POLICY UPDATE

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This is the third update in a series focusing on current policy issues regarding antimicrobial stewardship and antibiotic resistance. Our first update highlighted regulatory and voluntary initiatives aimed at enhancing antimicrobial stewardship in US hospitals and long-term care facilities; our second focused on antibiotic stewardship in outpatient healthcare. This update summarizes recent initiatives aimed at enhancing antibiotic stewardship in animal production. As always, we welcome feedback and discussion, including your suggestions for topics to explore in future policy updates. If you have comments or questions, please e-mail the CIDRAP-ASP staff at asp-cid@umn.edu.

Antimicrobial Stewardship in Animal Agriculture

Antimicrobial stewardship is a critical strategy to preserve available treatment options and slow the loss of effective antibiotics due to bacterial resistance (Spellberg 2013). Stewardship principles extend to veterinary medical practice and animal agriculture, in which a wide range of antibiotic drugs important to human medicine are used. By volume, the vast majority of antibiotics worldwide are sold for veterinary purposes, predominantly in large-scale operations for production animals such as dairy and beef cattle, swine, chickens, and turkeys, and in aquaculture (Flynn 2016; Wall 2016).

Antibiotics are critical drugs for treating illness in production animals; they are also commonly used to prevent the spread of disease and to promote growth, typically through the use of subtherapeutic doses for extended periods—a practice that creates ideal conditions for accelerating antimicrobial resistance (AMR). In this way, possible misuse or overuse of medically important antibiotics in animal production is considered to be a clear and substantial driver of AMR, even though there are gaps in data on the magnitude of the risk and specific mechanisms for transmission of antibiotic resistant bacteria or genes from animals to humans, such as through food distribution, environmental contamination, or contact with farm animals (Wall 2016; Robinson 2017; Holmes 2015; Robinson 2016; Al-Tawfiq 2016).

Routine antibiotic use in animals for disease prevention and/or growth promotion is also viewed as a major modifiable factor in reducing AMR. A number of recent reports have published policy recommendations for enhancing antibiotic stewardship in animal agriculture, aimed primarily at integrated, multisectoral efforts to reduce or eliminate the nontherapeutic use of medically important antibiotics. These recommendations are summarized below in Table 1.

Table 1. Summary of Selected Recent Policy Recommendations Pertaining to Antibiotic Stewardship in Animal Agriculture

Source	Policy Recommendations
Review on Antimicrobial Resistance. Tackling drug-resistant infections globally: final report and recommendations (May 2016) [Full text]	• Establish 10-year targets at the country level for reducing unnecessary use of antimicrobials, taking into account countries' production systems and economic development, with support from the World Health Organization (WHO), the Food and Agriculture Organization (FAO) of the United Nations, and the World Organization for Animal Health (OIE) in the design, implementation, and review of progress. • Harmonize a list of critical, last-line antibiotics in human medicine that should be restricted from use internationally in animal agriculture. • Improve transparency regarding information on antibiotics used in food production.

	• Improve collection and use of surveillance data on antibiotic use in agriculture and the spread of drug-resistant microbes among food animals. • Analyze costs of reducing the use of antibiotics in farming, particularly in low- and middle-income countries (LMICs).
Center for Disease Dynamics, Economics & Policy (CDDEP). Antibiotic use and resistance in food animals: current policy and recommendations (2016a) [Full text]	• Track rates of veterinary antibiotic use, resistance, and residues through nationwide surveillance and monitoring systems (focusing on India, currently one of the top consumers of agricultural antibiotics worldwide, with use expected to double by 2030). • Change incentives to discourage unnecessary antibiotic use in animals. • Educate farmers, veterinarians, and consumers about antimicrobial resistance (AMR). • Phase out the subtherapeutic use of antibiotics in animal agriculture.
Årdal C, Outterson K, Hoffman SJ, et al. International cooperation to improve access to and sustain effectiveness of antimicrobials. Lancet 2016 Jan 16;387(10015):296-307 [Abstract]	• At the national level, reduce or eliminate antibiotic use for growth promotion or prophylaxis in animals, coupled with (1) adequate investment in infection prevention and control interventions in livestock and for other agricultural uses, (2) effective mechanisms to remunerate veterinarians and prescribers while limiting their ability to profit from antimicrobial sales and reorienting their roles away from commercial gains, and (3) further research into the implications of this policy in LMICs. • At the global level, form a coalition of key countries to lead the way in restricting specific classes of antimicrobials for human use only; countries should work with the World Trade Organization to transition away from using antibiotics for growth promotion or prophylaxis, using health and sanitary/phytosanitary exceptions under trade agreements.
Food and Agriculture Organization (FAO) of the United Nations. The FAO action plan on antimicrobial resistance, 2016-2020 (Sep 2016) [Full text]	• Improve awareness of AMR among food and agriculture stakeholders and integrate AMR issues into food and agriculture policy-level discussions. • Develop capacity for country-specific integrated surveillance and monitoring of AMR and antimicrobial use in food and improve laboratory capacity to monitor AMR and detect antimicrobial residues in food products. • Strengthen governance related to antimicrobial use and AMR in food and agriculture. • Promote good practices in food and agricultural systems and the prudent use of antimicrobials, eg, by adopting at the country level international standards and guidelines relevant to addressing AMR, improving awareness and knowledge about responsible use of antimicrobials in food and agriculture sectors, and improving biosecurity, good practices, and other measures to support prudent use of antimicrobials throughout the food chain.
Wellcome Trust. Evidence for action on antimicrobial resistance (Sep 2016) [Full text]	• Phase out, as rapidly as possible, antibiotic use in agriculture without compromising the food system's capacity to meet increasing global demand. • Replace the use of antibiotics for growth promotion and disease prevention with improved animal husbandry practices. • Conduct research to identify alternative treatments and husbandry practices and improve their implementation globally. • Develop innovative insurance mechanisms for food producers to mitigate economic risks associated with transitioning to new antibiotic stewardship practices. • Develop and deliver antimicrobial stewardship education and training programs targeted at veterinarians, farmers, and others responsible for animal health.

The feasibility of specific types of interventions to achieve these goals may vary by country or region. In 2006, the European Union (EU) banned the use of medically important antibiotics as animal growth promoters, and in 2016, China announced that the use of colistin (a last-line antibiotic used to treat multidrug-resistant gram-negative bacterial infections in humans) as a growth promoter (feed additive) in animals would be replaced by non-human antibiotics (Walsh 2016; Al-Tawfiq 2017). In 2013, the United States began a 3-year transition to regulatory restrictions on the use of antibiotic agents in animals for growth promotion (see below).

In low- to middle-income countries (LMICs), alternative policies and mitigation strategies may be needed because of economic challenges as well as rapidly increasing demands for animal protein.

Robinson and colleagues (Robinson 2017) identified a number of pragmatic, near-term interventions in LMICs that could be considered, including the following:

- Enhancing management and biosecurity innovations
- Using non-antibiotic growth promoters (eg, enzymes, competitive exclusion products, probiotics, and prebiotics) and/or other animal health technologies (eg, vaccines, vector control, bacteriophages, and disinfectants)
- Improving diagnostics to enhance appropriate drug selection, dosing, and length of treatment and to identify prevalent resistance traits among pathogens to avoid the use of ineffective drugs
- Reducing dependence on antibiotics for semen preservation
- Lowering stocking densities and increasing genetic diversity of livestock
- Increasing the use of genetic traits for disease resistance
- Enhancing waste management
- Building the capacity of farmers to carry out good husbandry practices
- Developing animal health systems that focus on the productivity expectations of the farmer with mitigation of antibiotic resistance in mind
- Applying interventions to reduce access to counterfeit drugs
- Offering compensation schemes for expired antibiotics
- Strengthening laboratory capacity to diagnose bacterial pathogens and their antibiotic-resistance profiles
- Conducting consumer and farmer engagement campaigns
- Labelling food regarding antibiotic use in its production
- Implementing surveillance systems for antibiotic resistance
- Improving access to affordability of testing services for antibiotic residues in animal source foods and in the environment

FDA Policies on Judicious Use of Antibiotics in Food Animals

As of Jan 1, 2017, new rules are in effect governing the use of antimicrobial drugs in animals in the United States. Through a 3-year process of phasing in voluntary judicious-use guidelines and working directly with industry to secure compliance, the US Food and Drug Administration (FDA) completed a major step toward reducing unnecessary or inappropriate use of medically important antimicrobials in food-producing animals. In conjunction with the FDA's 2015 Veterinary Feed Directive (FDA 2015), the FDA's new rules eliminate the use of medically important antibiotics for growth promotion and permit the use of these drugs in animal feed or water only for therapeutic (disease treatment) or preventive purposes under the supervision of a veterinarian. The mechanism for implementing the new rule involved changes in animal drug labeling requirements (via approving or withdrawing new animal drug applications) and revising the marketing status of antimicrobials from nonprescription (eg, through over-the-counter sales of medicated feed in agricultural supply stores) to prescription use (FDA 2016). The National Action Plan for Combating Antibiotic-Resistant Bacteria supports these activities and the FDA's process for implementing them (White House 2015).

In 2012, the FDA issued *Guidance for Industry #209*, a document summarizing the rationale for antimicrobial stewardship of medically important antimicrobials in animals and the agency's near-term goals for enhancing the judicious use of antimicrobials in animal production. To minimize the development of AMR while maintaining the availability of antimicrobials for appropriate use, the FDA recommended that medically important antimicrobial drugs in food-producing animals should be

limited to uses that: (1) are considered necessary for ensuring animal health and (2) include veterinary oversight or consultation (FDA 2012). The following year, the FDA issued *Guidance for Industry #213* (FDA 2013) which provided recommendations for drug sponsors to voluntarily begin changing product labeling and approved conditions of use over 3 years, in accordance with the goals outlined in *Guidance for Industry #209*. (The FDA would consider further actions after the 3-year period if necessary.) As of Jan 3, 2017, the FDA reported that drug sponsors had fully complied, thereby completing implementation of *Guidance for Industry #213* to ensure that medically important antimicrobials cannot be used for growth promotion and may be used only under the authorization of a licensed veterinarian.

In September 2016, the FDA announced that the agency is seeking public input (extended until March 17, 2017) on how to establish appropriately targeted durations of use for the approximately 32% of medically important antibiotics with no defined duration of use, addressing a potential gap in the new rules (Pew 2016). The FDA is requesting additional information on the following issues:

- The underlying diseases requiring these drugs for therapeutic purposes and periods when livestock or poultry are at risk of developing these diseases
- More targeted antimicrobial use regimens for these diseases and husbandry practices that may help avoid the need for these antimicrobials or that may help make more targeted antimicrobial use regimens more effective
- Strategies for updating affected labeling of drug products that do not currently include a defined duration of use

Second International Symposium on Alternatives to Antibiotics

In December 2016, the US Department of Agriculture (USDA) and the World Organization for Animal Health (OIE) co-hosted a symposium on alternatives to antibiotics in animal production. The objectives were to highlight promising research results and novel technologies that provide alternatives to the nontherapeutic use of antibiotics in animal production, to assess challenges associated with their commercialization and use, and to provide actionable strategies to support their development (OIE 2016). The symposium focused on five product categories that could help to reduce the use of medically important antibiotics in animal health and production without causing microbial selection pressure leading to the development of AMR:

- Vaccines
- Microbial-derived products (eg, probiotic bacteria, bacteriophages)
- Phytochemicals (plant-derived compounds with antibacterial and growth-promoting effects)
- Immune-derived products (eg, immunoglobulins, antibodies)
- Innovative drugs, chemicals, and enzymes (eg, antimicrobial peptides, synthetic polymers, nanoparticles)

Participants also discussed issues pertaining to regulatory pathways (eg, in Europe, the United States, and Taiwan) for licensing these novel technologies and alternative approaches. The symposium's organizers noted that, in addition to fostering the development of alternatives to the continued reliance on antibiotics in animal production, antibiotic stewardship programs are urgently needed to ensure that the nutritional and food security demands of a growing world population are met without increasing the potential for developing antibiotic resistance (Gay 2016).

To support the development, registration, and commercialization of the technologies discussed at the symposium, reviews of the meeting will be published in two scientific journals, *Veterinary Research* and

Animal Nutrition. In addition, the Pew Charitable Trusts plans to publish an evaluation of alternatives to antibiotics, including a review of opportunities and challenges for their commercial use (Hoelzer 2016).

European Medicines Agency (EMA) Strategy on Antimicrobials

In October 2016, the European Medicines Agency (EMA) Committee for Medicinal Products for Veterinary Use (CVMP), which is responsible for regulating veterinary medicinal products sold in the EU, adopted a new 5-year (2016 to 2020) strategy on antimicrobials to ensure "the availability of effective antimicrobial medicines for the treatment of infectious diseases of animals while, at the same time, minimizing the risks to animals or humans arising from their use" (EMA 2016). The CVMP supports identifying critically important antimicrobial agents that should be excluded from veterinary use, as well as overall reductions in antimicrobial use, to limit the spread of AMR. The strategy's aims include the following:

- Consider and advise on public health risks arising from antimicrobial use in animals and to balance this against the need to protect animal health
- Maintain the effectiveness of antimicrobial agents authorized for veterinary use by monitoring and analyzing sales and usage data, encouraging surveillance for susceptibility changes, and reviewing the authorization of products when there may be a change in the benefit-risk balance
- Support the responsible use of antimicrobials in accordance with marketing authorizations
- Work with the European Commission, member states, international regulatory agencies, human and animal health organizations, and the pharmaceutical and livestock industries to provide guidance on the responsible use of antimicrobial agents in animals

United Nations' Declaration and the Conscience of Antimicrobial Resistance Accountability (CARA)

On Sep 21, 2016, the United Nations General Assembly (UNGA) convened a high-level meeting on AMR, marking the first One Health topic (integrating human, animal, and environmental perspectives) taken up by the UNGA (Laxminarayan 2016). The UNGA ratified a declaration [UN 2016] acknowledging the public health threat of AMR and calling for a coordinated global effort to develop and implement multisectoral national action plans, policies, regulations and initiatives to preserve global access to effective antimicrobials. The declaration identified the WHO's 2015 global action plan on AMR (WHO 2015) as the overall blueprint for these efforts. It directed the establishment of an ad hoc interagency coordination group to oversee the global agenda and called for a progress report at the UNGA meeting in 2018.

In support of the UNGA declaration on AMR, the Center for Disease Dynamics, Economics and Policy (CDDEP) in Washington, DC, formed a global alliance of human and animal health organizations to monitor progress toward achieving the goal of preserving access to effective antimicrobials. The Conscience of Antimicrobial Resistance Accountability (CARA), established by CDDEP in September 2016, is taking responsibility for observing AMR reduction efforts internationally and assessing progress through a set of objective accountability indicators, to be defined by the CARA steering committee (CDDEP 2016b; CDDEP 2016c).

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