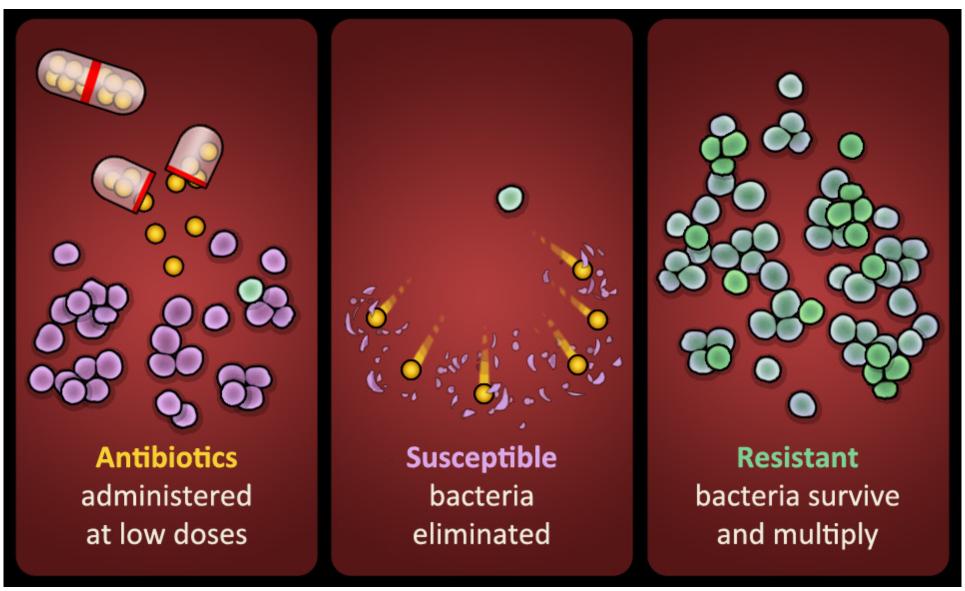
Curbing Antimicrobial Resistance in Food Animal Production

Antimicrobials are widely used in food animal production, and use is rapidly increasing.

In an era of growing demand for animal products, there is an increasing trend towards the industrial production of food animals, especially in lower- and middle-income countries (LMICs). One hallmark of this method of animal production is the use of antimicrobial drugs,[1,2] which in the majority of cases are administered to healthy animals for purposes other than treating or controlling disease (termed "therapeutic uses"). When antimicrobials are used for non-therapeutic purposes in food animal production (to promote growth or for preventing possible disease), they are often administered at doses below what is needed to treat disease-causing bacteria, for periods much longer than needed (often spanning much of an animal's lifespan), and in a manner that is not targeting a specific type of infection. It is common for these drugs to be delivered in the absence of disease diagnosis.

It has been estimated in a commissioned study by the Organization for Economic Cooperation and Development (OECD) that global antimicrobial consumption by food animals will increase by 67% between 2010 and 2030, with the United States and China accounting for 40% of total use. Data on antimicrobial use in food animal production are lacking for many countries. Available data, however, show great variation between countries, which can only partly be explained by differences in species of animals produced and the animal husbandry techniques used. These differences indicate that the way antimicrobial drugs are used in food animal production differs between countries as evidenced by the Nordic countries and New Zealand, which have managed to combine high productivity with lowered use of antimicrobials. Judging from observed trends in the rate of food animal production in LMICs, OECD has estimated a doubling of or greater antimicrobial use in India, Nigeria, Vietnam and Peru. Brazil, Russia, India, China and South Africa (BRICS countries) alone will witness a projected increase of antimicrobial consumption of 99 percent.[3]



When these drugs are used, there is a risk of developing resistant bacteria.

The risks of antimicrobial resistance have long been recognized, even dating back to Sir Alexander Fleming and the discovery and first use of penicillin. He warned in 1945 that "the ignorant man may easily underdose himself and by exposing his microbes to nonlethal quantities of the drug, make them resistant." Any antimicrobial use runs the risk of promoting the survival of only resistant bacteria, but the industrial setting, characterized by large numbers of animals kept in close proximity under unhygienic conditions, combined with non-therapeutic use, create the perfect scenario for generating and propagating resistant bacteria.

These bacteria leave the farm and come into contact with people through various pathways.

Scientific evidence has demonstrated that resistant bacteria can leave animal production sites through an array of pathways.[2,4] The most-commonly recognized pathway is food; resistant pathogens can reside on (or in) products derived from animals that were administered these drugs.[5-8] What is less often considered, however, is that these resistant pathogens can enter the environment directly through air and water releases from the production sites themselves,[9-11] or through management of animal wastes on cropland as fertilizer.[12-14] Studies suggest that 20-80 percent of administered antibiotics are excreted as unchanged active ingredients by humans and animals into waste water, sludge, and in manure.[32] Beyond environmental releases, non-domesticated animals such as flies, wild birds and rodents have been shown to transmit resistant bacteria.[15-18] Animal transport trucks have also been demonstrated to spread resistant bacteria beyond the farm gates.[19] Human vectors also play a role in transmitting bacteria to and from farms.[20]

When humans come into contact with these bacteria, they can become colonized and infected.

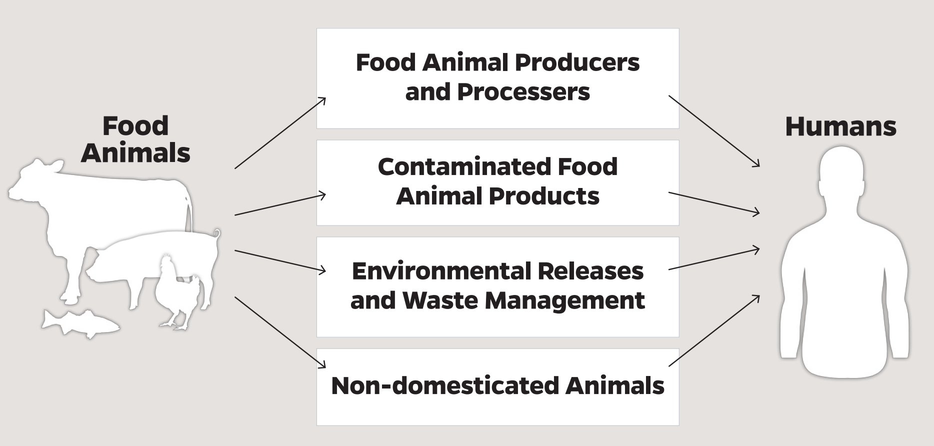
The presence of these resistant pathogens in food and in the environment poses risks to humans with which they have contact. Workers on industrial food production facilities where antimicrobials were used have been shown to be more likely than workers at farms not using antimicrobials to become colonized with antibiotic-resistant bacteria.[21] Research has demonstrated that proximity to industrial swine operations and crop fields where swine manure is applied as fertilizer is a risk factor for developing antibiotic-resistant infections.[12] In addition, numerous studies using molecular characterization techniques have demonstrated genetic similarity among isolates from infections in humans and isolates from retail chicken samples,[7,8,22] suggesting food as the primary pathway of transmission.

Recently, countries across Asia, Europe, and the Americas have reported evidence in food animal products of bacteria resistance to colistin, a last-line antibiotic critical in human medicine. The larger abundance of the colistin resistance mcr-1 gene in isolates from food animals compared to human isolates, the abundant use of colistin in livestock compared to human medicine, and the finding of the mcr-1 gene along with genetic determinants typically seen in animal environments, indicates a flow from animals to humans.[23]

Drug-resistant infections are a serious and significant health burden.

Research has shown that, compared to antimicrobial-susceptible infections, resistant infections (with organisms including *Staphylococcus aureus*, enterococci and other Gram-negative bacilli) are far more challenging and expensive to treat (by $6,000 - $30,000), more likely to result in lengthier hospital stays, and increase the likelihood of various morbidities and mortality.[24] While the data needed to attribute a fraction of the resistance burden to the misuse of these drugs in food animal production are not being collected, it is estimated that a large fraction of the global consumption of these drugs occurs in the animal sector (in the US, for example, 70% of all medically-important antimicrobials sold in 2012 were intended for use in animals). This may suggest that food animal antimicrobial use is responsible for a significant fraction of the overall burden, whose human and economic burdens have been estimated to escalate to 10 million deaths/year and a cumulative cost of $100 trillion by 2050.[25]

Pathways for Transmission of Antibiotic Resistant Bacteria from Food Animal Production to Humans



Countries have taken a range of actions to address the societal burden of resistant bacterial infections due to food animal production.

The most effective approach to minimize or eliminate the burden of resistant infections from antimicrobial misuse on farms is to enact strict controls over the way these drugs are used. Steps have been taken across countries, including the European Union, to implement a ban on the preventative use of antimicrobials without identification of a diseased animal.[1] Going further, expert bodies like the Pew Commission have called for the phase-out and ban of non-therapeutic antimicrobials.[30]

Appropriate, therapeutic use of antimicrobials in the agriculture or aquaculture setting can be defined as use of a microbial agent in a particular livestock or aquatic species that is:

1. Targeted to facilitate killing or inhibiting the disease-causing agent
2. Limited to a defined duration necessary to achieve treatment goals
3. Administered at a therapeutic dose sufficient to achieve treatment goals

The presence of disease within food animals should be determined by a veterinarian or laboratory diagnosis. Resources to confirm such a diagnosis, however, may not be available across all settings.

Short of this, other interventions may either address or bolster the evidence base for remedying the resistant infection burden from animal agricultural antimicrobial misuse.

- Changing the production environment – Certain elements of the production environment, such as animal density, barn ventilation and manure management practices, play a key role in promoting or minimizing the risk of transmission of resistant bacteria among animals. Modifications to the production environment, especially those that address production site hygiene, are likely to reduce the need for antimicrobial use.

- Adopting health-promoting husbandry practices – Husbandry practices that take advantage of the innate immunologic defenses of the animals may decrease the need for antimicrobial use. For example, providing piglets with a longer weaning duration allows transmittance of immunological factors from the sow to her offspring, boosting their capacity to respond to immunological challenges without supplementation with antibiotics. In its Global Action Plan, the WHO has called for the development of sustainable animal husbandry practices as a measure to reduce the non-therapeutic use of antimicrobials in food animal production.[26]

- Improving food animal surveillance efforts – Farm- and veterinarian-specific data (including information about specific drugs and the species to which they are administered) should be collected and evaluated to understand patterns of use and to identify and prioritize actors needing intervention. Further, collection and phenotypic and genotypic evaluation of bacterial isolates from the farms, processing plants, retail meats and human infections would allow for more meaningful determination of the human resistant bacterial infection burden origination from antimicrobial use on farms.

- Increasing the availability of trained veterinarians - An OIE survey found the infrastructure for veterinary services to be very weak in developing countries, even in those countries where animal production contributed significantly to the local economy. Increasing veterinary capacity across countries will further allow for more responsible use of antimicrobials, limiting their administration to situations where their use is medically necessary (as determined by diagnosis of a diseased animal).[27]

- Ensuring the development of new technologies including diagnostics and vaccines - Access to cost effective diagnostics help facilitate appropriate therapeutic administration of antimicrobials. Vaccines and other alternatives can also prevent the emergence of infections (both resistant and sensitive), thus also diminishing the selective pressure of antibimicrobial use.

- Development of novel indices of meaningful reductions in agricultural misuse of antimicrobials – Existing metrics to demonstrate the impacts of policies intended to mitigate misuse of antimicrobials are often limited to total sales figures or measures of mass of drug used per kg of animal products produced. These measures are limited because they do little to describe the nature and necessity of use. New indices should be developed that allow for evaluation of the changing nature of use by species and antimicrobial class.

- Limit use of certain antimicrobials to individual animal treatment - Some countries, including the United States, have taken steps to restrict the use of specific antimicrobials to treat individual food animals, rather than through mass administration through feed and water. For example, the U.S. Food and Drug Administration have limited fluoroquinolone and cephalosporins to single food animals and with a specific veterinary diagnosis.

To achieve the Sustainable Development Goals, antimicrobial misuse in food animal production must be addressed.

Limiting antimicrobial use in the agricultural setting to responsible and appropriate administration will aid in pursuit of numerous Sustainable Development Goals (SDGs).[28,29] While an argument could be made for a linkage between a reduced AMR burden and many of the SDGs, four goals in particular would be directly and meaningfully addressed through the elimination of non-therapeutic antimicrobial use in food animal production. Through limiting use only to medically-necessary circumstances, there would be a resulting reduction in the creation and spread of antimicrobial resistant bacteria, and thus a reduced risk and lessened burden of resistant infections in humans (addressing SDG 3: Good Health and Well-Being). Concurrently, addressing the generation of antimicrobial resistant pathogens would limit release of these microorganisms into surface and groundwater, providing for SDG 6, Clean Water and Sanitation. Elimination of nontherapeutic antimicrobial use in industrial food animal production may lead to more meaningful system change, with implications for dietary patterns reliant on animal protein (SDG 12: Responsible Consumption and Production), and minimization of emissions pressures related to the production of food animals (SDG 13: Climate Action).

Achieving the SDGs and addressing the global threat of AMR will necessitate a coordinated response across Member States, the tripartite partnership of the WHO-FAO-OIE and other UN agencies, as well as other stakeholders including the private sector and NGOs.

Here is what some countries have done

Some countries have demonstrated that it is possible to combine profitable food animal production with lowered use of antimicrobials. After taking meaningful measures to eliminate non-therapeutic antimicrobial use, Denmark remains one of the world's largest pork exporters, and Norway is the leading global producer of Atlantic salmon. The Swedish broiler sector has also seen a 30 percent increase in production during the last decade despite restrictions on antimicrobial use. The common denominator among these countries is a strong focus on good animal husbandry practices to prevent infections and improve animal health, thus reaching a high productivity, in combination with strict regulations on antibiotic use.

While many have suggested that non-therapeutic use of antimicrobials provides an economic benefit through increased productivity of producers, recent analyses call this assertion into question. A 2015 U.S. Department of Agriculture Economic Research Service (USDA/ERS) analysis of swine, poultry, and beef and dairy cattle operations found little to no benefit to producers or consumers.[30]

Some selected examples of action to ensure appropriate use of antimicrobials from countries include:

- Classification of antimicrobials as veterinary medicines, only available by veterinary prescription
- Removal of economic incentives for veterinarians or producers to prescribe and use antibiotics
- Improved animal health through improved hygiene and animal husbandry within farms
- Institution of veterinary guidelines for stewardship of antimicrobials in food animal production
- Surveillance and analysis of antimicrobial use and resistance patterns along the food animal supply chain and in the clinical setting
- Adoption of practices among food retailers and other business operators to procure food animals raised without non-therapeutic antimicrobial use.

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References

1. Pew Commission on Industrial Farm Animal Production. Putting Meat on the Table. 2008; http://www.ncifap.org/, 31 May 2016.
2. Silbergeld EK, Graham J, Price LB. Industrial food animal production, antimicrobial resistance, and human health. ***Annual review of public health.*** 2008;29:151-169.
3. Cecchini M, Langer J, Slawomirski L. Antimicrobial Resistance in G7 Countries and Beyond: Economic Issues, Policies and Options for Action. 2015; http://www.oecd.org/els/health-systems/Antimicrobial-Resistance-in-G7-Countries-and-Beyond.pdf, 28 May 2016.
4. Marshall BM, Levy SB. Food animals and antimicrobials: impacts on human health. ***Clinical microbiology reviews.*** 2011;24(4):718-733.
5. Waters AE, Contente-Cuomo T, Buchhagen J, et al. Multidrug-resistant Staphylococcus aureus in US meat and poultry. ***Clinical Infectious Diseases.*** 2011:cir181.
6. Aarestrup FM. Association between the consumption of antimicrobial agents in animal husbandry and the occurrence of resistant bacteria among food animals. ***International journal of antimicrobial agents.*** 1999;12(4):279-285.
7. Leverstein-van Hall M, Dierikx C, Cohen Stuart J, et al. Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains. ***Clinical Microbiology and Infection.*** 2011;17(6):873-880.
8. Vincent C, Boerlin P, Daignault D, et al. Food reservoir for Escherichia coli causing urinary tract infections. ***Emerging infectious diseases.*** 2010;16(1):88-95.
9. Chapin A, Rule A, Gibson K, Buckley T, Schwab K. Airborne multidrug-resistant bacteria isolated from a concentrated swine feeding operation. ***Environmental Health Perspectives.*** 2005:137-142.
10. Gibbs SG, Green CF, Tarwater PM, Mota LC, Mena KD, Scarpino PV. Isolation of antibiotic-resistant bacteria from the air plume downwind of a swine confined or concentrated animal feeding operation. ***Environmental Health Perspectives.*** 2006:1032-1037.
11. Sapkota AR, Curriero FC, Gibson KE, Schwab KJ. Antibiotic-resistant enterococci and fecal indicators in surface water and groundwater impacted by a concentrated swine feeding operation. ***Environmental Health Perspectives.*** 2007:1040-1045.
12. Casey JA, Curriero FC, Cosgrove SE, Nachman KE, Schwartz BS. High-density livestock operations, crop field application of manure, and risk of community-associated methicillin-resistant Staphylococcus aureus infection in Pennsylvania. ***JAMA internal medicine.*** 2013;173(21):1980-1990.
13. Fahrenfeld N, Knowlton K, Krometis LA, et al. Effect of manure application on abundance of antibiotic resistance genes and their attenuation rates in soil: field-scale mass balance approach. ***Environmental science & technology.*** 2014;48(5):2643-2650.
14. Xu Y, Yu W, Ma Q, Zhou H. Occurrence of (fluoro) quinolones and (fluoro) quinolone resistance in soil receiving swine manure for 11 years. ***Science of The Total Environment.*** 2015;530:191-197.
15. Cole D, Drum DJ, Stallknecht DE, et al. Free-living Canada geese and antimicrobial resistance. ***Emerg. Infect. Dis.*** 2005;11(6):935-938.
16. Graham JP, Price LB, Evans SL, Graczyk TK, Silbergeld EK. Antibiotic resistant enterococci and staphylococci isolated from flies collected near confined poultry feeding operations. ***Science of The Total Environment.*** 2009;407(8):2701-2710.
17. Ahmad A, Ghosh A, Schal C, Zurek L. Insects in confined swine operations carry a large antibiotic resistant and potentially virulent enterococcal community. ***BMC microbiology.*** 2011;11(1):1.
18. Henzler D, Opitz H. The role of mice in the epizootiology of Salmonella enteritidis infection on chicken layer farms. ***Avian diseases.*** 1992:625-631.
19. Rule AM, Evans SL, Silbergeld EK. Food animal transport: a potential source of community exposures to health hazards from industrial farming (CAFOs). ***Journal of Infection and Public Health.*** 2008;1(1):33-39.
20. rice LB, Stegger M, Hasman H, et al. Staphylococcus aureus CC398: host adaptation and emergence of methicillin resistance in livestock. ***MBio.*** 2012;3(1):e00305-00311.

21. Rinsky JL, Nadimpalli M, Wing S, et al. Livestock-associated methicillin and multidrug resistant Staphylococcus aureus is present among industrial, not antibiotic-free livestock operation workers in North Carolina. ***PLoS One.*** 2013;8(7):e67641.

22. Bergeron CR, Prussing C, Boerlin P, et al. Chicken as reservoir for extraintestinal pathogenic Escherichia coli in humans, Canada. ***Emerg. Infect. Dis.*** 2012;18(3):415-421.

23. European Medicines Agency. Updated advice on the use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health. 2016; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/05/WC500207233.pdf, 31 May 2016.

24. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. ***Clinical Infectious Diseases.*** 2006;42(Supplement 2):S82-S89.

25. Review on Antimicrobial Resistance. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. 2014; http://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf, 31 May 2016.

26. World Health Organization. Global Action Plan on Antimicrobial Resistance. 2015; http://www.who.int/drugresistance/global_action_plan/en/, 31 May 2016.

27. So AD, Ramachandran R, Love DC, Korinek A, Fry JP, Heaney CD. A Framework for Costing the Lowering of Antimicrobial Use in Food Animal Production. 2016; http://amr-review.org/sites/default/files/ReAct_CLF_Hopkins_UKAMRReview_CommissionedPaper.pdf, 31 May 2015.

28. United Nations Development Programme. Sustainable Development Goals (SDGs). 2015; http://www.undp.org/content/undp/en/home/sdgoverview/post-2015-development-agenda.html, 1 June 2016.

29. So, A. D., Shah, T. A., Roach, S., Ling Chee, Y., & Nachman, K. E. (2015). An Integrated Systems Approach is Needed to Ensure the Sustainability of Antibiotic Effectiveness for Both Humans and Animals. ***The Journal of Law, Medicine & Ethics***, 43(S3), 38-45.

30. Sneeringer S, MacDonald J, Key N, McBride W, Mathews K. ***Economics of Antibiotic Use in US Livestock Production.*** United States Department of Agriculture, Economic Research Service; 2015.

31. Superbugs: MEPs want to curb use of antibiotics in farming. (2016, March 10). Retrieved from http://www.europarl.europa.eu/news/en/news-room/20160303IPR16930/Superbugs-MEPs-want-to-curb-use-of-antibiotics-in-farming

32. Andersson, D. I., & Hughes, D. (2014). Microbiological effects of sublethal levels of antibiotics. Nature Reviews Microbiology, 12(7), 465-478.