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Antimicrobial resistance and its association with tolerance to heavy metals in agriculture production

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ABSTRACT

Antimicrobial resistance is a recognized public health challenge that since its emergence limits the therapeutic options available to veterinarians and clinicians alike, when treatment is warranted. This development is further compounded by the paucity of new antibiotics. The agri-food industry benefits from the availability of antimicrobial compounds for food-animal production and crop protection. Nonetheless, their improper use can result in the selection for bacteria that are phenotypically resistant to these compounds. Another class of agents used in agriculture includes various cationic metals that can be included in animal diets as nutritional supplements or spread on pastures to support crop growth and protection. Heavy metals, in particular, are giving rise to concerns among public health professionals, as they can persist in the environment remaining stable for prolonged periods. Moreover, bacteria can also exhibit resistance to these chemical elements and the genes encoding this phenotype can be physically localized to plasmids that may also contain one or more antimicrobial resistance-encoding gene(s).

This paper reviews our current understanding of the role that bacteria play in expressing resistance to heavy metals. It will describe how heavy metals are used in agri-food production, and explore evidence available to link resistance to heavy metals and antimicrobial compounds.

In addition, possible solutions to reduce the impact of heavy metal resistance are also discussed, including using organic minerals and reducing the level of trace minerals in animal feed rations.

Contents

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1. Introduction

Antimicrobial compounds once considered the magic bullet to target bacterial infections are quickly losing their efficacy due to the emergence and dissemination of resistant bacteria. Added to this is the fact that there are few new antimicrobial compounds in development pipelines. Therefore studies that focus on preventing/reducing the emergence of resistance is an important key step to support efforts to maintain the efficacy of our existing arsenal of antimicrobial agents. In human medicine in most countries these valuable drugs can only be obtained *via* a prescription provided by a medical doctor. In contrast, for animal production requirements in some countries certain classes of antibiotics are freely available.

Antimicrobial agents of proven efficacy are a cornerstone of veterinary practice. These drugs are used in the treatment of clinically ill animals and when necessary, they can also be administered for prophylaxis of large numbers of animals during stressful periods. As an example in dairy farms where mastitis caused by aetiological agents including *Staphylococcus aureus*, coagulase-negative staphylococci, *Streptococcus agalactiae* among others can lead to altered milk quality and productivity problems, several classes of antimicrobial compound such as aminoglycosides, cephalosporins, penicillins and tetracyclines have been used to prevent or treat this infection. Usually about 2 months before calving, cows are *dried off* (not milked) to provide the animal with an opportunity to rest and to facilitate the regeneration of mammary tissue in order to achieve optimal animal health and higher milk quality and quantity during the ensuing lactation. In order to counter against any clinical, or sub-clinical mastitis and prevent infection that are quite likely to occur during the dry period, antimicrobial compounds are usually infused into the animals' teats. The most commonly used drugs include cephalosporins, cloxacillin, nafcillin and a combination of penicillin and streptomycin products (Blowey and Edmondson, 2010).

It was estimated that globally each kilogram of meat harvested from cattle, chickens and pigs would lead to the consumption of 45 mg, 148 mg, and 172 mg of antimicrobial compound respectively. This number is expected to increase by 67% from 2010 to 2030, with up to one-third of the increase resulting from farms being replaced by large scale intensive units in middle-income countries (Van Boeckel et al., 2015). Intensive farming systems with high animal stocking densities, a common feature in many countries has facilitated the spread of contagious diseases. Often in these situations, the implementation of robust biosecurity and hygiene practices that are essential to prevent the spread of any infections, are lacking. In some primary production systems antimicrobial agents are used as a substitute for good husbandry practices.

Further, in some jurisdictions therapeutic antibiotics can be administered to food-producing animals, as growth promoters to improve feed conversion rates, stimulate animal growth, and prevent disease. Antibiotics such as avoparcin, penicillin, streptomycin, and tetracycline have all been used previously, as growth promoters. Since the risk of antibiotic resistance caused by these growth promoters is better understood, the European Union finally banned their use in 2006 (Cogliani et al., 2011). Nonetheless in some regions where standards are lower or the enforcement of such regulation is not strong enough, these agents are administered to food-producing animals.

Increasing public disquiet about the use of antimicrobial agents in farming practice and the emergence of multi-drug resistant (MDR) bacteria has placed pressure on the agri-food industry to act. Individuals managing livestock such as farmers and veterinarians are also at higher risk of being infected by resistant bacteria including livestock acquired-methicillin-resistant *Staphylococcus aureus* (LA-MRSA). Consumers are becoming more aware of the fact that this practice can result in either the resistant bacterium, the active ingredient or its derived metabolite (or residue) persisting in food products. This development places the consumer at risk. The globalization of the food chain makes the fight against antimicrobial resistance an international issue. The effort of one nation to reduce its application of antimicrobial drugs in agri-food production alone will not yield the required outcome in terms of limiting consumer exposure. Thus all countries exporting food must develop a code of practice to mitigate the risks to the consumer and preserve these valuable chemotherapeutic agents for future generations.

Apart from antimicrobial agents themselves, a similar issue also exists for heavy metals. Heavy metals also exhibit antimicrobial features. Metallic copper coated surfaces are used in some clinics to reduce the risk of nosocomial infections (Grass et al., 2011). As a result, these elements can also contribute to the problem by playing an indirect role in the selection for resistant bacteria. In general, even when no antimicrobial compounds are used, certain heavy metals can maintain or even increase the bacterial resistance against certain agents. Heavy metals occur ubiquitously in the environment, and on occasion at high concentrations in certain settings. The most commonly encountered heavy metal contaminations in order of abundance are: lead (Pb), chromium (Cr), arsenic (As), zinc (Zn), cadmium (Cd), copper (Cu) and mercury (Hg) (Wuana and Okieimen, 2011). Certain products containing heavy metals such as zinc (Zn) and copper (Cu) are used in agriculture production for various purposes. Efforts to reduce the use of antimicrobial compounds on farms may be compromised owing to the potential links between this and other mechanisms elaborating resistance to heavy metals.

This paper reviews the current knowledge describing the role bacteria play in expressing resistance to heavy metals. It will focus on how heavy metals are used in agri-food production, and explore evidence demonstrating the correlation between heavy metals and antimicrobial resistance in different environments. The impact of co-selection in terms of public health risk of antimicrobial resistance will be discussed. Potential mitigating strategies are also highlighted.

2. Heavy metals in agri-food production

2.1. Application (point sources)

Heavy metals are used in the modern agriculture industry from