

What do we know about antimicrobial resistance and its association with antimicrobial use in food-producing animals?

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Why is this important?

Antimicrobial resistance (AMR) is one of the most important threats to humans and animals globally. It occurs when bacteria change over time and no longer respond to drugs that we rely on when treating infections, including severe life-threatening illnesses in hospitalized patients. AMR occurs when we expose bacteria to antimicrobials. Recently, the World Health Organization recommended producers, veterinarians and stakeholders involved in livestock industries to reduce the use of antibiotics. The idea is that by limiting the use of antimicrobials, bacteria will have fewer opportunities to develop AMR.

Although the link between antimicrobial use and emergence of resistance is clear, the same cannot be said about effects of restrictions of antimicrobial use on AMR. A recent systematic review carried out by our team in Calgary and commissioned by the World Health Organization suggested that, as a general rule, restricting antimicrobial use in livestock will be effective to curb AMR in animals and humans. However, bacteria may keep the antimicrobial resistance genes that are linked to AMR even in the absence of antimicrobials. These genes can be activated as soon as bacteria are again exposed to antimicrobials, resulting in new episodes of treatment failures. Further, these genes can be easily shared among bacteria, which can have significant impacts in the dissemination of AMR. Knowledge on whether the prevalence of resistance genes is impacted by diminished antimicrobial use will constitute an important part of discussions implicating the use of antimicrobials in food animals.

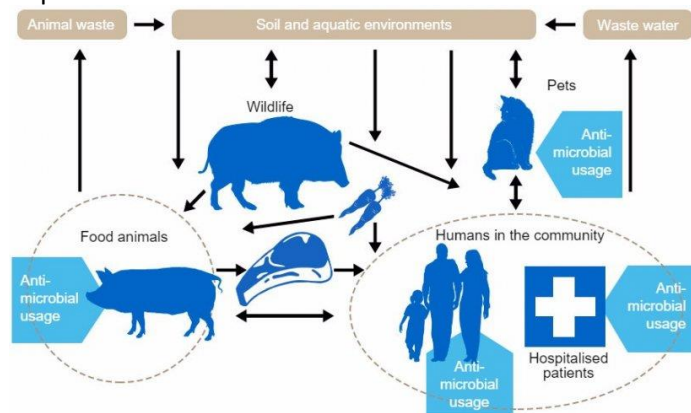
What did we do?

We reviewed the literature to explore potential effects of restrictions of antimicrobial use in the presence of antimicrobial resistance genes. Our objective was to determine what the most likely effects are of reducing the use of antibiotics on the prevalence of resistance genes.

We started with a list of full texts (n = 430). From that list, studies were retained if reporting on the following:

1) population studied included food animals and/or humans; 2) intervention was a restriction in use of antimicrobials in food animals; 3) presence of a comparator group that did not undergo such an intervention; and a comparison of intervention to non-intervention; and 4) outcome defined as the prevalence of antimicrobial resistance genes.

We then used standardized forms to extract data from eligible studies, and classified samples as: 1) environmental (e.g., dust, facilities swabs, milk filters); 2) animal or individual (e.g., faeces, nasal, milk); or 3) food (e.g., milk at retailer, beef, pork). We then compared the presence of resistance genes in bacteria isolated from systems where a restriction of antimicrobial use was in place to the same in bacteria where no restriction was implemented.



What did we find?

Forty-eight studies were included in this systematic review, with 41 studies reported on resistance genes in bacteria from at least one animal species and 7 reported findings in humans. Organic farming and antibiotic-free or related labels (e.g. raised without the use of antimicrobials) were the most reported interventions. The gene linked to resistance against vancomycin was the most frequently reported resistance gene (12 studies).

A positive effect of intervention (reduction in the presence of genes in groups with restricted antimicrobial use) was reported from 29 studies for at least one gene. The opposite (restrictions being associated with increased presence of genes) was reported from 3 studies. A ban on avoparcin was associated with diminished presence of the *vanA* gene in samples from animals and humans. For the *mecA* gene, the gene causing methicillin-resistance in *Staphylococcus aureus* (MRSA), studies agreed on a positive effect of intervention in samples only from animals, including dairy cows. Comparisons involving a number of other genes indicated a reduced presence of genes in groups with restricted antimicrobial use. Yet, for most studied genes, no effects of interventions were detected.

The type of intervention was associated with presence of the *vanA* gene (causing vancomycin resistance). Imposed restrictions of antimicrobial use (externally-imposed ban on specific antimicrobials) were less effective than voluntary restrictions (organic farming) to reduce the presence of the *vanA* gene. Effects of animal species, antimicrobial class and gene studied was also detected for other resistance elements.

What does it mean?

This systematic review examined the genetics of AMR and its associations with restrictions in the use of antimicrobials in food-producing animals. Restrictions of antimicrobial use in livestock were linked to the presence of some resistance genes, including important genes such as *vanA* and *mecA*.

For most studied genes, there were no effects of interventions. We believe that the reason for that is because AMR is multifactorial; bacteria do not need to harbor different resistance genes to be resistant to antimicrobials. Further, the baseline resistance profile of herds using more antimicrobials will depend on which drugs are currently in use. Screening for AMR genes not linked to antimicrobials that are currently in use will result in comparable presence of genes in groups using and not using antimicrobials. Most importantly, when an effect of intervention was observed, in the vast majority of cases (> 95%) the group with restricted drug use had a diminished presence of AMR genes. Therefore, reducing the use of antimicrobials in livestock will likely result in either an equal or reduced prevalence of most genes.

The livestock industry has been contemplating the adoption of protocols promoting reduced antimicrobial use (e.g. selective dry cow therapy, where only some cows are treated with antibiotic at drying off). Our findings support that reduced antimicrobial use will result in reduced rates of specific resistance genes. Nevertheless, we must emphasize the need for investigation of factors other than antimicrobial use that may be driving the presence of AMR in livestock; some genetic elements were not affected by the diminished use of antimicrobials. For those, an efficient strategy to limit risks will necessarily involve the identification of factors driving their presence in bacteria other than antimicrobial use. Potential factors include biosecurity protocols, stocking density, and animal welfare.

Summary Points

- Restricting the use of antimicrobials in food-producing animals will reduce the presence of some antimicrobial resistance genes in bacteria causing diseases in animals and humans;
- However, effects of restrictions were not seen for a number of resistance genes, prompting the need for future investigation of factors other than antimicrobial use driving antimicrobial resistance in bacteria isolated from livestock.