An Integrated Systems Approach is Needed to Ensure the Sustainability of Antibiotic Effectiveness for Both Humans and Animals

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Background
Antimicrobial resistance is a critical public health challenge, and the contribution of the widespread use of antimicrobials in food animals to bacterial drug resistance and human infection demands greater policymaker attention. Global consumption of antimicrobials in food animal production by 2030 is projected to rise by two-thirds due to increases in both food animal production and demand for animal products. In the United States (U.S.), the volume of antibiotics sold for use in food-producing animals is at least three times greater than that sold for human use. A One Health approach that emphasizes the connections among the health of humans, animals, and the environment is needed to address antibiotic resistance in an integrated manner. This approach holds the promise of collaboration across multiple disciplines, including doctors, veterinarians, food safety professionals, and environmental health experts.

Bacteria become resistant to an antibiotic through either genetic mutation or horizontal transfer of genes. While antibiotics are used for treating infections in food animal production, globally they are often administered in feed and water for other purposes. In this paper, non-therapeutic antibiotic administration, as distinguished from treatment, is defined as uses that occur in the absence of a veterinarian’s diagnosis of disease in a single animal or within a flock or herd. Therapeutic uses are also characterized by the determination of a specific microbiological agent believed to be responsible for the disease risk, and are confined to a pre-determined duration that typically does not extend across the majority of the lifespan of the animal.

The World Health Organization (WHO), along with the Food and Agriculture Organization (FAO) and the World Organization for Animal Health (OIE), has held several consultations and concluded in a scientific assessment report that “there is clear evidence of adverse human health consequences due to resistant organisms resulting from non-human usage of antimicrobials.” Prolonged courses of low-dose antibiotics, which are typical for non-therapeutic uses of antibiotics in food animals, increase the selective pressure for drug-resistant bacterial strains. Studies have shown that the cross-species transmission of these antibiotic-resistant bacteria occurs through direct contact with animals or indirectly through contaminated food, water, and animal waste from livestock operations, which reenters the food chain through groundwater and fertilizers in farm fields (See Figure 1). The U.K. government’s Swann Committee, the U.S. Food and Drug Administration (FDA) Task Force and the WHO have all found enough evidence of risk of cross-species transmission of resistance to recommend that antibiotics important for treating infec-

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tions in humans should not be used for non-therapeutic purposes. Despite these recommendations, certain antibiotics classified by WHO in its top tier — “critically important” for human medicine — are used for non-therapeutic purposes in animals in the U.S. The European Medicines Agency has taken steps to better control non-therapeutic use of critically important antibiotics in animals in the European Union.

Non-therapeutic use of antibiotics may result from the belief that the cost of antibiotic treatment to the producer is offset by gains in productivity, either in increased weight in food animal production or reduced costs from avoiding clinical and subclinical disease. However, a study based on Perdue company data found that productivity gains in poultry production due to the use of antibiotic growth promoters (AGPs) failed to offset the cost of antibiotics, and several other studies of commercial broilers have found no link between non-therapeutic use of antibiotics and increased productivity. Antibiotics did not result in higher productivity when fed to pigs during finishing, but significantly improved productivity in nursery pigs. Moreover, the phase-out of AGPs from swine production in Denmark did not impact long-term swine productivity. While economic impact may vary by the antibiotics administered, the type of animal and when in the lifecycle antibiotics are applied, studies show that response to AGPs diminish under better nutrition and hygiene practices.

Regional and Country-Level Policies Regulating Non-therapeutic Use of Antibiotics

In 1986, Sweden became the first country to institute a national ban on use of AGPs in food animal production and prohibited the use of antimicrobials without a veterinary prescription. Denmark, the Netherlands, and Germany were also early adopters of antimicrobial control policies and took the first step by banning avoparcin for growth promotion in 1995-96. The market authorization of avoparcin in the EU was subsequently withdrawn in 1997. Since then the EU has implemented a ban on the use of all AGPs and requires veterinary prescriptions for the use of antimicrobials in food animals.

Several countries outside of Europe such as Japan and Taiwan have instituted various regulations, ranging from requiring veterinary oversight for the use of antimicrobials in food animals to guidance or bans on the use of antibiotics for growth promotion. In 2013, the FDA issued guidelines for drug sponsors that encouraged the voluntary withdrawal of antibiotics for growth promotion. However, this measure falls short because it allows drug sponsors to re-label drugs from “growth promotion” uses to “disease prevention,” without effectively changing the overall use of antibiotics. In the U.S., voluntary FDA guidelines have been complemented by market-based reforms stemming from consumer demand for animal products labeled “antibiotic-free.” For over a decade, some restaurant chains have provided antibiotic-free animal products. Nevertheless, these are still voluntary initiatives that are unmonitored and unverified by the FDA and could be reversed by the companies concerned.

While the country and regional level actions take a step in the right direction, there are variations among countries in implementing regulations. An OIE survey of 178 countries found that nearly half of the countries still allowed the use of AGPs. Effective country-level actions are not sufficient to prevent the spread of resistance. For example, ciprofloxacin-resistant Salmonella enterica Serotype Kentucky has emerged in
Danish, French, and English patients, most of whom having travelled internationally two weeks before the onset of illness. Both the biology and emerging epidemiology strongly support the need for global coordination.

**Gaps in Global Coordination**

At the global level, various UN and multilateral agencies set norms that shape trade in food products across borders, including microbial and chemical food contaminants. A triad of agency relationships forms the heart of international food safety standards and guidelines that could influence the regulation of antibiotic residues and drug-resistant organisms across borders (see Figure 2).

The WHO, along with FAO and OIE, has developed a framework of recommendations for limiting the non-therapeutic use of antimicrobials in food animals and established the Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR). The AGISAR Committee provides technical support to WHO on containment of antimicrobial resistance in the food chain, from supporting country-level pilot programs on integrated surveillance to updating the list of critically important antimicrobials for human medicine. The WHO and FAO work collaboratively through the Codex Alimentarius Commission to set international standards for safe antibiotic residue levels and feeding practices as well as develop microbiological risk profiles. Moreover, the OIE’s Terrestrial Animal Health Code provides guidance on assessing the risk of antimicrobial use, controlling antimicrobial resistance in food animals, and harmonizing national surveillance and monitoring programs for antibiotic use and resistance in food animals. The OIE also identifies antimicrobials of veterinary importance and sets guidelines for antibiotic susceptibility testing.

These documents provide the normative guidance for consideration by the World Trade Organization (WTO) when a dispute arises. Though the WTO does not develop these international standards, it encourages governments to establish national sanitary and phytosanitary measures consistent with such international standards, guidelines and recommendations.

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**Figure 2**

*Gaps in Global Coordination for Addressing the Use of Antimicrobials in Food-Producing Animals*
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The WTO Sanitary and Phytosanitary (SPS) Agreement states that “members shall ensure that such measures are not more trade-restrictive than required to achieve an appropriate level of protection, taking into account technical and economic feasibility.” Several cases of trade restrictions have resulted from detection of antibiotic residues in meat, poultry, and fish.

This patchwork of global and country-level regulations bearing on the transmission of foodborne AMR still leaves significant gaps, particularly related to collecting data on the use and resistance patterns of antibiotics in animals, tracking the global trade and sales of veterinary antibiotics, ensuring the infrastructure for safeguarding the human food chain, researching alternatives to antibiotics for use in food production, and developing sustainable practices to limit antibiotic use in food animals.

The WHO’s 2014 Global Report on Antimicrobial Resistance Surveillance highlights the lack of harmonized global standards in sampling methodology, diagnostic protocols and reporting procedures across integrated AMR surveillance and monitoring systems in the food chain. It particularly emphasized the need to collect and integrate “data on transmissible [resistance genes] in zoonotic, commensal and pathogenic bacteria from humans, animals and food.” Moreover, there are no international standards setting limits on the presence of resistant bacteria and resistance genes in food, and accordingly, there are currently no international guidelines describing the appropriate response.

Existing regulations fail to adequately monitor veterinary antibiotic use and resistance patterns. In fact, very few OIE member states have official systems to collect antibiotic use data. In response, the OIE has initiated a process to collect quantitative data on antibiotic use and establish a global database. While some European countries track how antibiotics are used in animals, the U.S. does not collect comparable data. Where countries only collect antibiotic sales data primarily from manufacturers, these data need to be supplemented with geographic and species-specific information.

Ongoing global coordination efforts also do not track the movement of antibiotics intended for veterinary use in global trade. The UN Comtrade data track antibiotics (code 2941), but only some classes of antibiotics are separated out in the data, and one cannot distinguish whether antibiotics are destined for human or veterinary use. Along with changing the nature of high-density animal production, collaborative research efforts to find alternatives to the non-therapeutic use of antibiotics are needed. The OIE and the U.S. President’s Council of Advisors on Science and Technology (PCAST) have called for investing in the fundamental research needed to develop alternatives to antibiotics in agriculture.

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**Box 1**

**Denmark’s Experience with Regulating Antibiotic Use in Agriculture**

Denmark’s experience in regulating the use of antibiotics in food animals suggests ways to structure effective, country-level surveillance systems. The Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP), established in 1995, collects data on the presence of resistance in zoonotic, pathogenic and commensal bacteria from animals, food, and humans. Building on this experience, the Danes later established the VetStat Monitoring Program to track the consumption of antibiotics in livestock. The species-specific sales data collected under VetStat can help investigate the links between antibiotic use in animals and resistance.

Complementing these robust surveillance measures, Denmark initially banned the use of avoparcin, a glycopeptide antibiotic, in 1995 and virginiamycin, a streptogramin antibiotic, in 1998, followed by voluntary restrictions and then eventually a ban on the use of all AGPs along with all EU countries in 2006. The prevalence of vancomycin-resistant enterococci (VRE) in poultry decreased after the ban of avoparcin, from over 80% in 1995 to less than 5% in 1998.

Denmark passed legislation severing ties between the sale of antibiotics and veterinarian income, required veterinary prescriptions for antibiotic use, and prohibited veterinarians from prescribing fluoroquinolones. While the ban on AGPs nearly doubled the annual therapeutic use of antibiotics, there was a net decrease in the use of antibiotics in animals during the same time period. To limit the increasing therapeutic use of antibiotics, the Danish government introduced a new regulation called the “yellow card system” that limits antibiotic use based on the size of the swine farms. Farmers who were outliers consuming the highest level of antibiotics per pig got warning letters, and if they did not work to decrease their farms’ use of antibiotics, financial penalties were applied as well. Since the regulation was implemented, the therapeutic use of antibiotics has decreased by almost 25%.

Despite the comprehensive national policies to limit the use of antibiotics in animals, addressing drug resistance in domestic food animals is still a challenge. For example, prevalence of MRSA in pigs has increased, and the number of new cases of livestock-associated MRSA rose by nearly a third in 2013. Also, Denmark still cannot fully prevent antibiotic-resistant pathogens from entering the food supply through cross-border trade. DANMAP surveillance has shown increased antibiotic resistance in travel-associated infections and imported meat products. These findings point to the need for a framework of global coordination to limit the non-therapeutic use of antibiotics.
International Agreement
A framework for global coordination is needed to address the risk of cross-border transmission of resistance genes or antibiotic-resistant pathogens, ensure global cooperation such that all countries contribute to collective efforts and reap the benefits, integrate this issue with relevant international trade, environmental and health law, and create public goods such as vaccines and alternatives to antibiotics.

An international agreement might enable the implementation of this global coordination. Whether the agreement is by treaty, convention or regulation, a spectrum of hard (binding) and soft (non-binding) norm instruments might be deployed to ensure monitoring, implementation, reporting of progress, and financing of the required activities. Such a framework for global coordination should be guided by the following principles:

- Acknowledging the different levels of development and local context of countries, flexibility is allowed for implementing the requirements without compromising on the ultimate goals and outcomes;
- Recognizing that the risk of cross-border spread of drug-resistant pathogens is a shared one, the obligation to provide financial and technical support to countries not sufficiently resourced to meet these requirements would also be shared;
- Production of food animals would be conducted in a manner that does not necessitate the routine use of antibiotics and other pharmaceutical crutches;
- Economic incentives that encourage inappropriate antibiotic use should be eliminated, and marketing and promotion of antibiotics for non-therapeutic use should be prohibited; and
- To minimize disruption of food supplies and livelihoods of farmers and farm workers, transition periods would be tied to milestones linked to the availability of such support.

Among the key elements of the framework are:

- An internationally recognized procedure for setting limits on the presence of antibiotic-resistant pathogens or resistance genes in food and for developing recommendations on which antimicrobial medicines should be reserved solely for human use;
- R&D for alternatives to antibiotic use in animal husbandry and aquaculture would be targeted to enable a more effective transition to sustainable approaches to agriculture and a “One Health” strategy to tackling antibiotic resistance;
- A mechanism of accountability provided by the monitoring and surveillance of cross-border trade of antibiotics and food products;
- Enforcement from the tracking of indicators of potential, cross-border risk of antibiotic resistance through a globally coordinated surveillance system;
- Adequate financing for implementing the framework, including for a global surveillance and enforcement system, and capacity building for countries; and
- Appropriate trade measures that are consistent with the goals of the framework.

Existing recommendations and guidelines on the human and animal use of antibiotics provide a foundation for this work, and previous instruments — from the Framework Convention on Tobacco Control (FCTC) and International Health Regulations to the Pandemic Influenza Preparedness Framework and the Global Code of Practice on International Recruitment of Health Personnel — offer, with appropriate modification, useful precedents. The heavy concentration of the food industry and key import and export markets also suggests that an international agreement might be initially set in motion among targeted parties rather than waiting for a more universally inclusive arrangement. An agreement among Japan, the U.S., the EU,
and Brazil alone would affect at least a quarter of all global imports and 40% of all global exports of meat, by value.\textsuperscript{41} However, any such plurilateral agreement must take into account the needs and impact on other countries, because a coordinated global response is needed.

As depicted by the flows across the red line in the global and local value chain diagram of food animal production (Figure 3), global coordination on the non-therapeutic use of antibiotics might focus on several key points where there is cross-border movement, both of antibiotics and of food products. The tracking of antibiotic use, marketing, promotion, sales and resistance patterns is a key feedback loop in this accountability mechanism. The inspection, monitoring and global data collection of antibiotic-resistant pathogens or genes carried in food products is both sentinel and safeguard against cross-border transmission. National policies tailored to the specific domestic context will be required to ensure compliance and the continued flow of food products across borders.

Countries party to this agreement will differ in their domestic use of antibiotics in food animal production, in their level of food exports, and in their infrastructure for enabling effective monitoring for accountability. An international agreement could offer a flexible set of options to regulate the use of antibiotics in food animals. A structured risk analysis framework, such as that described in Codex guidelines, can serve as a starting point for assessing what potential hazards from AMR microorganisms or their determinants pose the greatest threat to human health and to the disruption of trade in food products.\textsuperscript{42} In addition to national level risk analysis, international standard setting is needed to reduce duplication of efforts, provide guidance to countries without the capacity to carry out such analysis, and lower the risk of trade disputes related to antibiotic resistance threats.

A host of local interventions might abate the inappropriate use of antibiotics in the veterinary sector. These include regulation of veterinary oversight (training, limiting financial incentives for veterinarians to prescribe antimicrobials, prescription requirements, and handling of the distribution as well as the disposal of unused veterinary drugs), of the domestic use and export of antibiotics for use in food animals by industry (marketing authorization, advertising, training and research), and of the roles and responsibilities of others in the supply chain, including wholesale and retail distributors. The development of flexible modules could support countries seeking to implement such measures. As done under FCTC, the Secretariat could also prepare self-assessment checklists.

**Figure 3**

**Simplified Conceptual Framework of Global and Local Value Chain of Food Animal Production**

to help parties comply with requirements laid out in the modules.

Technical assistance must accompany the requirements under any international agreement. Some of this support might come in the form of reviews, guidelines, and checklist tools built on a common evidence base and applicable across a range of settings. Other technical assistance would need to be tailored to the country-specific situation. Countries with little infrastructure in place for food safety may require financial resources and expert training to meet these obligations under an international agreement. To keep such information free of financial conflict of interest, public resources will be required to support implementation.

Similarly, an R&D agenda might inform the delivery of this technical assistance, improve point-of-care testing for monitoring the potential spread of AMR determinants, and pave the way to alternatives to antibiotic use in animal husbandry and aquaculture. Such technological alternatives could smooth and lower the costs of transition and compliance. Importantly, both the agenda priority-setting process and the resourcing of this research should be transparent, reflective of the public’s interest, and managed in a manner that avoids unnecessary conflict of interest. Public sector financing might piggyback on existing multilateral research programs, like the Consultative Group on International Agricultural Research (CGIAR), be housed at WHO or the Special Programme for Research and Training in Tropical Diseases (TDR), or become part of global initiatives set up to tackle the challenges of antibiotic innovation.

Ensuring predictable financial commitments, a broad donor base, and funding levels that match the scale of activities are challenges facing the implementation of such international agreements. Participating countries could provide appropriations to a Secretariat set up to administer the obligations under such an arrangement, as is the case with International Agency for Research on Cancer or CGIAR. Similar to the support of the Global Influenza Surveillance and Response System, the food industry might contribute to the public good of food safety inspection and monitoring and surveillance as well as research efforts. Alternatively, a tax on antibiotic revenues at the manufacturer or importer level might be levied to offset the costs of the negative externalities caused by the use of their products, as in a Pigouvian tax. However, even without quantifying precisely the negative externality, a user fee applied to the use of antibiotics in animals could be an effective disincentive against low-value usage of these important drugs.

To keep antibiotics effective, the stewardship of these life-saving drugs must involve a One Health approach. This requires integrating surveillance data collection, monitoring and enforcement, research, technical assistance, and financing under the umbrella of an international agreement. Even in the face of efforts to pass effective domestic measures, countries like Denmark show us that there remain challenges of drug resistance in food animals, and porous borders afford limited protection against trade from countries that do not share these safeguards. An international agreement would help ensure the global coordination needed to accomplish these aims.

References


41. Analysis based on UN Comtrade data from International Trade Center Statistics.

