
WHO GUIDELINES ON USE OF MEDICALLY IMPORTANT ANTIMICROBIALS IN FOOD-PRODUCING ANIMALS

Executive summary¹

In May 2015, the Sixty-eighth World Health Assembly recognized the importance of the public health problem posed by antimicrobial resistance by adopting the global action plan on antimicrobial resistance (“global action plan”). The global action plan proposes interventions to control antimicrobial resistance, including reducing the unnecessary use of antimicrobials in humans and in animals. The global action plan also emphasizes the need to take a cross-sectoral, “One Health” approach for controlling antimicrobial resistance, involving efforts by actors from many disciplines including human and veterinary medicine. Recognizing the urgent need for cross-sectoral action to address antimicrobial resistance, the assemblies of the Food and Agriculture Organization of the United Nations (FAO) and World Organisation for Animal Health (OIE)

also adopted resolutions supporting the global action plan on antimicrobial resistance in 2015.

Many antimicrobials used in food-producing animals are identical, or closely related, to antimicrobials used in humans. Most antimicrobials used in plant production, including orchards, are also identical, or closely related, to antimicrobials used in humans. Antimicrobials are used in food-producing animals to treat and control bacteria infections in the presence of disease and for disease prevention and growth promotion in the absence of disease. Antimicrobial use in food-producing animals can lead to selection and dissemination of antimicrobial-resistant bacteria in food-producing animals, which can then be transmitted to humans via food and other transmission routes.

¹ Full guidelines are available at: http://who.int/foodsafety/publications/cia_guidelines/en/index.html

Why are these guidelines needed?

The development of these guidelines was driven by the need to mitigate the adverse human health consequences of use of medically important antimicrobials (i.e. antimicrobials used in humans) in food-producing animals. In 2005, a WHO expert committee was set up to establish criteria for classifying medically important antimicrobials as important, highly important, or critically important for human medicine. These criteria were then used to establish the WHO List of Critically Important Antimicrobials for Human Medicine (WHO CIA List), which has since been updated regularly. WHO published the fifth revision of the WHO CIA List in 2017.

These guidelines present evidence-based recommendations and best practice statements on use of medically important antimicrobials in food-producing animals, based on the WHO CIA List. These guidelines aim primarily to help preserve the effectiveness of medically important antimicrobials, particularly those antimicrobials judged to be critically important to human medicine and also help preserve the effectiveness of antimicrobials for veterinary medicine, in direct support of the WHO global action plan.

How were these guidelines developed?

These guidelines were developed using the WHO guideline development process described in the WHO handbook for guideline development (second edition). These included:

- (i) identification of priority questions and critical outcomes;
- (ii) retrieval of the evidence in a transparent manner using standard methods for systematic reviews;
- (iii) narrative literature reviews produced by topic-expert scientists;
- (iv) assessment and synthesis of the evidence;
- (v) use of this evidence for the formulation of recommendations;
- (vi) planning for dissemination, implementation, impact evaluation and future updating of the guidelines

The process of the guideline development was managed by the WHO Steering Group, while the Guideline Development Group (GDG) consisting of external experts was responsible for the drafting of these guidelines. Priority questions on the effects of limitations of use of medically important antimicrobials in food-producing animals on antimicrobial resistance in human and animal populations, including overall use and specifically for growth promotion, disease prevention, and treatment were agreed on by the WHO Steering Group. These questions guided systematic reviews and narrative literature reviews and the evidence identified was summarized in evidence-to-recommendation tables to enable the GDG to use the appropriate evidence to formulate each recommendations. The GRADE (grading of recommendations, assessment, development and evaluation) approach was used to appraise and use the evidence to develop recommendations. The whole process was supervised by the WHO Guidelines Review Committee, which approved the final guidelines.

RECOMMENDATIONS AND BEST PRACTICE STATEMENTS

Recommendations

Recommendation 1: Overall antimicrobial use

We recommend an overall reduction in use of all classes of medically important antimicrobials in food-producing animals.

Strong recommendation, low quality evidence

Justification

The GDG determined that this recommendation should be strong, despite the low quality evidence, because the beneficial human health benefits (lowered prevalence of antimicrobial resistance in bacteria isolated from humans) strongly outweigh any potentially harmful or undesirable outcomes. The evidence from the systematic reviews and narrative literature reviews reveals that restricting use of antimicrobials in food-producing animals reduces the prevalence of antimicrobial resistance in bacteria isolated from food-producing animals that are, and can be, transmitted to humans. Extensive research into mechanisms of antimicrobial resistance, including the important role of horizontal gene transfer of antimicrobial resistance

determinants, supports the conclusion that using antimicrobials in food-producing animals selects for antimicrobial resistance in bacteria isolated from food-producing animals, which then spread among food-producing animals, into their environment, and to humans. Furthermore, the systematic reviews concluded that broad restrictions covering all antimicrobial classes appear to be more effective in reducing antimicrobial resistance compared to narrow restrictions of one antimicrobial class or drug, even though there are examples of marked reductions in antimicrobial resistance following restriction of a single antimicrobial. Finally, reduction in use of antimicrobials in food-producing animals is in accordance with the WHO global action plan.

Recommendation 2: Growth promotion use

We recommend complete restriction of use of all classes of medically important antimicrobials in food-producing animals for growth promotion.

Strong recommendation, low quality evidence

Justification

The GDG determined that this recommendation should be strong despite the low quality evidence due to the potentially large human health benefits of lowered prevalence of antimicrobial resistance in bacteria isolated from humans

resulting from the complete restriction of use of antimicrobials in food-producing animals for growth promotion. Evidence from the systematic reviews and a large body of information on the mechanisms of antimicrobial resistance supports the conclusion that antimicrobial use

in food-producing animals, particularly for growth promotion, selects for antimicrobial resistance in bacteria isolated from food-producing animals. Resistant bacteria then spread among food-producing animals, into their environment, and to humans. This conclusion, supported by narrative literature reviews, is based upon consistent evidence from systematic reviews that restriction of growth promotion use of antimicrobials in food-producing animals reduces the prevalence of antimicrobial resistance in bacteria isolated from food-producing animals that are, and can be, transmitted to humans. Furthermore,

potential undesirable consequences associated with complete restriction of growth promotion use of antimicrobials in food-producing animals (e.g. increased use of veterinary antimicrobials, adverse effects on animal health, animal welfare, food safety, the environment and animal production, increased costs of animal production, and economic impacts) appear to be relatively small or non-existent. Finally, many countries have successfully achieved complete restriction of growth promotion use of antimicrobials in food-producing animals, demonstrating the feasibility of this recommendation.

Recommendation 3: Prevention use (in the absence of disease)

We recommend complete restriction of use of all classes of medically important antimicrobials in food-producing animals for prevention of infectious diseases that have not yet been clinically diagnosed.

Strong recommendation, low quality evidence

Justification

The GDG determined that this recommendation should be strong, despite the low quality evidence, because complete restriction of all classes of medically important antimicrobials in food-producing animals has potential to confer the large human health benefit of lowered antimicrobial resistance in bacteria isolated from humans. This conclusion is based upon the systematic reviews, narrative reviews and evidence from documented additional observational studies. In particular, a study on the use of third generation cephalosporins for disease prevention in chickens in Canada found evidence that restriction of this use reduced the prevalence of antimicrobial resistance in bacteria transmitted to humans. Extensive research into mechanisms of antimicrobial resistance also supports the conclusion that using antimicrobials in food-producing animals selects for antimicrobial resistance in bacteria isolated from food-producing animals, which then spread among food-producing animals, into their environment,

and to humans. Furthermore, the potential undesirable consequences associated with complete restriction of use of antimicrobials for the prevention of infectious diseases that have not yet been clinically diagnosed in food-producing animals (e.g. adverse effects on animal health and welfare) appear to be relatively small. Finally, several countries have successfully achieved restriction of disease prevention use of antimicrobials in food-producing animals, demonstrating the feasibility of this recommendation.

Remarks

The GDG acknowledges that, when a veterinary professional judges that there is a high risk of spread of a particular infectious disease, use of antimicrobials for disease prevention is justified, if such a judgement is made on the basis of recent culture and sensitivity testing results. The antimicrobials used should start with those of least importance for human health e.g. start with classes not used in humans, and then as listed on the WHO CIA

List (important and then highly important). Antimicrobials classified as critically important in human medicine on the WHO CIA List should be used only when the most recent culture and sensitivity results of bacteria known to

have caused the disease indicate that the critically important antimicrobial is the only option. National antimicrobial resistance and antimicrobial use surveillance programmes should evaluate the effects of implementation.

Recommendation(s) 4: Control and treatment use (in the presence of disease)
Recommendation 4a
We suggest that antimicrobials classified as critically important for human medicine should not be used for control of the dissemination of a clinically diagnosed infectious disease identified within a group of food-producing animals.
<i>Conditional recommendation, very low quality evidence</i>
Recommendation 4b
We suggest that antimicrobials classified as highest priority critically important for human medicine should not be used for treatment of food-producing animals with a clinically diagnosed infectious disease.
<i>Conditional recommendation, very low quality evidence</i>

Justification

The GDG concluded that although evidence from the systematic reviews and additional studies indicates it will achieve the human health benefit of lowered antimicrobial resistance in bacteria, this recommendation should be conditional due to the very low quality of available evidence. Evidence from the systematic reviews and extensive research into mechanisms of antimicrobial resistance supports the conclusion that using antimicrobials in food-producing animals selects for antimicrobial resistance in bacteria isolated from food-producing animals, which then spread among food-producing animals, into the environment, and to humans.

Furthermore, the undesirable consequences associated with such a restriction of use of antimicrobials appear to be relatively small or non-existent. Finally, several countries have successfully accomplished such a restriction of antimicrobials in food-producing animals, demonstrating its feasibility.

Remarks

To prevent harm to animal health and welfare, exceptions to recommendations 4a and 4b can be made when, in the judgment of veterinary professionals, bacterial culture and sensitivity results demonstrate that the selected drug is the only treatment option.

Best practice statements

Best practice statements represent recommendations that GDG feel are important, but that are not appropriate for formal recommendations with ratings of quality of evidence. Based upon the evidence presented

from the systematic reviews and narrative literature reviews, the GDG formulated two best practice statements on use of medically important antimicrobials in food-producing animals.

Best practice statement 1

Any new class of antimicrobials or new antimicrobial combination developed for use in humans will be considered critically important for human medicine unless categorized otherwise by WHO.

Best practice statement 2

Medically important antimicrobials that are not currently used in food production should not be used in the future in food production including in food-producing animals or plants*.

*Although these guidelines only pertain to use of medically important antimicrobials in food-producing animals, the GDG concluded that this best practice statement ought to apply to all antimicrobial uses in food-producing animals and in plants. All such uses have the potential to select for antimicrobial resistance, which can be subsequently transferred to humans.

Rationale

- A number of medically important antimicrobials not currently used in food-producing animals are antimicrobials 'of last resort' for the treatment of serious and life-threatening infections in humans. Examples include carbapenems, oxazolidinones (e.g. linezolid), and lipopeptides (e.g. daptomycin). Preserving the effectiveness of these antimicrobials for treatment of serious and life-threatening infections in humans must be a best practice.
- Development and eventual marketing of new classes of antimicrobials intended for treatment of serious and life-threatening infections in humans is likely.
- Since the use in food-producing animals of antimicrobials covered by these best practice statements has not been reviewed for human safety, there are concerns about unauthorized (e.g. extra-label) use in food-producing animals.
- It is not possible to obtain direct evidence of the antimicrobial resistance consequences of use of new classes of antimicrobials not currently used in food-producing animals. Therefore, we rely upon experience that includes a large body of evidence from mechanistic studies of antimicrobial resistance.
- These best practices are consistent with the OIE statement that "Antimicrobial classes/sub-classes used only in human medicine are not on the OIE List of Antimicrobials of Veterinary Importance (OIE List)."

IMPLEMENTATION OF THESE GUIDELINES

These guidelines apply universally, regardless of region, income and setting, however, the GDG acknowledged that implementation of these guidelines in low and middle-income countries may require special considerations. These include assistance with animal health management to reduce the need for antimicrobials, including improvements in disease prevention strategies, housing and husbandry practices. Furthermore, many

countries may need technical and laboratory capacity building assistance for conducting the recommended bacterial culture and sensitivity testing. International organizations such as FAO and OIE may be able to assist in implementation of these guidelines. Finally, the GDG emphasized the need for countries to conduct surveillance and monitoring of antimicrobial usage in food-producing animals to monitor and evaluate the implementation of these guidelines.

FUTURE REVIEW

WHO will follow research development associated with use of antimicrobials in food-producing animals and review and updates these

recommendations five years after publication of the guidelines, unless significant new evidence emerges, necessitating earlier revision.



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