

Critically important antimicrobials are generally not needed to treat non-severe clinical mastitis in lactating dairy cows

D.B. Nobrega^{1,2}, S. Ali Naqvi^{2,3}, S. Dufour^{2,4}, R. Deardon^{1,5}, J.P. Kastelic¹, J. De Buck^{1,2}, and H.W. Barkema^{1,2,3}

¹Dept of Production Animal Health, University of Calgary; ²Mastitis Network, University of Montreal; ³Dept of Community Health Sciences, University of Calgary; ⁴Dept of Pathology and Microbiology, University of Montreal; ⁵Dept of Mathematics and Statistics, University of Calgary

Why is this important?

Antimicrobial resistance (AMR) is an important global threat to both human and animal health. Without urgent action, we are heading toward a post-antibiotic era where 10 million deaths per year globally will be attributable to AMR. Because antimicrobial use (AMU) contributes to the emergence of AMR, refining AMU is critical and strategies to reduce AMU are essential.

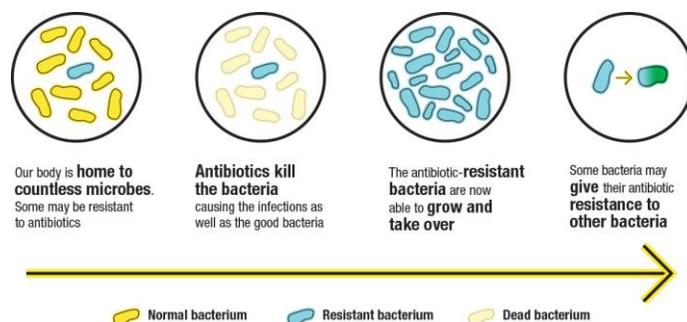
The World Health Organization classifies antimicrobials into categories based on availability of alternatives and risk of AMR-emergence due to nonhuman AMU. Critically important antimicrobials (CIA) are those used to treat specific diseases in humans. The use of CIA in food-producing animals may be associated with increased risk of non-treatable human infections. Thus, there is ongoing debate on whether these antimicrobials should be used to treat infections in food-producing animals. As such, some countries have made efforts to control or restrict overall use of CIA in food-producing animals.

Ideally, alternatives of comparable or superior efficacy should be available in order to reduce use of CIA. Alternatives would allow for effective treatment of bacterial infections in animals while reserving CIAs for human medicine. In dairy cattle, mastitis accounts for most AMU, including CIA. It is important to understand whether CIA are indispensable for treating this infection or whether a non-CIA alternative could be used with equal (or greater) effect.

The objective of this study was to conduct a meta-analysis to assess whether CIA and non-CIA have comparable efficacy to treat non-severe bovine clinical mastitis (CM) caused by the most common bacterial pathogens.

What did we do?

The researchers conducted a network meta-analysis using a total of 26 studies. Non-severe CM was defined as signs of inflammation in the mammary gland or altered milk secretion with no signs of systemic involvement. Intervention was defined as administration of antimicrobials, either systemically or intramammarily. Animals were considered untreated if they received no therapy of any kind or were treated with a placebo. Researchers then analyzed these studies to compare the effectiveness of CIA versus non-CIA in curing non-severe CM caused by particular bacterial pathogens, including *Escherichia coli*, *Klebsiella* spp., non-*aureus* staphylococci, *Staphylococcus aureus*, and non-*agalactiae* streptococci.



What did we find?

The results from this meta-analysis are applicable **only** to the treatment of non-severe clinical mastitis caused by the following pathogens.

E. coli: No evidence supporting the need for CIA; no protocol including CIA had better cure rates than protocols relying on non-CIA. Additionally, the probability of a cure was similar for treated vs. untreated cows, suggesting AMU is not necessary when dealing with this pathogen.

Klebsiella spp.: No evidence supporting the need to use CIA; no protocol using CIA resulted in increased cure compared with protocols using non-CIA. Additionally, probability of a cure was not lower when no antimicrobials were used.

Non-aureus staphylococci: No protocol using CIA resulted in increased cure when compared with protocols using non-CIA. None of the analyzed studies investigated treated vs untreated cows for this pathogen.

Staphylococcus aureus: The bacteriological cure rate was not different when comparing CIA versus non-CIA. There were no studies comparing treated vs. untreated cows for this pathogen.

Non-agalactiae streptococci: No protocol using CIA resulted in higher cure rates compared with protocols using non-CIA. However, administration of antimicrobials (versus no treatment) was associated with higher probability of cure.

What does it mean?

The researchers found that CIA and non-CIA had comparable efficacy to treat non-severe CM in dairy cattle caused by the most common bacterial pathogens. As such, ceasing the use of CIA for treatment of this illness will not result in adverse effects on health and welfare. Further, the findings suggested that AMU is not necessary ~~at all~~ in non-severe cases of CM caused by *E. coli* or *Klebsiella* spp., as cure was obtained without treatment. Use of culture-based, selective treatment programs would be valuable in helping producers and veterinarians determine which pathogen is present and whether there is a need to treat an infection with antimicrobials. When antimicrobials are needed, veterinarians should choose non-CIA of comparable or superior efficacy for treating animals as part of their antimicrobial stewardship program.

Of note, the WHO list of CIAs did not consider economics when classifying different antimicrobials. However, it is important that producers and veterinarians are aware of these economic considerations. Restrictions of AMU in dairy cattle could increase milk price, thereby decreasing gross revenue for dairy farmers as well as affecting markets. Despite comparable efficacy, economic factors such as the cost of antimicrobials, duration of milk withdrawal, duration of therapy, and route of administration should be included in the equation when selecting an antimicrobial for mastitis treatment.

This study's results should be used as an important part of a discussion for implementing strategies to manage CM in dairy herds.

Summary Points

- Antimicrobial resistance is a major threat to human and animal health, with particular antimicrobials deemed critically important. Reducing use of these critically important antimicrobials in food-producing animals is essential.
- Critically important antimicrobials and non-critically important antimicrobials demonstrated comparable efficacy when used to treat non-severe clinical mastitis caused by *Escherichia coli*, *Klebsiella* spp., non-aureus staphylococci, *Staphylococcus aureus*, and non-agalactiae streptococci.