to control damages generated by the occurrence of disease. Any policies are also likely to impact farmers, many of whom will be unable to maintain their level of production. Ultimately, this also raises concerns of fairness of food affordability. Antimicrobial use in animal agriculture contributes partially to a rise in therapeutic failures in humans; even though the quantitative contribution to this failure remains unclear, this justifies policy to decrease AMU in animal production (Tang et al., 2017). Nevertheless, we should track in detail the potential economic impacts of regulatory instruments, and elaborate the need for compensations (Bonnet et al., 2018; Lhermie et al., 2018). This assessment demonstrates that AMR is characterized by multiple and sometimes conflicting perspectives. Any solution to tackle AMR involves balancing interests and ethical concerns.

4.2 Temporal scale

Sustainability assessment seeks to evaluate policies to be implemented; but one of the difficulties is the disconnect between the political system time frame, which is generally short, and the resource ecosystem, which is longer. As sustainability is associated with a long-term perspective, evaluation of sustainability should consider the capability of the present system to cope with policies targeting long-term goals. In addition, as in every SES, the AMU-AMR SES will exhibit properties that emerge from the interactions of many interrelated factors, and understanding such systems involves focusing on a web of intricate interrelationships among subsystems, dynamics of stocks and flows, delays, and feedback loops (Ostrom, 2007).

4.3 Spatial scale

Unlike several natural resources, one can reasonably speculate that bacteria susceptibility was homogeneously distributed at the beginning of the Anthropocene. A major difficulty with AMU-AMR SES is that although it is possible to set boundaries to AMU exchanges, no geographic boundaries can contain AMR extension, as recently illustrated by the dissemination of New Delhi metallo-β-lactamase type 1-producing *Enterobacteriaceae* and *non-Enterobacteriaceae* around the globe (Bushnell et al., 2013). This is just one example of the tremendous increase of commodities and people being vectors of AMR dissemination. As suggested by Ali (2013), spatial scale should consider not only the geographical jurisdiction of the policy influences, but also the influences exerted by one or a group of countries across other policies not targeting AMR. Furthermore, it is possible that a sustainable policy implemented in one country will not be appropriate in another country, because of cultural and social elements. Policies coordination within and beyond the states represents a challenge that requires a coalition of global actors operating in various fields, including human and animal health and food safety and security (Dar et al., 2016).

4.4 Accumulation and carrying capacity

Recent trend analyses have shown a relative progression of AMR in both human and animal health (Center for Disease Dynamics Economics & Policy, 2018; ECDC, EFSA,EMA, 2017a). As for many other resources, we observe an accumulation effect that arises from two different mechanisms. First, AMR constitutes by nature a negative externality of AMU, meaning that the users do not have to bear the full costs of AMR (Coast et al., 1998). An assumption is to consider bacteria susceptibility as a public good; its overuse is described as a "tragedy of the commons", leading unavoidably to an overconsumption of antimicrobials, reinforcing AMR (Herrmann and Laxminarayan, 2010). Second, the capability of microorganisms to exchange genetic material in support of resistance, at a low or even no metabolic cost, allows an unstoppable progression of AMR over time (von Wintersdorff et al., 2016). As selection and dissemination of AMR go hand in hand, the accumulation happens over time and space, and must be accounted for at the time of policy evaluation. This accumulation process challenges the resilience of the system and leads one to question the existence of a threshold beyond which, at a community scale, the bacteria susceptibility will not be preserved.

Indeed, the vast majority of research and policies regarding AMR have implicitly neglected the value of susceptible strains to human society and focused instead on AMT efficacy and resistance costs. But the ability of susceptible strains to outcompete or prevent colonization of resistant strains under favorable conditions must be considered as a regulating ecosystem service, from which humans benefit (Jørgensen et al., 2017). Consequently, the carrying capacity of the global AMU-AMR SES should be addressed. Assessing the existence of a carrying capacity and the influence of anthropogenic interventions would be very complex; however, questions about its existence induce one to think about which definition of sustainability we should embrace. In a recent paper, the Rockefeller Foundation Lancet Commission recommended framing policies integrating nature and economy, accounting for depreciation of natural capital, to advance planetary health (Whitmee et al., 2015). The challenge represented by AMR should be met by adopting policies recognizing the importance of ecosystem services related to bacteria susceptibility.

5. Indicators to be used

Sustainability assessment seeks to determine the policy influences on the status of resources (Pope et al., 2017). Common tools are risk analysis and benefit-cost analysis, used for decision analysis; the main challenge consists of successfully merging these approaches. The characteristics of a sustainable policy (including the absence of policy as an option) should be assessed by understanding the consequences of a policy on the natural resources system. Evaluation requires the definition of indicators. Altogether, the key of sustainability assessment is to determine which indicators at the frontier of biological and social domains will be able to capture the social, environmental, and economic implications of a specific time and space scaled SES. The categories of indicators found in the literature and those we propose for the purpose of this article are depicted in Fig. 3.

Fig. 3: Pentagon of proposed indicators to be assessed. At the center of the pentagon (pale and dark blue), indicators are presented by categories, and superposed to the Driver-Pressure-State-Impact-Response model (pink part). In the green part of the figure, we propose more specific indicators, based on their availability and accuracy. AM: antimicrobials; AMU: antimicrobial use; QALYS: Quality-Adjusted Life Year; VSL: Value of a Statistical Life.

5.1 Environmental indicators (Pressure, State)

As the word "environmental" can take different meanings, environmental impacts (soil erosion, greenhouses gas emissions, water and energy consumption, biodiversity, etc.) related to animal agriculture fall beyond the scope of this paper, although we recognize that any changes in agricultural practices will affect the environment.

At first, we define the status of the state through a set of measured indicators: level of bacteria susceptibility, presence of resistance among animal and human communities and in the environment, and geographic extension of resistance. The following challenge is the definition of the level of susceptibility. It requires one to define the outcomes of interests, *i.e.*, which bacteria, which antimicrobial, and the cut-off separating a susceptible from non-susceptible strain. Depending on the country, AMR surveillance networks are implemented to monitor the emergence of resistance, and the prevalence of resistant strains of bacteria of interest, either commensal or zoonotic (Ferreira and Staerk, 2017; Sharma et al., 2018). As an example in food producing animals, the European Food Safety Agency (EFSA) recommends the monitoring of AMR in zoonotic agents (*Salmonella* spp., *Campylobacter* spp.), and commensal bacteria (*E. coli*, *Enterococcus faecium*, *Enterococcus faecalis*) (ECDC, EFSA, EMA, 2017b). A large panel of antimicrobial substances are used for this monitoring, including substances that are not used in animal agriculture. Additionally, the presence of resistance of specific interest in human health (*E. coli* presenting extended-spectrum beta-lactamase, AmpC and carbapenemases enzymes producers) is tracked. Given the technical feasibility and availability of such data, a set of indicators of susceptibility to be included in our model should be identified per production category (beef cattle, dairy cattle, fattening pig, broiler, laying hen, etc.).

Regarding the cut-off, there is currently no adopted international standard defining antimicrobial susceptibility, even though the susceptibility breakpoints established by the Clinical & Laboratory Standards Institute (CLSI) in the U.S. and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) in the E.U. are the most used worldwide. However, the complexity of collecting harmonized data on bacteria susceptibility trends among countries (Dar et al., 2016; Wernli et al., 2017) opens the gate to add complementary indicators. For farming systems, three categories of environmental indicators have been proposed: measured indicators based on field data, but also simple indicators based on causal variables, and predictive indicators based on outputs from models (Bockstaller et al., 2015).

Antimicrobial consumption represents a simple and easy way to monitor indicators of the pressure that can be linked to the state. The specification of what consumption is has to be indicated by defining pharmacological indicators, such as the classes of antimicrobials, their pharmacokinetics and pharmacodynamics, and epidemiological indicators, such as the treated animal species, the populations' consumptions and the level of exposure. Currently, we observe a harmonization of the methods of collection of AMU data, led by international organizations such as WHO and EU agencies, that will allow in the future mid-term trends analysis (ECDC, EFSA, EMA, 2017b; EMA, 2018; WHO/FAO/OIE, 2016).

5.2 Economic indicators (Drivers)

Economic indicators regroup a set of indicators capturing the viability of the farming system (Latruffe et al., 2016). A combination of indicators appears relevant to assess economic viability, as sustainability assessment requires accounting for long-term consequences, for the farmer and across generations. The viability can be assessed through profitability (comparison of revenues and costs), productivity (ability of the inputs to generate an output), liquidity (cash availability), and stability (share and development of equity capital). Depending on the farming system, autonomy is another potential indicator. It has to be understood in terms of financial autonomy; as an example, a high dependence on public subsidies might threaten farmers' autonomy in the case of policies linking subsidies' payments to an environmental objective.

5.3 Social indicators (Drivers, Impacts)

Social sustainability refers to people in the SES, in which two categories can be distinguished.

The farm communities are the first one, and social sustainability is related to their well-being. Many indicators of well-being are reported in the literature among which four categories emerge: education, quality of life, working conditions, and physical health. Several tools for farm level sustainability assessment have been developed, presenting discrepancies in the list of indicators (de Olde et al., 2017). Among them, the Sustainability Assessment of Food and Agriculture systems (SAFA) model developed by the FAO in 2013 uses 19 indicators to track social well-being (FAO, 2013). Specific indicators related to health seem particularly relevant for our purposes, as the exposure of farmworkers to resistant bacteria is likely to be higher than in outpatient populations.

Consumers are the second one. At the society level, the quality of the food commodities needs to be appraised as a function of the sanitary quality (absence of residues or pathogens), which constitutes a "must have", and the meeting of nutritional requirements, following international quality standards (FAO, 2018).

Antimicrobials limit the losses generated by diseases, and therefore constitute tools that help to ensure food security. Several indicators of food security developed by international organizations (FAO, World Bank, WHO) are reliable at different scales of analysis (individual, household, national, global). They integrate the following four dimensions: availability, access, utilization and stability (FAO IFAD UNICEF, 2017) .

Animal welfare represents an issue that overlaps in the farm communities and the society levels. As already discussed, a decrease in AMU in animal agriculture might worsen animal welfare on farms. At the same time, as social pressure rises regarding farm animals husbandry and raising conditions, one can consider that animal welfare constitutes per se an indicator of sustainability. Evaluating animal welfare is not a simple task; yet, the main sustainability assessment models refer to commonly accepted tools for evaluation, such as the Welfare quality protocols for animal welfare (Welfare Quality Network).

5.4 Public health indicators (Impacts)

The link between AMU in animal agriculture and AMR in humans has been evidenced in multiple studies (Tang et al., 2017). However, determining the relative risk for public health due to AMU in agriculture remains challenging. Hence, the contribution of risk analysis becomes useful, before implementation of policies (Havelaar et al., 2007; Salisbury et al., 2002). Here, we adapt a part of the methodology proposed by the Codex Alimentarius for foodborne AMR and by the OIE for AMR arising from AMU in animals to address these questions (Codex Alimentarius, 2011; OIE, 2013) . The objective of risk analysis is to provide a method to assess the risk for human health, and determine risk management strategies. Though an entire risk analysis is not the purpose of our paper, risk assessment is a useful tool to characterize the relationship between the pressure and the changes in the state. The hazard, in our adaptation, is the potential of a pressure to exert a change in the state i.e., the selection and dissemination of resistant bacteria. The identification of the hazard should include specifications regarding the antimicrobial agent, and microorganism.

The exposure assessment seeks to estimate the level of exposure to the hazard. This approach can be used to determine the transmission routes and their relative importance. It involves the collection of various data, regarding the bacteria, the antimicrobials, and the animals treated. Data regarding humans (population density, transfer of resistant bacteria between humans, human food consumption, etc.) have to be considered too. The exposure assessment also requires one to clearly define the biological exposure pathway of humans to resistant bacteria**.** At this point**,** the likelihood of selection, dissemination and transfer of resistant bacteria from animals to humans is determined. The probability of exposure is quantified with regards to concentration, timing, frequency, interactions, route, and species. The next step consists of hazard characterization (consequence assessment). Hazard characterization describes the relationships between exposure to the hazard and human health effects. This step requires one to document human host and adverse health effects: susceptibility of exposed populations, variation in frequency of illness, epidemiological patterns, and severity of infections, as well as dose-response relationships.

The integration of the results obtained in the previous exposure assessment and hazard characterization leads to risk characterization. The indicators that have to be considered at this step are related to the morbidity and mortality of infections with resistant bacteria, their severity, duration, the potential adverse effects, and the availability of therapeutic alternative strategies. Then, indicators commonly used in health economics allow one to present the different outcomes of the sustainability assessment in the common metric of monetary units. Mortality risk reductions can be monetized by the Value of a Statistical Life (VSL). Morbidity risk reductions can be monetized by the willingness-to-pay per Quality-Adjusted Life Year (QALY).

5.5 Policy indicators (Responses)

The WHO identified five high-level policy areas, namely, universal access, surveillance, responsible use, infection control and innovation. At a global level, some response indicators, such as the number of countries with specific AMR plans, the presence of monitoring system(s), or regulations targeting specific classes of antimicrobials, are of interest; some information is already available (OIE, 2017; WHO/FAO/OIE, 2016). Identifying and promoting these general policies are of course necessary; yet, regulations are implemented at national levels, and decision-making regarding AMU is made by individuals subject to any imposed government constraints. Therefore, the indicators encompass the feasibility of the response, depending on the time horizon of the policy planning and on available resources. The relative importance of public investments in research, monitoring and surveillance, policy planning, and field implementation and control have to be reported. Response indicators should also consider the progression of the policies from the framing as well as the deadlines fixed (if any) to observe an improvement in the SES, because of the expected delays between enactment and the effects on the other indicators. The last challenge is to measure the level of synergy between the responses proposed, as strategies are interdependent (Hoffman and Outterson, 2015). There is little doubt regarding the importance of international organizations to foster synergy and help to transpose success stories, as some countries have already succeeded in tackling AMR. Yet, as AMR is a global threat, we must qualify and quantify free-riding behaviors at a national scale on a higher scale, to inform policy-makers regarding the necessity of encouraging coordinated actions.

5.6 Analytical methods

Numerous sustainability methods have been developed and used for sustainability assessment (de Olde et al., 2017; Onat et al., 2017; Sala et al., 2015). These are designed to either assess performance of policies, provide information regarding trends of improvement or warning, and/or provide information to policy-makers to formulate strategies. Ness et al. (2007) develops a conceptual framework for sustainability assessment tools, categorizing methods according to their temporal focus (retrospective or prospective) and the object of the focus (change in policy or product oriented). Jeswani et al. (2010) proposes to combine cost-benefit analysis with risk analysis to evaluate sustainability goals and issues (Fig. 2).

We introduce here two analytical methods, which are well-suited for assessing AMU, incorporating all of the discussed indicators. The first consists of dynamic models to perform cost-benefit analyses that incorporate optimal decision-making over multiple periods of time. The dynamic nature of bacteria susceptibility, prone to change over time, and dependent on a set of variables, which include the amount of antimicrobials used, as well as the interactions between the different stakeholders with potentially opposite objectives, favors developing dynamic models and to do cost-benefit analyses that consider multiple periods of time. These can be constructed using structural biological and economic relationships incorporating the indicators as measures. Dynamic structural econometric models that combine statistics and econometrics have previously been applied to model agricultural disease management (Carroll et al., 2019b), agricultural productivity (Carroll et al., 2019a), pesticide spraying decisions (Sambucci et al., 2019), water management (Timmins, 2002), environmental policy (Ryan, 2012; Fowlie, Reguant and Ryan, 2016), bus engine replacement (Rust, 1987), fisheries (Huang and Smith, 2014, Shin et al., 2019), renewable fuel policy (Lin Lawell, 2017; Thome and Lin Lawell, 2019), and climate change policy (Auffhammer et al., 2016, Zakerinia and Lin Lawell, 2019). Dynamic models would enable policy-makers to analyze, explore, and experiment with a variety of possible policies without actually having to implement those policies, thereby facilitating the optimal design of policy.

The second analytical method consists of multi-criteria decision analysis. Multi-criteria decision analysis can be employed in system dynamics modeling in situations when there are competing evaluation criteria. This approach presents the advantage of including quantitative and qualitative data in the analysis (Marsh et al., 2017). Such methods also permit identification of alternative paths which can then be discussed by the stakeholders in the system (O'Connor, 2010). Consideration of multiple criteria is particularly relevant in situations where researchers of policy-makers may not assign a monetary value to environmental and social impacts. A multi-criteria objective function with tradeoffs between animal and human welfare would produce a single index social welfare function to be assessed by simulation, or optimized with specified controls such as AMU by animal group over time, as presented in Fig. 4. Functional relationships would be estimated with data collected or generated by various techniques including expert judgements and experiments, as well as primary and secondary data collection.

Fig. 4: Representation of the trends of aggregated and weighted indicators in several potential policy scenarios. Each curve represents one policy scenario, likely to reinforce or threat the sustainability of antimicrobial use.

6. Conclusion

For decades, antimicrobials have been used in animal agriculture for economic purposes, first to control damages generated by infectious diseases, and sometimes to promote growth, the latter being currently banned in many developed countries. Yet, antimicrobials have a specific characteristic among all production inputs, lying in the fact that their use generates a negative externality, AMR, representing a public health hazard. Food retailers, consumer groups, and governments demand that AMU in animal agriculture be curtailed. Therefore, our society faces a tradeoff, with farming systems still dependent on AMU on one side, and public health threats and increased social pressures expecting a strong decrease in AMU on the other side.

Notwithstanding its complexity, evaluating AMU sustainability is necessary for advising policy-makers on the potential impact of regulations. AMU decision-making relies on an interdependent mix of economic, behavioral, ethical, and cultural factors. We advocate assessing the sustainability of AMU in the Social-Ecological Systems framework, using already identified indicators, and employing analytic methods in dynamic cost-benefit analysis and multi-criteria decision analysis.

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