Animal production and antimicrobial resistance in the clinic

One of the major public health challenges this century is the development of antimicrobial resistance in many important and common pathogens, such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*.[1] The *Lancet* Series on antimicrobials tackles the issue head-on by presenting evidence on universal access to antibiotics, sustainability, and effectiveness.[2–6] The Series focuses on the use and misuse of antimicrobials in human medicine but does not ignore other sources of antimicrobial resistance development: waste and contamination from the pharmaceutical industry, animal agriculture, and the natural arms race that has been fought among microbes in the environment since the dawn of evolution.

A substantial share of antimicrobial consumption is attributed to animal production. Recent findings conservatively estimate that, from 2010 to 2030, global consumption of antimicrobials in livestock production will increase by two thirds, and that it will double in the rapidly growing economies of Brazil, Russia, India, China, and South Africa.[7] In China, already the largest producer and user of antibiotics in the world,[8] the livestock sector could consume a third of the antibiotics produced worldwide by 2030.[7] Alison Holmes and colleagues[3] suggest that misuse of antimicrobials in animal production is an evident and substantial driver of antimicrobial resistance. Other studies show how the global food trade can obscure the lines that connect antibiotic use in food-animal production with antibiotic-resistant human infections.[9] The evidence that links antimicrobial use in animal production and the development of antimicrobial resistance in medically important pathogens is growing, thanks largely to advances in genetic analysis which allow the origins of genes conferring such resistance to be traced.

Using whole-genome sequencing and phylogenetics, an international team of researchers described the evolution of meticillin-resistant *S aureus* (MRSA) in livestock from meticillin-susceptible *S aureus* in humans.[10] This livestock-associated MRSA (clonal complex CC398) now frequently infects people both inside and outside of the livestock industry,[11] and is an unequivocal example of the evolution of a multidrug-resistant pathogen that emerged in livestock and was subsequently transmitted to humans. Genetic fingerprinting and epidemiological studies have also established links between multidrug-resistant urinary tract infections and *E coli* from poultry.[12] Moreover, a multicountry analysis of the human gut antibiotic resistome[13] showed the abundance of resistant genes to be greatest for those antibiotics also used in animals. Whole-genome sequencing of samples along food systems can reveal and begin to quantify the two-way traffic of antimicrobial-resistant bacteria between the farm and the clinic,[14] but this will require sampling frames that account for the specificities of antimicrobial use, the complexity of environmental transmission pathways, and the vast diversity of animal production systems globally.

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See Comment page 102

See Series pages 168, 176, and 188

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While molecular epidemiology is bringing new clarity to this issue, some of the strongest evidence that links agricultural antibiotic use to antimicrobial resistance in people comes from simple, natural experiments involving the introduction or withdrawal of antimicrobials from food animals. For instance, the introduction of fluoroquinolones to broiler chicken production in the USA was associated with a rapid increase in ciprofloxacin-resistant campylobacteriosis in humans.[15] Similarly, the voluntary withdrawal of ceftiofur in ovo injections in broiler chicken production in Canada resulted in a precipitous decrease in human infections caused by third-generation cephalosporin-resistant *Salmonella enterica*.[16] Despite these clear examples, there are insufficient data to resolve and quantify the total public health burden of antibiotic use in food-animal production.

Antimicrobials are used for various reasons in animal production, including for growth promotion, disease prevention, and disease treatment. These uses involve different classes of drugs applied at different doses, and their relative importance and methods of implementation vary greatly across animal production systems and in different parts of the world. The subtherapeutic use of antimicrobials to promote growth, in particular, comes under heavy criticism.

In 2006, the European Union banned the use of antibiotics for growth promotion in livestock, and indications are, for example in the pork and poultry sectors in Denmark,[17] that the prevalence of antimicrobial resistance among livestock has decreased since then. The use of antimicrobial growth promoters is still hotly debated in the USA, where non-binding guidance was issued in 2012 which recommended that livestock producers avoid using antibiotics as growth promoters.[18]

Consumer pressure has an important role in reinforcing such voluntary bans. In 2014, the USA-based Chick-fil-A company announced plans to remove antibiotics from its chicken production system within 5 years.[19] Poultry giants McDonald's and Costco were quick to follow suit.[20,21] Ramanan Laxminarayan and colleagues[2] among others have questioned the growth response to antimicrobials in livestock, suggesting that a ban on antimicrobial growth promoters would lead to only moderate production losses worldwide. Although the evidence on efficacy for growth promotion varies, and there is a fine line between growth promotion and disease prevention, there are perceived, if not actual, economic incentives for livestock and aquaculture producers to use antimicrobials; otherwise agricultural consumption of antimicrobials would not be so high. In production systems with optimum breeding, feeding, and sanitary conditions the effect of reduced antimicrobial use will be very different from that in the suboptimum production conditions typical of low-income and middle-income countries.

In developing countries, there can be a dual problem of lack of access to antimicrobials among smallholders and overuse in intensive production.[22] Agricultural practices in developing countries have a higher dependency on antibiotics because of a more disease-prone environment and lower levels of biosecurity than in high-income countries.[23] Global policies intended to reduce antibiotic consumption must be highly context-specific lest they have negative effects on livelihoods, nutrition, and food security.

Christine Årdal and colleagues[6] call for a combination of quick wins and long-term efforts. Although there is a need for more robust evidence to elucidate the complex transmission routes from animals to humans, the health, agriculture, and veterinary sectors also need to take urgent action based on existing evidence. Although we recognise the challenges involved in enforcement of legislation on antimicrobial use in low-income and middle-income countries acknowledged by Osman Dar and colleagues[5] and the importance of ensuring that antibiotics remain available to control animal diseases, we strongly support working towards a global prohibition on animal growth promotion or routine disease prevention with any antibiotic deemed critically important to human medicine.[24] With growing transportation networks and international trade, pathogens travel quickly around the world making antimicrobial resistance a global problem in need of global solutions such as coordinated policy interventions. But antimicrobial resistance is also a multisectoral issue that involves consumers of animal source foods, the retail industry, farmers in livestock and aquaculture whose livelihoods rely on the ability to keep healthy animals, the feed industry, animal health practitioners, regulatory bodies, the pharmaceutical industry, and the public health sector. To be successful, policy interventions will require buy-in from diverse stakeholders.

If we are to ensure the future universal access, sustainability, and effectiveness of antimicrobials to treat disease in people and their livestock, these issues must be tackled from the health perspectives of people, animals, and the environment. This perspective sits at the very core of the One Health approach, which recognises that the health of people is connected to the health of animals and the environment. Such an inclusive approach will be needed to reduce selection pressure for antimicrobial resistance genes and protect our medically important antibiotics.

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National action for global gains in antimicrobial resistance

Few public health problems are of greater global importance today than antimicrobial resistance. Multidrug resistant pathogens are a challenge in high-income countries, and many countries, including the USA and the UK, have created national plans as well as legislation and regulation to address antibiotic resistance issues. However, middle-income and low-income countries are likely to bear the brunt of this problem. Many of our citizens do not have access to antibiotics. In the *Lancet* Series on antimicrobial access, sustainability, and effectiveness, Ramanan Laxminarayan and colleagues[1] make the case that far more people die from lack of access to antibiotics than from antimicrobial resistance. They estimate that 75% of community-acquired pneumonia deaths in children younger than 5 years could be averted by universal access to antibiotics.[1] Marc Mendelson and colleagues[2] echo this finding in their Series paper, and highlight the need for improved access to diagnostics so that infectious diseases can be identified and treated correctly. Even for those with access to first-line antibiotics, more expensive second-line antibiotics are not affordable for our countries. Some new antibiotics are needed, but conserving the antibiotics we already have is the highest immediate priority.

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See Comment page 102

See Series pages 168, 176, and 188

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