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Impacts of antibiotic use in agriculture: what are the benefits and risks?☆

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Antibiotic drugs provide clear benefits for food animal health and welfare, while simultaneously providing clear risks due to enrichment of resistant microorganisms. There is no consensus, however, on how to evaluate benefits and risks of antibiotic use in agriculture, or the impact on public health. Recent soil resistome work emphasizes the importance of environmental reservoirs of antibiotic resistance (AR), and provides a starting point for distinguishing AR that can be impacted by agricultural practices from AR naturally present in a system. Manure is the primary vehicle introducing antibiotic drugs, AR bacteria and AR genes from animals into the environment. Manure management, therefore, impacts the transfer of AR from agricultural to human clinical settings via soil, water, and food. Ongoing research on the ecology of naturally occurring and anthropogenically derived AR in agroecosystems is necessary to adequately quantify the benefits and risks associated with use of antibiotics in food animals.

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Introduction: which drugs, bacteria and genes should be measured in agroecosystems?

The use of antibiotics in animal production entwines ethics, economics, and environmental concerns. Antibiotics are critical for minimizing pain and treating disease, which are among the 'five freedoms' accorded to livestock by contemporary animal husbandry [1]. Antibiotics also improve feed efficiency, which allows the same amount of meat to be produced with a smaller number of animals. Greater efficiency results in less cropland area necessary to grow animal feed, decreased manure production, and concomitant economic benefits for both consumers (e.g. lower prices) and producers (e.g. greater profits).

There is a broad consensus that antibiotic use enriches bacteria carrying antibiotic resistance genes (AR genes), and that antibiotic resistant bacteria (AR bacteria) and AR genes from agricultural settings can be physically transferred to humans. However many of the applied details of how, and at what rate bacteria and genes move from animals to humans through agricultural systems (soil, water, wildlife, insects, dust, food,) remain to be determined [2–8] (Figure 1). This review will focus on cattle, swine and poultry systems. Antibiotic use in aquaculture was recently reviewed elsewhere [9].

There are three main components to any discussion on AR: the antibiotic drugs, the AR bacteria, and the AR genes. The World Health Organization (WHO) list of antimicrobials of importance to human medicine contains 32 drug classes (260 individual drugs) listed as important, highly important, or critical for human medicine [WHO, http://apps.who.int/iris/bitstream/10665/77376/1/9789241504485_eng.pdf?ua=1]. Which drugs, bacteria, and genes are most relevant in the discussion of clinical consequences [10••]? Of the 260 drugs on the WHO list of antimicrobial agents important for human medicine, only 39 are recommended or registered for use in cattle, swine, and poultry in the U.S [11,12] [Food Animal Residue Avoidance Database (FARAD), United States Department of Agriculture, http://www.farad.org/vetgram/search.asp] (Table 1). This includes drugs administered to individual animals and groups of animals to maintain animal health, and drugs used for growth promotion. The drugs available for use in animal agriculture vary by country, and the U.S. data are not necessarily representative of other countries. Recent U.S. Food and Drug Administration guidance regarding the labeling of over the counter antibiotics in food animals will also change how antibiotic drugs are used in cattle, swine and poultry.

To determine which agricultural antibiotics have a real possibility to impact clinical outcomes, veterinary drug information needs to be combined with information from

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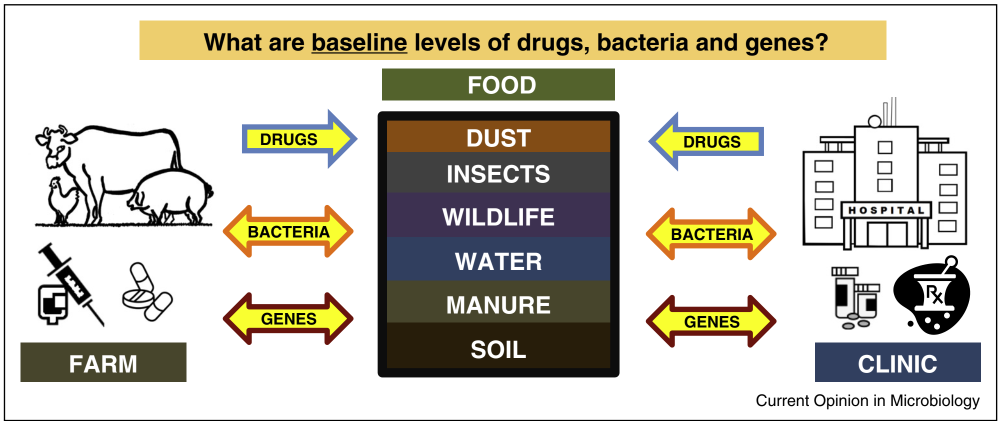
Figure 1



Movement of antibiotic resistance between farm and clinic. The environment is a reservoir of resistance, and a conduit of resistance between farm and clinic. The specific mechanisms by which antibiotic resistant bacteria and their genes are transported through the 'black box' of the environment remain uncertain. In order to accurately assess benefits and risks of antibiotic use in agriculture, it is essential to measure baseline levels of antibiotic drugs, resistant bacteria, and resistance genes when working with agriculturally impacted samples.

the Centers for Disease Control and Prevention (CDC) prioritized list of bacteria posing antibiotic resistance threats [CDC Threat Report, http://www.cdc.gov/drugresistance/threat-report-2013/], and with information regarding the ecology of pathogens [3,13] (Table 2). For example, tetracycline-resistant *Neisseria gonorrhoeae* is a pathogen listed as an Urgent Threat by CDC (the top category), and the antibiotic tetracycline is listed by CDC as a 'resistance of concern' for this pathogen. Although tetracycline is widely used in agricultural applications including over the counter sales of products added to feed and water, the fact that *N. gonorrhoeae* is a sexually transmitted disease with no known foodborne or environmental transmission suggests that agricultural use of the drug has limited impact on total burden of tetracycline resistance for *N. gonorrhoeae*. In contrast, tetracycline resistance is not listed by CDC as a 'resistance of concern' for *Campylobacter*, and is not generally recommended for treatment of *Campylobacter*. However, given its significance as a foodborne pathogen, any tetracycline resistant *Campylobacter* present in food animals would be more likely to impact human health. In a third example, multidrug-resistant *Acinetobacter* inhabits soil, water, foods and arthropods and causes outbreaks associated with natural disasters [14]. Even though none of the drugs recommended for treatment [15] are used in food animals, the fact that *Acinetobacter* lives in the soil suggests that it has the theoretical potential to acquire resistance from agroecosystems.

For each antibiotic drug, there are a suite of genes that code for resistance. Resistance to tetracycline, for instance, can occur by three different mechanisms, encoded by over 25 different genes [16]. If the goal is to measure or track tetracycline resistance — how much is on a farm, and how much is it reduced over time when a specific management strategy is implemented — which combination of these 25 different genes should be monitored, and in which types of bacteria? Different strains of the same organism may carry numerous AR genes [17], while the same AR genes may be carried by multiple taxa [18,19,20•,21]. Taxa that survive well outside of the animal may have a greater potential to impact clinical disease due to the likelihood of surviving harsh environmental conditions until reaching an acceptable host [18,22•,23]. These taxa would, therefore, provide better targets for measuring and tracking clinically relevant antibiotic resistance. Complicating the measurement of agricultural AR (agAR) and its potential for impacting human health are the physical, chemical, spatial, temporal and biological complexities of natural systems, and the 'many ecologies' of resistance [24–30]. As a result it can be expected that there will be different strategies and targets for the reduction of resistance in beef, dairy, swine, and poultry, operations [FAO/WHO/OIE, Expert Meeting on Critically Important Antimicrobials Report, Rome, Italy, November 2007].

Defining baseline levels of drugs, bacteria and genes

The second challenge for evaluating benefits and risks of agricultural antibiotic use is that AR occurs naturally in the environment. A quantitative understanding of resistance transmission can be confounded by naturally occurring and baseline levels of resistance [31]. AR genes have been found in samples that pre-date the dawn of agriculture [32], and are ubiquitous in food, animal, human, and environmental samples [4,10••,20•,33••,34,35,36•]. For example, soil is a natural source of antibiotic-producing bacteria and a reservoir of resistance across the globe [10••,34,35]. To understand the ecology and evolution of AR in agroecosystems and to accurately evaluate the