Antimicrobial Stewardship under Global Framework

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Antimicrobials are naturally occurring semi-synthetic or synthetic substances that kill or inhibit the replication of microorganisms. Remarkable achievements have been reached in human medicine due to the availability and efficacy of antimicrobials, from the treatment of previously fatal infections to surgical procedures, otherwise impossible. Promoting and supporting antimicrobial stewardship (AMS) at the global, national, and local levels is dependent on building strong supporting pillars. From the Food and Agriculture Organization (FAO) perspective, these pillars are (1) awareness, (2) governance, (3) practices, and (4) surveillance.

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1. Awareness

1.1. Effective Awareness Raising—Global Level

To more effectively raise awareness and transform it into action, the objective and target audience for awareness raising must be clear. At a global level, Food and Agriculture Organization (FAO) leverages and synergizes its organizational strengths by partnering with other organizations and entities to keep Antimicrobial resistance (AMR) on the global agenda in an ongoing effort to secure ongoing high-level commitment to address this challenge. An example of one recent initiative, in collaboration with Johns Hopkins University/React, introduces AMR/animals and antimicrobial use (AMU) into strategic policy venues where these issues might be taken up for discussion by key stakeholder groups, from government officials to civil society.

Providing access to knowledge is also critical so that those advising policymakers and politicians have up-to-date information that will inform the brief of those partaking in international dialogues. In addition to publishing data, FAO started a monthly Knowledge Dissemination Dialogue webinar series as a means of making experts and knowledge more accessible to all countries. These data-rich webinars bring participants up to date on specific scientific and technical topics related to AMR. These may include, among others, microbiology, epidemiology, environmental or behavioral science, plant and animal production, and health. They are open, free of charge, and available on the FAO YouTube channel [1] and provide an opportunity for everyone, everywhere, to learn about cutting-edge approaches to address AMR from some of the world's most respected "thinkers and doers".

Social media and communication channels that can be widely and easily accessed through cell phone technology are key in order to reach wider audiences. Thus providing context-specific information on AMR and simple messages and actions for different sectors through different social media channels are increasingly gaining traction.

1.2. Barriers to Change—Local Level

AMR can be considered a social problem, thereby requiring social solutions [2]. Consequently, theory and methods from across the social sciences are necessary to undercover and understand the multiple and interacting environments and drivers from which AMR emerges and is transmitted among people, animals, plants, and the environment. These environments and factors are influenced and impacted by the activities of those manufacturing, regulating, selling, prescribing, and using antimicrobials, with many practices along value chains being enabled, encouraged, or constrained by broader sociocultural, political, and economic structures. Benchmarking tools (farmer-to-farmer comparison) can also have a potential role in enabling livestock producers to see how their AMU compares to comparators in the national and production system context, and therefore they can represent a relevant approach to engaging livestock producers in changing behaviors.

To begin understanding these influencers and drivers, the FAO has been exploiting the power of mixed-methods qualitative and quantitative approaches to identify the knowledge, attitudes, and practices that drive AMR, including patterns of antimicrobial use and practices for on-farm infection prevention and control. This “bottom-up approach” emphasizes that interventions and strategies to address AMR must be evidence-based and should draw upon knowledge, attitudes, and practices displayed by a wide range of stakeholders with the power to affect AMR in the agrifood sector, including farmers, animal health professionals, agrifood producers, policymakers and citizens [3].

The benefits to AMR of this bottom-up approach are exemplified by an international study supported by the Fleming Fund of the United Kingdom. Broadly, patterns of knowledge, attitudes, and practices among users, sellers, and prescribers of antimicrobials within livestock systems were assessed across five sub-Saharan African countries, including Ghana, Kenya, Tanzania, Zambia, and Zimbabwe [3]. On a typical mission, the FAO research team, working alongside government officers, would conduct focus groups and in-depth interviews among farmers, agrovets (sellers of veterinary medicines), and animal health professionals from the public and private sectors. Qualitative data from these interviews would then be examined for reoccurring themes and inform the development of quantitative knowledge, attitudes, and practices survey. To administer the survey, enumerators from local communities would be trained in ethnographic methods, and thereafter, the survey would be administered to around 200 farmers. Community engagement is critical. After analyzing the survey data for risk factors related to the emergence and spread of AMR, the research team would return to the community to discuss results, with a focus on further understanding the factors driving risky practices and the barriers to the adoption of best practices.

Results from the studies such as the ones described above highlight several important challenges to addressing AMR within low- and middle-income countries and in the animal health sector. First, across countries and livestock production systems, a person’s knowledge and attitude toward AMR did not predict their AMR-relevant practices [3]

[4]. That is, those who recognized that AMR was a problem driven by inappropriate use of antimicrobials were no more likely to use antimicrobials prudently. This knowledge-practice gap stresses that, alone, awareness-raising campaigns, which to date have played a major role in global and national strategies to address AMR (e.g., World Antimicrobial Awareness Week), are unlikely to motivate better practices and thus ultimately have limited effect on reducing AMR [5]. Awareness campaigns need to be targeted with clearly associated theories of change and expected outcomes that can be measured to determine reasons for suboptimal success. A second major barrier to addressing AMR in agrifood systems in the countries studied was the limited influence of animal health professionals in the treatment of livestock [3][6][7]. The professional animal health sector in many low- and middle-income countries, due to long-term divestment in public services since the 1980s and 1990s, does not always have the capacity to ensure sick animals receive the proper diagnosis and proper treatment. Consequently, even if farmers believed animal health professionals should always be consulted when their animals were sick, a lack of access to this source of reliable information limited the translation of these attitudes into action. Together, these observations highlight the importance of structural factors (e.g., historical, economic, and political) in patterning AMR.

To address these barriers, the FAO has begun implementing AMR Farmer Field School (FFS) programs in selected countries. In a typical FFS, a group of farmers (15–20) meets on a weekly basis at a demonstration farm over the course of a production cycle (e.g., 6 weeks for broiler poultry). The school proceeds under the guidance of a trained FFS facilitator, who is often a local animal health or agricultural extension worker. FFS are well suited to addressing the knowledge-practice gap as the approach is based on the principles of adult-centered learning (e.g., “learning-by-doing”) and the exchange and creation of knowledge through group-level problem solving. In addition, while the schools themselves cannot address resource constraints in the animal health sector, they can provide an opportunity for farmers to work with their local animal health professionals to develop trust and thus maximize the capacities available. A recent evaluation study comparing participants in layer poultry farming FFS in Kenya and Ghana to non-FFS participants shows that FFS participants reported more prudent practices, including reducing and even eliminating the use of antimicrobials in layer production. In addition, FFS participants reported greater investments in biosecurity and were more likely to call an animal health professional upon the first sign of disease in their flocks [8].

2. Governance

2.1. Global AMR Governance

The United Nations General Assembly (UNGA) Resolutions in December 2015 [9] and September 2016 [10] recognized the magnitude of AMR as a global threat. The latter resolution contains the Political Declaration of the High-level Meeting on Antimicrobial Resistance, which served as the basis for the establishment of the ad hoc Interagency Coordination Group (IACG) on Antimicrobial Resistance [10]. The report of the IACG reinforces the role of AMR governance, both at the global and the national level. In furtherance of IACG’s mandate for improved coordination, recommendations were made to strengthen accountability and global governance by establishing three inter-related structures [11]: (1) An Independent Panel on Evidence for Action against Antimicrobial Resistance in a One Health context (Independent Panel, IPEA); (2) A One Health Global Leaders Group (GLG) on Antimicrobial Resistance, supported by a Joint Secretariat managed by the Tripartite Organizations (FAO, World Organization for Animal Health (WOAH, formally known as OIE), and WHO); and (3) A multi-stakeholder partnership platform (MPP) to facilitate multi-stakeholder engagement on AMR. The Independent Panel aims to inform the agenda of the Global Leaders Group (GLG). The latter's discussions are also used to drive the agenda of the multi-stakeholder partnership platform (MPP) and the issues resulting from MPP discussions subsequently feed into the work of the GLG and the Independent Panel [11].

In 2018, FAO, WOAH, and WHO signed a Memorandum of Understanding (MoU) regarding cooperation to combat health risks at the animal/human/ecosystems interface, in the context of the "One Health" approach and including antimicrobial resistance. In 2022, United Nations Environment Program (UNEP) signed the MoU, making it quadripartite. The new quadripartite MoU provides a legal and formal framework for the four organizations to tackle the challenges at the human, animal, plant, and ecosystem interface using a more integrated and coordinated approach. The quadripartite has, among other initiatives, developed a joint strategy on AMR, which includes as part of its outcomes the support to countries to develop policy and legislative effective and country-owned AMR responses.

2.2. AMR Governance at the National Level

Two key dimensions of AMR governance at the national level are discussed here. The first involves the coordination of AMR national policies through a multidisciplinary entity. The second entails the strengthening of regulatory (policy, legal and institutional) frameworks that are relevant for AMR. Many national action plans (NAPs) [12] display both these dimensions, in addition to the identification of governance and regulatory frameworks as specific objectives.

A national-level coordinating mechanism must bring together all stakeholders, including government ministries, parliamentarians, civil society organizations, the private sector, academia, and regional and international partners. Such a coordinating body should have a clear mandate or terms of reference (which may include overseeing the implementation of the AMR policy), an established budget, a defined accountability framework, and should integrate actions and interventions vertically within a sector or horizontally across sectors [13]. According to the FAO AMRLEX [14], the data set of national and supranational legislation set up by FAO, only a few countries have formally established coordinating mechanisms for AMR governance by law. In the absence of a legal foundation, the coordinating entity would depend solely on fluctuating political will; accountability is reduced, implementation may be inhibited, and effectiveness and sustainability could prove challenging [15].

The second element of AMR governance at the national level involves the alignment of sector-specific national policies and legislation with relevant international standards [16], such as those of the Codex Alimentarius, applicable to the sector as well as international best practices to prevent and control AMR. With the purpose of guiding countries in the analysis of their legal frameworks, FAO developed a Methodology to analyze AMR-relevant legislation in the food and agriculture sectors (2015) [17]. This methodology was applied in 27 countries across different continents and also by three regional organizations, with financing from the Multi-Partner Trust Fund (MPTF) for AMR, FAO, WOAH, and WHO developed a One Health Legislative Assessment Tool, which is designed to replace the methodology, to guide country-level assessment of the weaknesses and gaps in legislation across sectors relevant for AMR. The outcomes of the assessments can then be used to inform legislative reform as a next step. The tool comprises a cross-cutting chapter on AMR governance, as well as sectoral chapters on human health, food safety, veterinary legislation, pesticides, plant health, and the environment.

2.3. Implementation of Codex Standards

As noted above, good governance is also supported through the availability of internationally recognized standards that support AMR governance at the national level. FAO, together with WHO, is a parent organization of the Codex Alimentarius Commission, an intergovernmental body responsible for establishing food safety and quality standards that protect consumers and facilitate fair practices in the food trade. Codex has recently completed work in updating and developing new standards to support the management and containment of foodborne AMR [18]. Over a period of almost 5 years, Codex members and observers, together with input on the science from FAO and WHO, worked to develop an up-to-date triad of standards fit to address the AMR problems of today. It was initiated in response to the global action plan on AMR. The standards are anchored in a One Health approach and provide a global reference, together with those of other standard-setting organizations such as the WOAH, on which to build national AMR stewardship initiatives on aspects ranging from monitoring of AMU to principles to guide the use of antimicrobials across the food chain.

During their development, the international standards adopted by the Codex Alimentarius Commission brought countries from around the world together to recognize and discuss the challenges posed by AMR in the food chain and the actions that need to be taken by all countries to manage and contain the problem. Getting agreement on all aspects of the new and revised Codex texts was challenging and required years of discussion and negotiation, further challenged with all interactions being moved to the virtual domain due to COVID. There were many bridges to build, and the importance of addressing an issue as significant as AMR in a One Health manner encouraged countries to build those bridges. This good will reared means there is now an opportunity to seek the engagement and support of countries to implement what was agreed in the Codex standards: developing surveillance programs, taking a risk-based approach, addressing AMR along the food chain, and adhering to agreed principles on the responsible and prudent use of antimicrobials to name but a few. The Republic of Korea is leading the way here, supporting FAO with a five-year project to implement the Codex standards on AMR. This project focuses in particular on developing monitoring and surveillance programs and implementing measures to minimize and contain foodborne AMR. Working with pilot countries in Asia and Latin America that are in different stages of their national AMR response planning and implementation, the project will enable FAO to gain practical experience in implementing these Codex standards, which can then be shared to help drive and facilitate their implementation elsewhere and support a somewhat harmonized approach to the management and containment of AMR along the food chain.

3. Practices

3.1. Reducing/Limiting Antimicrobial Use When Not Necessary

Fundamental to antimicrobial stewardship in the agrifood sectors is limiting the use of antimicrobials. Reducing the use of antimicrobials when they are not needed or when they are used improperly is the first step in antimicrobial use (e.g., wrong dose, route, or indication, for example, for viral infections). Stewardship may lead to the maintenance of the efficacy of the drugs as well as an economic savings for producers. Consultation of health professionals and access to appropriate diagnostics is critical for appropriate use. FAO has developed a number of tools and guidelines for raising animals (e.g., fish, beef and dairy cattle, swine, poultry, and bees) healthily with decreased use of antimicrobials.

3.2. Good Production Practices

In addition to using antimicrobials responsibly, a large number of practices can be employed to reduce the future need for antimicrobials in plant and animal production.

In plant production, FAO has provided some suggestions on how to reduce the need for antimicrobials in plant production, specifically through the use of integrated pest management (IPM) practices [19]. Additional tools for plant producers are under development.

A wide range of animal production practices contributes to increasing animal wellbeing and making them more resistant and resilient to diseases, therefore minimizing the need to use antimicrobials.

In addition, functional animal nutrition to promote animal health is one of the most powerful tools available to decrease the need for antimicrobials in animal production. Nutrition affects the critical functions required for host defense and disease resistance. Animal nutrition strategies should therefore aim to support these host defense systems and reduce the risk of the presence in feed and water of potentially harmful substances, such as mycotoxins, antinutritional factors (e.g., lectins, and protease inhibitors) and pathogenic bacteria and other microbes.

General dietary measures to promote gastrointestinal tract health include the selective use of a combination of feed additives and feed ingredients to stabilize the intestinal microbiota and support mucosal barrier function.

Good nutrition allows the expression of the genetic potential of animals for different traits, including resistance to disease or stress, growth, milk or egg production, and reproductive functions. These depend on the availability of sufficient (preferably local) feed resources around the year, the genetic makeup of the animals, climatic and disease conditions, and husbandry practices.

Livestock nutrition programs are supported by diverse classes of feed additives, which have already been developed, marketed, and used in daily practice. Many of these functional additives are based on traditional fermentation techniques (prebiotics, probiotics, and synbiotics) and preservation technologies (organic acids). Other feed additives, such as phytochemicals, have their roots in traditional health practices and ethno-veterinary medicine. Evaluating locally available feed ingredients and traditional remedies based on herbal products abundantly available in the local environment should be integrated into the feeding strategy to reduce the need for the use of antimicrobials in livestock production.

Good nutrition also supports the critical functions required for a healthy gastrointestinal tract, host defense, and health. Various feeding practices can be used to reduce the presence of potentially harmful contaminants (e.g., pathogenic bacteria and natural toxins such as mycotoxins) and antinutritional factors in feed and water. Such practices include:

- Ensuring drinking water quality. The consumption of water of appropriate quality is a prerequisite for animal health. Regular control of the quality, supply and accessibility of water, and regular sanitation of water storage and delivery systems using disinfecting agents, are important measures to keep animals healthy. However, this could prove a challenge in regions with water shortages or high levels of water pollution;

- Ensuring feed safety and quality. Measures to ensure feed safety and quality include: minimizing the presence of microbiological, chemical, and physical hazards; ensuring appropriate levels of available protein, energy, and other nutrients and micronutrients to meet the requirements of the animal and ensure productivity, and ensuring appropriate physical characteristics such as particle size and pellet durability and hardness. Risk management in relation to the safety of feed and feed ingredients is an essential part of good feed production and manufacturing practices;

- Precision feeding. Knowledge of the nutritional requirements of species and breeds, and their specific needs at different life phases, has advanced feeding regimes, furthering sustainable production levels over the entire lifespan. Milestones in advancing feeding practices include the increasing availability and use of high-quality proteins, vitamins, chelated minerals, feed preservatives, and enzymes such as phytases, which all improve feed utilization. While these practices are proven to be effective at the producer level, their success partly depends on the safety and quality of feed and feed ingredients, which vary in nutrient and digestible energy content. In many countries, the availability of feed and feed ingredients of sufficient quality at every time of the year is an increasing concern. Agricultural practices, feed processing (mixing and pelleting), and the level of education of animal nutritionists and producers are key determinants of successful animal nutrition programs.

Feed additives. These are intentionally added ingredients not normally consumed as feed by themselves, whether or not they have nutritional value, which affects the characteristics of feed or livestock products. Diverse classes of feed additives have been developed, marketed, and used in livestock practices. The total market value was estimated at USD 38 billion in 2021 and was expected to reach USD 50 billion by 2026. These comprise prebiotics, probiotics, synbiotics, organic acids, and phytogenic compounds. A wide range of feed additives can be recommended to foster gastrointestinal and overall health, even under physiological or environmental stressful conditions such as weaning and regrouping, heat stress, undesirable antinutritional factors, and contaminants such as toxins. Such feed additives are promoted based on their effect on gut health, thereby improving feed utilization, the gut-associated immune system, and resilience to infectious diseases. While AGPs aim to stabilize the intestinal microbiota, a similar result can be achieved with non-antimicrobial compounds, which balance the microbiome and stimulate digestive enzymes and nutrient transport across a functional intestinal barrier. An improvement of intestinal health directly results in an improvement of the immune competence of an animal and hence overall resilience against infectious diseases. Improving gut health increases feed efficiency and, in turn, growth rate and productivity over the entire lifespan in all livestock species. Therefore, feed additives can not only replace AGP use in the improvement of gut health and immune competence but can also gradually reduce the need for antimicrobials for veterinary medical purposes. However, the efficacy and consistency of many feed additives can vary and are affected by feed composition, animal health and welfare, management practices, and the physical and social environment. FAO has already issued publications providing detailed information on relevant good practices, for example, the FAO/IFIF manual of Good Practices for the Feed Sector [20], the FAO/IDF Guide to Good Dairy Farming Practices [21], FAO Good Practices for Biosecurity in the Pig Sector [22], and continues working to promote them with a variety of stakeholders in the animal production sector.

4. Surveillance

Surveillance and research are essential to guide stakeholder decisions on how best to slow the emergence and spread of AMR for the good of food security and the health of humans, plants, animals, and the environment, globally. Strong surveillance and monitoring programs collect risk-based epidemiological and microbiological data on AMR, AMU, and antimicrobial residues relevant to each agriculture sub-sector and specific value chain that can be integrated with surveillance in humans and the environment. In general, surveillance for tracking antimicrobial resistance among bacteria and fungi recovered from human specimens is far more advanced than those for isolates from sick and healthy animals, from plants, food, and the environment, especially in low- and middle-income countries.

This information then allows for timely assessment of hazards to feed risk assessments to develop appropriate interventions and monitor their effectiveness over time for minimizing and containing AMR. Reliable data are needed on antimicrobial-resistant microorganisms—their distribution, AMR profiles, and prevalence—in addition to data on the extent of antimicrobial use (AMU) and antimicrobial residues along the food and feed chains, as well as through the various environments impacted by terrestrial (plant and animal) agriculture and aquaculture.

Harmonized data to estimate AMR levels in the food and agriculture sectors are still scarce. A recent study shows an increasing trend for antimicrobial resistance in common indicator pathogens (*Escherichia coli*, *Campylobacter* spp., nontyphoidal *Salmonella* spp., and *Staphylococcus aureus*) found in livestock. The study also shows AMR hotspots in several parts of the world [23].

The use of antimicrobials in human medicine is relatively well documented, but there are information gaps and inconsistencies in global estimates of volumes of antimicrobials used in animals. Previous studies have estimated that 73% of all antimicrobials sold globally are used in animals raised for food [24]. Studies of antimicrobial use trends and projections showed that in 2017, 93,309 tons of active ingredients was utilized for chicken, cattle, and pigs (which account for more than 90% of all food animals), and this amount was projected to increase by 11.5%

by 2030 [25]. Pigs had the fastest projected growth in antimicrobial consumption (45%), while cattle had the smallest (22% of the global increase). Chickens contributed 33% to the total increase in antimicrobial use. Asia consumed the largest volume of antimicrobials with an expected growth of 10.3% by 2030. While Africa used lower quantities of antimicrobials in 2017 compared to other regions, it has the highest projected increase by 2030 (37%), but this amounts to just 6.1% of the world total in 2030. Aquaculture contributes 8% of animal protein intake to the human diet, and per capita consumption is increasing faster than for meat and dairy. It is estimated that it will use 5.7% of total antimicrobials by 2030, the highest use intensity per kilogram of biomass. The Asia – Pacific region represents the largest share (93.8%) of world consumption, with China alone contributing 57.9% of the total in 2017 [25]. Overuse and abuse of these drugs are observed as a replacement for good biosecurity practices in animal production. This contributes to the increased emergence and spread of antimicrobial resistance in pathogens, causing drug-resistant infections in animals and humans across the globe [26]. In parallel, the WOAH has published its Annual Report on Antimicrobial Agents Intended for Use in Animals [27]. Based on mostly sales and import data reported, it was estimated that a total of 69,455 tons of antimicrobial agents intended for use in animals were used in 2018. When analyzing trends in AMU from 2016 to 2018, the collected data, representing 65% of the global animal biomass, indicates an overall decrease of 27% in the mg/kg at the global level, moving from 120 mg/kg in 2016 to 88 mg/kg in 2018.

The AMU in plant production and protection has been less documented compared to the knowledge that we have regarding humans and animals. It seems to be comparatively small [28] but nevertheless should be further explored from a One Health perspective and to contribute to future risk management decisions.

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