Trade-offs related to agricultural use of antimicrobials and synergies emanating from efforts to mitigate antimicrobial resistance

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1. Abstract

Use of antimicrobials in livestock and fish production has been increasing drastically in the last decades, with trends pointing towards further increases over the coming years. The situation is particularly complex in low- and middle-income countries (LMIC), where excessive use in intensifying systems and limited access to drugs in some areas are a problem. In more intensive farms, antimicrobials are commonly used to treat and prevent disease in livestock and fish, often masking poor husbandry practice and high level of endemic diseases. On the other hand, the poorest farmers could increase productivity with better access to veterinary drugs to appropriately treat sick livestock. Tackling problems around antimicrobial resistance (AMR) requires a multi-sectoral and multi-disciplinary approach, facilitating synergies, and mitigating trade-offs. On one hand, crucial knowledge gaps exist on transmission on AMR genes at the human, animal and environmental interface, while social science insights are needed to improve understanding of drivers and decision making around use of antimicrobials in agricultural and aquaculture settings. This evidence will then help to define and evaluate interventions needed to achieve development outcomes and to sustainably contain the risks around AMR. Directly linked are important synergies in such that improving husbandry and strengthen disease prevention would promote more productive and sustainable production systems, while at the same reducing need for use of antimicrobials. This in turn would reduce selection pressure and reduce antimicrobial residues in animal source foods.

The proposed CGIAR AMR-strategy recognizes these trade-offs and sees opportunities to promote synergies by mitigating AMR risks. The strategy aims to address knowledge gaps and evaluate interventions to reduce use of antimicrobials in agriculture, with focus on livestock and aquaculture. Coordinated through a proposed CGIAR AMR-

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hub at ILRI, the strategy comprises five areas of interventions which are 1) understand knowledge, attitude, and practices, for antimicrobial use or reduction in use and role of formal and informal markets; 2) research AMR transmission dynamics at the human-animal-environmental interface in different agricultural systems; 3) design and evaluate interventions and incentives to reduce or more effectively use antimicrobials in agriculture in LMICs; 4) support evidence-based policy dialogue for antimicrobial surveillance and AMR strategies; and 5) capacity development. Building on the existing AMR research portfolio in CRPs A4NH and LIVESTOCK, the CGIAR AMR-hub brings together researchers from ILRI, IFPRI and WorldFish and aims to closely work with strategic partners from the academic and NGO sector.

2. Context and challenge

The problems around antimicrobial use (AMU) and resistance in low- and middle-income countries (LMICs) are increasingly complex, and while the importance of agricultural use for resistance selection and emergence and the importance of different transmission routes that result in public health implications is poorly understood, there is no doubt, that use in livestock production and in aquaculture are significant and contribute to the burden of human AMR. The discovery of antibiotics and their use to treat bacterial infections has revolutionized the way infectious diseases in people, livestock, fish, and, to a much less extent, crops, are managed. The trade-offs of these practices however are obvious. If these drugs stop working, millions of human lives and livelihoods are at risk, yield of animal-source foods will reduce because of disease burden, contributing to economic impact of AMR and jeopardize global food security. To make matters worse, the discovery of new antimicrobials has slowed down, increasing the reliance on existing compounds to treat infectious diseases.

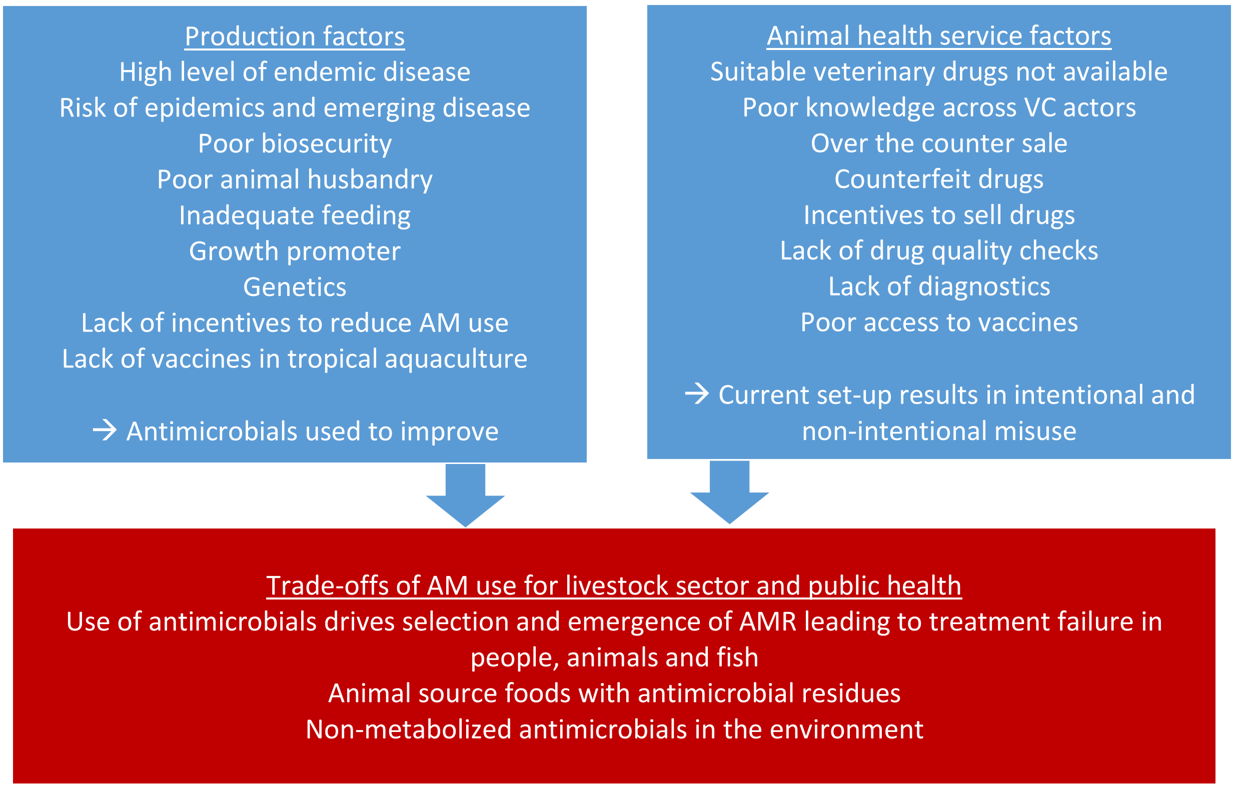

***Figure 1**. summary of trade-offs linked to drivers of antimicrobial use in livestock production and aquaculture and animal health service delivery*

Similar to the situation in humans, antimicrobials are used in sick animals for treatment purposes, which in itself can lead to wrong use due to lack of diagnostics and thus use of the wrong drugs, or dosages used are too low or drugs not consumed long enough. In aquaculture, treatment of single animals is not possible as treatments are commonly applied trough feed and water, leading to consumption of drugs also by healthy fish. Unlike in humans, AMU in agriculture (or aquaculture) has additional reasons and factors driving the use or misuse of antimicrobials can broadly be categorized into factors linked to production and factors linked to animal health service delivery (Figure 1). The growing demand for food requires agricultural food systems to adapt and promotes high-input intensifying systems, which may act as a driver to increase use of antimicrobials to increase productivity. This is especially a problem of growing concern in intensifying pig, poultry, dairy and aquaculture systems in LMICs with poor husbandry practices and biosecurity and where enforcement of regulations is patchy. Intensification of production systems changes the way livestock and fish are produced and puts extra pressure on husbandry practices and can change transmission pattern of endemic and epidemic diseases, which in itself is an important incentive to use more drugs to prevent and treat infectious diseases. On the other hand, it is easier for intensive farms to adopt good practices which can reduce disease risks. Other reasons of use are to mask the effect of poor husbandry practices, or to promote growth and enhance feed efficiency. Another problem is the limited use of preventive measures, such as vaccines, which would be key to combat the high level of endemic production diseases and help to mitigate the impact of epidemics. For some diseases, vaccines do not yet exist, but mostly the lack of access and limited incentives to use vaccines are the key problems leading to low vaccination coverage in poor areas.

The other important group of drivers of AM use are related to inadequate animal health service delivery systems. Poor knowledge on proper use (among farmers, community animal health workers, veterinarians and drug seller) affects use patterns of antimicrobials with increasing intentional and unintentional mis-use. In addition, sale of drugs, incl. antibiotics is an important source of income for many, which may act as a disincentive to promote preventive measures. Part of the problem is also the lack of access to adequate diagnostic tools which leads to non-targeted use of antibiotics and other drugs, both of which are widely available over the counter. In vet-drug outlets, the selection of drugs is often limited, leading to overuse of some compounds, in addition drug quality in some countries is highly variable. Sale and use of cheap substandard and counterfeit drugs are rife in some areas, fueling bad practice of veterinary drug use and hampering attempts to reliably monitor drug use.

The fact that the same drug classes are used in humans and animals and the sheer amounts of drugs administered to livestock and in aquaculture, fuels discussions on the resulting public health risks. Past research in LMICs has mainly focused on determining prevalence of AMR genes and investigated antimicrobial residues, providing evidence on widespread occurrence of resistance to old and comparably cheap and easy accessible antibiotics and antiparasitic drugs. But there are comparably few studies that conclusively proof transmission of AMR from food animals to humans. There is thus a need for more high-resolution genomic data based on systematically collected samples that allow understanding of directions and intensities of transmissions.

Another area of concern for public health is antibiotic residues in products. In livestock production in LMICs withdrawal times are often not respected and inappropriate use of antibiotics in livestock production leads to residues in animal source foods. Similarly, antibiotic residues in fish and shrimp are likely in countries without surveillance systems. While the direct health impacts of this are very small, residues can interfere with food processing and provide additional pathways through which drugs can exert selection pressure for resistance. Drug residues reduce access to demanding markets and are a common reason for rejection of food imports to Europe.

Of course, use of antimicrobials in people and animals can also foster resistance in animal pathogens. There is limited evidence for the extent and economic impact of this, but for some livestock diseases (e.g. mastitis) resistance to antibiotics is common.

Further it is important to notice, that people, livestock and fish metabolise only a fraction of consumed antibiotics, with up to 90% of antibiotics ending up in the environment, which is of particular concern in areas with poor sanitary systems. It is known that antibiotics alters the environmental microbiome, however long-term impacts are as yet unknown.

While the poorest have limited or no access to drugs, and struggle to treat sick animals, in other production systems, producers have easy access to drugs and use them in ways that provide most immediate advantage but may have long term risk. Overall there is a clear trend in increased use of antimicrobials is LMICs, calling for interventions to curb use. But different contexts need different solutions in order to achieve change of behaviour and to address trade-offs of AM use.

Research efforts to deal with the synergies and trade-offs

There are obvious synergies coming out of tackling AMR risks. Most of all, any investment towards improving husbandry systems and strengthen disease prevention, removes important reasons for drug use, while promoting more productive and sustainable production systems and animal source foods derived from healthier animals. Improving access to quality veterinary drugs and animal health services in general, may help to change outdated institutional arrangements by promoting public-private partnerships in animal health service delivery, which in turn creates jobs, esp. for the young. Using antimicrobials more responsibly can also facilitate improved access to international markets. And last but not least, given the close links to public health, tackling agriculture associated AMR fosters inter-sectoral collaboration of which benefits for all involved are tangible.

The complexities around agricultural associated antimicrobial resistance and related trade-offs as outlined in the context section above are addressed by the CGIAR through research in two CRPs and several bilateral projects. The CRP A4NH in its flagship 'Improving Human Health' dedicates a set of activities on understanding AMR at the interface of human, animal and environmental health aiming to identify solutions to common problems arising for agriculture and health in a development context. Using a multi-disciplinary approach combining bio- and social sciences the program also aims to measure impact on public health of AMR mitigation in the livestock and aquaculture sector. The Livestock Health flagship in the CRP LIVESTOCK looks at AMR from a herd health perspective with the aim to promote prudent and effective use in livestock, understanding trade-offs related to productivity and develop and scale interventions that lead to reduced use at farm level, improve diagnosis and develop needed vaccines, and setting up responsible animal health service delivery models.

AMR research priorities in CRPs A4NH and LIVESTOCK and bilateral projects, underpin the proposed CGIAR wide strategy to tackle AMR to be mainly implemented by ILRI, IFPRI and WorldFish, through a dedicated CGIAR AMR-Hub at ILRI. This strategy includes 5 areas of intervention with a set of proposed activities as outlined in Table 1.

Table 1. *Overview of CGIAR AMR activities and interventions*

Area of intervention	Activities
Understand knowledge, attitude, practices, and incentives for antimicrobial use or reduction in use and role of formal and informal markets.	• Collect and collate data on use of antimicrobials in livestock, aquaculture, and crops (antibiotic classes, dosage); • Understand stakeholder behavior and incentives that drive decision-making for AM use; • Assess quality and governance of antimicrobials used in humans, livestock, fish, and crops; • Understand incentives and rationales for antimicrobial use in agricultural systems • Conduct research on formal and informal AM markets and access of producers to markets.
Research AMR transmission dynamics at the human-animal-environmental interface in different agricultural systems;	• Collect data on the extent of antimicrobial-resistant bacteria found in livestock, fish, humans, the environment, and food • Conduct research to understand the transmission and genetic mechanisms of resistance in agriculture and the implications for human and animal health • Model AMR in LMICs to understand the relative contribution of agricuturally-associated AMR to the human AMR burden and risk of drug resistant infections in different contexts
Design and evaluate interventions and incentives to reduce and more effectively use antimicrobials in agriculture in LMICs	• Develop and evaluate the impact of a range of local interventions in agricultural systems to reduce AMR risks to human populations, taking a transdisciplinary approach which engages researchers and stakeholders from different sectors; • Develop and test gender-sensitive pest and pathogen controls to better manage livestock and fish diseases and reduce the use of AMs; • Explore feasibility of incentive-based systems, especially intensifying production systems • Understand the costs and benefits of interventions to tackle AMR, at different levels of analysis (stakeholder, value chain, national) • Characterise gender-differential impacts of interventions on poor farmers, vulnerable groups and address other societal objectives such at attaining nutrition security • Understand the potential of market demand/pull for responsibly-produced foods (animal source foods, fish, and crops).
Support evidence-based policy dialogue for antimicrobial surveillance and AMR strategies	• Synthesize evidence on antimicrobial use and AMR to influence public policy and the development of credible, enforceable regulations that reduce AM use • Generate evidence to promote good practices in the governance, supply, use, and disposal of agriculture-associated AMs and identify incentives that facilitate their adoption; • Engage policymakers in agriculture and health, and encourage integrated policy approaches supported by experimental evidence, in the context of One Health solutions • Pilot and evaluate approaches for surveillance of use of aAMs, treatment failure, and AMR • Contribute to mapping existing and projecting future use of antimicrobials in the face of increasing intensification.
Capacity development	• Support capacity building and increase awareness of AMR in the agricultural sector (veterinarians, livestock and fish producers, and service providers) • Support exchange programs for LMIC researchers with the AMR Centre of Excellence in Denmark and other affiliated institutions • Provide and facilitate access to research facilities for researchers from LMICs • Organize and run training programs on AMR, including research and mitigation, using modern online and interactive formats as appropriate to the intended audience.

Development of the TOC and impact pathways

In A4NH, mitigating AMR risks is expected to be achieved through policy and development impact pathways. The generated outputs, allowing better characterisation of AMR risks and closer collaboration of agricultural and public health stakeholders, provide the basis for policy recommendation and will influence the design of development programs. Through this, sub-IDOs targeted are 'reduced livestock and fish disease risks' and 'increased safe use of inputs' leading to the IDO 'improved human and animal health', while the sub-IDOs 'enhance institutional capacity or partner research organisations' will contribute to the IDO ''enabling environment improved'. Similarly, the CRP LIVESTOCK explicitly refers to AMR in its TOC where integrated technological solutions, including inputs that improve animal husbandry and which act to protect and enhance investment, result in improved animal health. Gaps of access to antimicrobials and understanding of AM use practices provide entry points for targeted capacity building and engaging policy makers, which will lead to changed practices contributing to the sub-IDO 'reduced biological and chemical hazards in the food systems' and with this to the IDO 'Improved human and animal health'. Integration of AM-use reducing interventions in herd health packages will contribute to the sub-IDO 'closed yield gaps through improved agronomic and animal husbandry practices' linked to the IDO of increased productivity.

3. Metrics in CRPs

AMR research is reflected in indicators in CRPs A4NH and LIVESTOCK, namely as 'Public and private sector policymakers are implementing measures to reduce health risks from AMR in hotspot livestock systems', and '5.6 million people in livestock keeping households experiencing 15% (or actual) reduction in prevalence of zoonotic pathogens and applying rational use of antibiotics in the livestock food system, translating into reduced risk for increase in anti-microbial resistance and improved food quality for 2.7 million consumers in 7 countries'.

Along the impact pathways, we track progress by measuring science, capacity and policy outcomes. Science quality is measured through peer-reviewed papers published and their uptake in the scientific community. Number of people benefitting from capacity development, incl. farmers, animal health service providers, policy makers, and MSc and PhD students supported can be easily measured. Several technologies are being tested for their potential to reduce AMU including disinfection, vaccines, and pro-biotics. Impacts of these, such as productivity gains ad socio-and economic impacts, are carefully monitored, evaluated and documented to derive best-practice recommendation for scaling. Both CRPs already are engaging with national policy in several countries (notably Kenya, Ethiopia and Vietnam), and number of policies influenced through research outputs will be monitored.

4. Critical partnerships

Partnerships with academic institutions from the veterinary and the public health sectors have been critical to define the research agenda and to promote close interactions with the public health sector. The Swedish University for Agricultural Sciences (SLU) coordinates AMR activities in CRP LIVESTOCK and brings vast experiences on AM use management in European settings and how to translate these to a LMIC contexts. Through A4NH, the academic partners London School of Hygiene and Tropical Medicine (LSHTM) and University of Liverpool play key roles in facilitating interactions with the public health sector. For the research in the field, such as testing of interventions, partnerships with the national agricultural research systems and local and international NGOs have been key.

5. Lessons learnt, including knowledge gaps and good practices in employing these approaches at scale

AMR currently gets a lot of attention for research and development with various national and international initiatives and funding opportunities, with many of them pursuing intersectoral solutions. A major challenge with all these ongoing endeavors is to coordinate actions to avoid duplication, or worse, promote contradicting messages. There is a need to ensure all knowledge gaps are addressed properly, to fully engage the pharmaceutical private sector in the process and to propose solutions that are acceptable to all stakeholders and reach the livestock producers in the different production systems. The CGIAR AMR-strategy is a way to demonstrate good practice by strategically focusing on trade-offs and fostering synergies by promoting collaboration across sectors, linking different CG centers and CRPs and including external partners to address expertise gaps in the CG system and to link with the public health sector, which is outside the remit of the CG system.

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