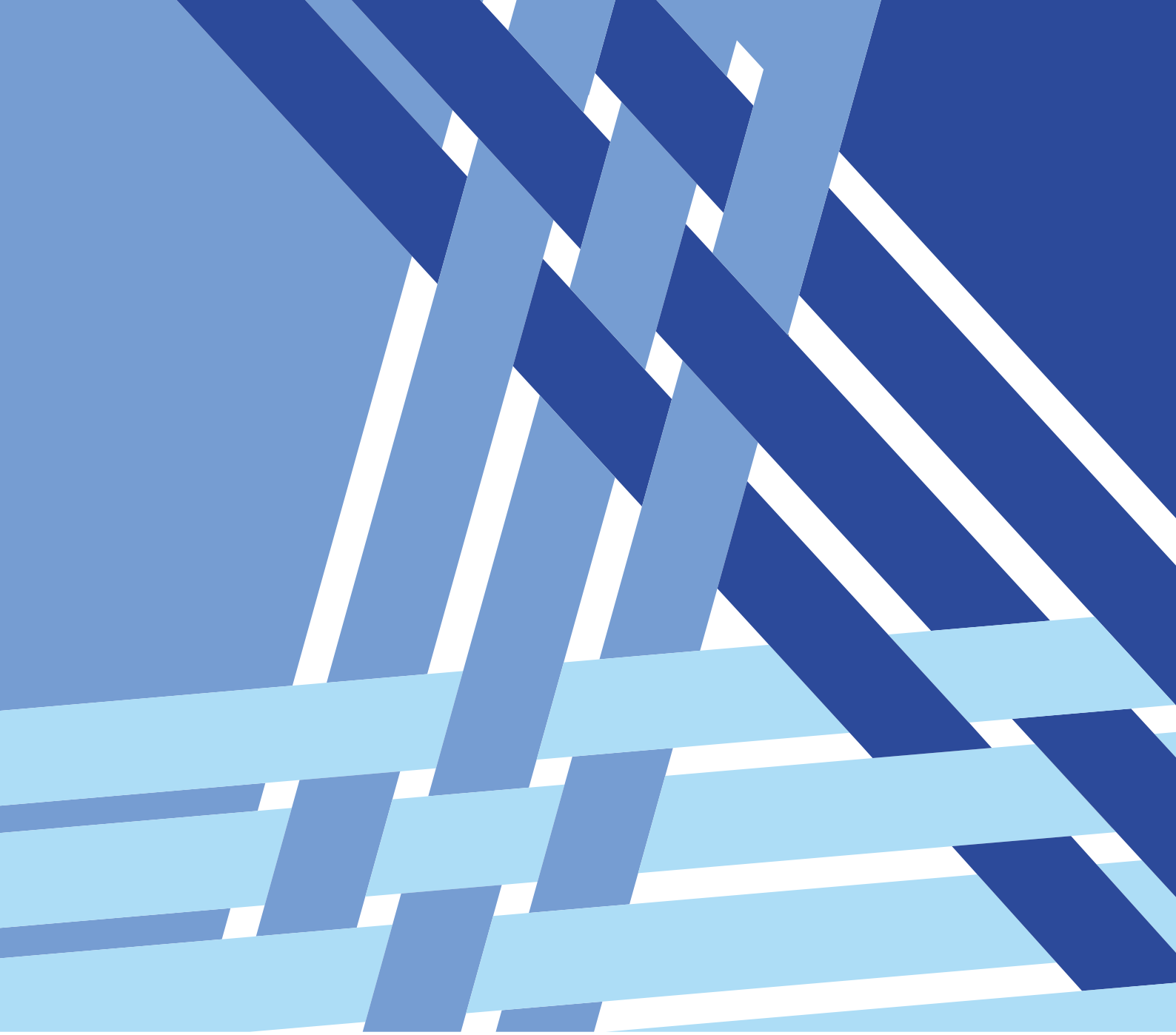

WHO GUIDELINES ON USE OF MEDICALLY IMPORTANT ANTIMICROBIALS IN FOOD-PRODUCING ANIMALS

World Health Organization

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WHO guidelines on use of medically important antimicrobials in food-producing animals
ISBN 978-92-4-155013-0

Suggested citation. WHO guidelines on use of medically important antimicrobials in food-producing animals. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

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Design and layout: Blossoming.it

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ACKNOWLEDGEMENTS

The World Health Organization (WHO) would like to thank the many individuals who contributed to these guidelines,[I] especially Hanan Balkhy, Peter Collignon, John Conly, Cindy Friedman, Aidan Hollis, Samuel Kariuki, Hyo-Sun Kwak, Scott McEwen, Gérard Moulin, Antoinette Ngandjio, Bernard Rollin, Flavia Rossi, and David Wallinga who served as members of the Guideline Development Group (GDG); Peter Collignon for serving as Chair at the first GDG meeting in October 2016; and to both Scott McEwen and Peter Collignon for serving as Co-Chairs at the second GDG meeting in March 2017. WHO appreciates the contribution of participants at the February 2016 guidelines scoping meeting, including members of the WHO Advisory Group of Integrated Surveillance for Antimicrobial Resistance (AGISAR).

Several groups and individuals gathered and presented evidence that the GDG considered in the development of these guidelines. Two research teams, one at Bond University in Australia, led by Chris Del Mar, and the other at the University of Calgary in Canada, led by William Ghali, conducted systematic reviews on the effects of restrictions on the use in food-producing animals of medically important antimicrobials on antimicrobial resistance in bacteria isolated from food-producing animals and humans. Hattie Webb conducted a narrative literature review on transfer of antimicrobial resistance determinants from food-producing animals to humans. Scott McEwen led a narrative literature review on the potential unintended consequences associated with restrictions on antimicrobial use in food-producing animals. Ellen Silbergeld provided a narrative literature review on biological plausibility for associations between antimicrobial use in food-producing animals and increased risks of human exposures to, and infections by, antimicrobial-resistant zoonotic pathogens. John Conly and Mauricio Ferri served as Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodologists, and prepared the evidence profiles tables, summary-of-findings tables, narrative evidence summaries, and the outcomes and ratings questionnaire. Special thanks go to Frederick Angulo for providing technical supports to WHO secretariat throughout the development of these guidelines.

Additional thanks go to the external review group, which included Saeed Murie Al-Shahrani, Casey Barton Behravesh, Delia Grace, Dik Mevius, Paturkar Ashish Motiram, Hnin Thidar Myint, Langelihle Simela, Linda Tollefson, Jan L. M. Vaarten, Haruo Watanabe, and Khadija Id Sidi Yahia.

WHO also acknowledges the contributions of WHO Steering Group as well as contributions of Henk Jan Ormel from the Food and Agriculture Organization of the United Nations (FAO) and Elisabeth Erlacher-Vindel of the World Organisation for Animal Health (OIE), who served as special members of the WHO Steering Group.

Assistance and guidance was provided by Susan Norris of the secretariat of the WHO Guidelines Review Committee throughout the development and finalization of the guidelines.

[I] A full list of contributors is included as Annex I. Annex 2 includes a summary of the declared interests and thier management.

Overall coordination

The work to develop these guidelines was initiated by the Department of Food Safety and Zoonoses of the WHO under the coordination of Awa Aidara-Kane, with the support of Yuki Minato.

Funding

The Governments of Japan and the Netherlands provided financial support for this work. The views of the funding bodies did not influence the development or content of these guidelines.

ACRONYMS AND ABBREVIATIONS

AFRO	WHO Regional Office for Africa
AGISAR	WHO Advisory Group on Integrated Surveillance for Antimicrobial Resistance
AMRO	WHO Regional Office for the Americas
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COI	Conflict of Interest
DOI	Declaration of Interest
EMBASE	Excerpta Medica database
EMRO	WHO Regional Office for the Eastern Mediterranean
ERG	External Review Group
EURO	WHO Regional Office for Europe
FAO	Food and Agriculture Organization of the United Nations
FERG	Foodborne Diseases Epidemiology Reference Group
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GREAT	Guideline-driven Research Priorities Evidence Synthesis Application of Evidence Transfer of Knowledge
IndMED	Indexing of Indian Medical Journals
LILACS	Latin American and Caribbean Health Sciences Literature
MEDLINE	Medical Literature Analysis and Retrieval System Online
OIE	World Organisation for Animal Health
OIE List	OIE List of Antimicrobials of Veterinary Importance
PICOTS	Population, intervention, comparison, outcome, time, setting
SEARO	WHO Regional Office for South-East Asia
UN	United Nations
WPRO	WHO Regional Office for the Western Pacific
WHO CIA List	WHO List of Critically Important Antimicrobials for Human Medicine

GLOSSARY OF TERMS

Antimicrobial
A medicine that inhibits the growth of or destroys microorganisms. For the purposes of these guidelines, "antimicrobial" is considered an equivalent term to "antibiotic".

Clinically diagnosed disease in food-producing animals
Disease diagnosed by a veterinary professional based upon clinical judgement supported when appropriate by microbiological testing. For the purposes of these guidelines, appropriate use of microbiological testing is the use of results from culture and sensitivity test results, and other appropriate sensitivity testing methods to justify the use of a medically important antimicrobial.

Food-producing animals
Animals used in production of food. The term "food-producing animals" includes all terrestrial and aquatic animals (that is, includes aquaculture) used to produce food. For the purposes of these guidelines, "food-producing animals" is considered an equivalent term to "food animals".

Medically important antimicrobials
Antimicrobial classes used in human medicine[I], and therefore listed on the WHO CIA List where they are categorized according to specified criteria, as "important", "highly important" or "critically important" for human medicine. Categorization criteria, definitions for the categories and a complete list of medically important antimicrobials are available on the WHO website.[2]

Critically important antimicrobial
Antimicrobial in an antimicrobial class providing the sole therapy, or one of limited available therapies, to treat serious bacterial infections in humans AND used to treat infections in humans caused by either: *(i)* bacteria that may be transmitted to humans from nonhuman sources, or *(ii)* bacteria that may acquire resistance genes from nonhuman sources. Several of the antimicrobial classes rated critically important have been further classified as "highest priority critically important antimicrobials". A complete list of critically important antimicrobials is available on the WHO website.[2]

[I] Medically important antimicrobials also includes those antimicrobials used in non-medical settings (e.g. food-producing animals) that are members of the same class as those used in human medicine and where there is the potential for these antimicrobials to select for resistance to human pathogens. For example, both the medical drug ciprofloxacin and the veterinary drug enrofloxacin are members of the fluoriquinolone class of antimicrobials, and the use of enrofloxacin in food-producing animals has selected for resistance to all drugs in the same class, including ciprofloxacin.
[2] http://who.int/foodsafety/areas_work/antimicrobial-resistance/cia/en/

Highest priority critically important antimicrobial

A critically important antimicrobial belonging to an antimicrobial class that meets three criteria: (i) It is used for treating infections in high absolute numbers of humans, or is commonly used in healthcare settings to treat patients with serious bacterial infections for which the antimicrobial class is the sole, or one of few alternatives, to treat serious infections in humans; (ii) it is frequently used for any indication in human medicine, or else is commonly used in patients with serious infections in healthcare settings n healthcare settings; and (iii) it is used to treat infections in humans for which there is evidence of transmission of resistant bacteria or resistance genes from non-human sources to humans. A complete list of highest priority critically important antimicrobials is available on the WHO website.[2]

Growth promotion use of antimicrobials in food-producing animals[3]

Growth promotion use of antimicrobials refers to the use of antimicrobials to increase the rate of weight gain and/or the efficiency of feed utilization in animals by other than purely nutritional means. The term does not apply to the use of antimicrobials for the specific purpose of treating, controlling, or preventing infectious diseases, even when an incidental growth response may be obtained.

Disease prevention use (or prophylactic use) of antimicrobials in food-producing animals[3]

Disease prevention use (or prophylactic use) of antimicrobials refers to use of antimicrobials in healthy animals considered to be at risk of infection or prior to the onset of clinical infectious disease. This includes use for control of the dissemination of a clinically diagnosed infectious disease identified within a group of animals, and prevention of an infectious disease that has not yet been diagnosed clinically.

Treatment use (or therapeutic use) of antimicrobials in food-producing animals[3]

Treatment use (or therapeutic use) of antimicrobials refers to use of antimicrobials for the specific purpose of treating an animal(s) with a clinically diagnosed infectious disease or illness.

[3] Codex Alimentarius, Texts on Foodborne Antimicrobial Resistance, 2015 http://www.fao.org/3/a-i4296t.pdf

EXECUTIVE SUMMARY

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 FAO and OIE also adopted resolutions supporting the global action plan 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 bacterial 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.

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 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 I: 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 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.
Conditional recommendation, very low quality evidence
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.
Conditional recommendation, very low quality evidence

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 I

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.

BACKGROUND

The increase in prevalence of antimicrobial resistance is a worldwide problem. Infection with antimicrobial resistant bacteria can have more severe consequences for human health than infections with antimicrobial susceptible bacteria. Such consequences include treatment failure, increased or longer hospitalization, and prolonged illness. Although many factors contribute to the rise in antimicrobial resistance in bacteria infecting humans, antimicrobial use in both humans and food-producing animals is an important contributor.

There is considerable evidence supporting the need to reduce antimicrobial use in humans and in food-producing animals to prevent and control antimicrobial resistance. In May 2015, the Sixty-eighth World Health Assembly adopted the global action plan on antimicrobial resistance[1], which aims to combat the increasing health threat posed by antimicrobial resistance. The global action plan aims to control antimicrobial resistance using a variety of interventions, including reducing use of antimicrobials in humans and animals. The global action plan also emphasizes the need for a cross-sectoral, "One Health" approach for control of antimicrobial resistance with efforts contributed 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 both the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE) adopted resolutions supporting the global action plan on antimicrobial resistance in 2015.

Antimicrobials that are identical, or closely related, to antimicrobials used in humans, are also used in food-producing animals. Antimicrobials used to treat humans are also used in plant production, including in orchards. Antimicrobials are used in food-producing animals for treatment and control of clinical bacterial infections but also for disease prevention and growth promotion in the absence of disease. The apparent growth promotion benefits of antimicrobials were first identified when fermentation by products from streptomycin and penicillin production for humans were fed to food-producing animals in the United States of America during the 1940s. By the 1950s, drug companies were widely marketing and selling antimicrobials for addition to animal feeds for growth promotion. Although the biological mechanism for the purported growth promotion benefits of antimicrobials has not been fully demonstrated, antimicrobials continue to be added to animal feed for growth promotion and disease prevention worldwide.

Use of antimicrobials in food-producing animals can lead to selection for, and dissemination of, antimicrobial resistant bacteria in food-producing animals, their wastes, and their surrounding environment. Prolonged use of antimicrobials in humans or animals increases the risk of multidrug resistance. Furthermore, bacteria that are pathogenic (e.g. *Salmonella spp., Campylobacter spp*.) and commensal (e.g. *Escherichia coli, Enterococcus spp.*) in humans, including resistant bacteria, are transmitted from food-producing animals to humans via

[1] http://www.who.int/antimicrobial-resistance/global-action-plan/en/

food and other transmission routes. Finally, infection with antimicrobial resistant bacteria, including antimicrobial resistant foodborne bacteria (such as non-typhoidal *Salmonella* spp., *Campylobacter* spp., and *Escherichia coli*) can have more severe consequences for human health than infections with susceptible bacteria. These include treatment failure, increased or longer hospitalization, and prolonged illness.

An important food safety issue

The use of antimicrobials in food-producing animals, subsequent selection of antimicrobial resistance in bacteria among food-producing animals, then transfer of those antimicrobial resistant bacteria from food-producing animals to humans via food, is an important food safety issue. Foodborne diseases are a major cause of human morbidity and mortality. According to recent estimates from the WHO Foodborne Diseases Epidemiology Reference Group (WHO FERG), foodborne diseases caused 600 million illnesses, 420,000 deaths, and 33 million Disability Adjusted Life Years in 2010 *(1)*. There is considerable variation in the burden of foodborne diseases among populations in certain sub-regions, with the highest burden of foodborne diseases observed in Africa *(1)*.

Foodborne diseases are particularly important in children. According to the WHO FERG estimates, although children 5 years of age and less represent only 9% of the global population, this age group represents 40% of the foodborne disease burden.

Food-producing animals are the predominant source of many foodborne diseases, including infections caused by nontyphoidal *Salmonella* and *Campylobacter (2)*. According to WHO FERG, nontyphoidal *Salmonella* caused an estimated 80 million infections and 60,000 deaths, while *Campylobacter* caused 95 million infections and 21,000 deaths in 2010. The WHO FERG estimates do not include estimates of the human health burden of antimicrobial resistant foodborne diseases. However, studies including national surveillance studies have found a notable prevalence of antimicrobial resistance in nontyphoidal *Salmonella* and *Campylobacter* infections in humans. For example, studies in Asia have found that most *Campylobacter* isolated from symptomatic humans are resistant to fluoroquinolones, the antimicrobial class commonly used to treat *Campylobacter* infections in adults *(3).*

Rising public health concern about use of antimicrobials in food-producing animals

The potential effects of using antimicrobials in food-producing animals have caused public health concern for decades. Early concerns focused mainly on the use of antimicrobials in animal feed for growth promotion. In 1960, government of the United Kingdom of Great Britain and Northern Ireland (UK) established the Netherhorpe Committee to investigate whether use of antimicrobials in animal feeds constituted a danger to humans. This was followed, in 1968, by the UK government-appointed Swann Committee (Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine) which concluded that administration of antimicrobials to food-producing animals poses hazards to human and animal health because it leads to the emergence of strains of bacteria which are resistant to antimicrobials *(4)*.

Concerns about the effects on public health were not limited to Europe. From 1969, onward, scientific, regulatory, and professional organizations in the United States of America (USA) have deliberated on the public health consequences of use of antimicrobials in food-producing animals, particularly in animal feeds. These include the American Academy of Microbiology, the Infectious Disease Society of America, the Institute of Medicine, Food and Drug Administration, the National Academy of Sciences and the Office of Technology Assessment. For example, in 1988, the US Institute of Medicine (part of the National Academy of Sciences) concluded that sparse data showed that resistant *Salmonella*, which had developed resistance due to use of antimicrobials in food-producing animals, had been transmitted from food-producing animals to humans through food products and had caused clinical illness in humans *(5)*. In 1994, the American Society of Microbiology concluded that resistant bacteria and genes encoding for resistance could

spread from animals to humans, particularly in contaminated food products *(6)*.

By the beginning of the 1990s, widespread use of fluoroquinolones and third-generation cephalosporins in food-producing animals, particularly as mass medications, were adding to the concern about the implications for human health. Several governments commissioned deliberations on the public health consequences of use of antimicrobials in food-producing animals. These include Canada in 1997 (National Consensus Conference - Controlling Antimicrobial Resistance: An Integrated Action Plan for Canadians), Australia in 1998 (Joint Expert Advisory Committee on Antibiotic Resistance), and the United Kingdom in 1998 (Ministry of Agriculture, Fisheries and Food).

Response to concern about use of antimicrobials in food-producing animals

In 1997, WHO organized a consultation on the "medical impact of the use of antimicrobials in food animals" in Berlin, Germany. The experts convened at that meeting concluded that use of antimicrobials in food-producing animals leads to selection of antimicrobial resistance. They also concluded that resistant bacteria and resistant determinants are transmitted to humans in food or through direct contact with food-producing animals. Furthermore, the expert group concluded that although the magnitude of the public health impact of use of antimicrobials in food-producing animals was uncertain, there was enough evidence to cause concern *(7)*.

In 2000, WHO, recognizing the public health threat posed by use of antimicrobials in food-producing animals, developed with the participation of FAO and OIE, the WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food (hereon called the "Global Principles" in this document) *(8).* These Global Principles, which form part of the comprehensive WHO Global Strategy for Containment of Antimicrobial Resistance *(9)*, provided recommendations aimed at reducing the use of antimicrobials in food-producing animals for the protection of human health.

Some countries began to use the recommendations from WHO consultations to implement restrictions on the use of selected antimicrobials in food-producing animals. In 1999, Denmark was able to discontinue the use of antimicrobials in food-producing animals for growth promotion by using a combination of regulatory action and voluntary measures by food-producing animal producers. An expert committee convened by WHO in 2002 to evaluate the impact of terminating the use of antimicrobials for growth promotion in Denmark found that this intervention had been accomplished with no major consequences for animal health, nor economic consequences for consumers or producers *(10)*. The experts further concluded that it led to a large reduction in antimicrobial use, reduction in antimicrobial resistance in food-producing animal reservoirs, and reduction in the public health threat of antimicrobial resistance.

In 2001, the Executive Committee of the Codex Alimentarius Commission recommended that the public health threat posed by antimicrobial use in food-producing animals should be assessed via consultations convened by FAO, OIE, and WHO *(11).* The three agencies agreed that these consultations should use a food safety risk analysis approach. This involves holding an initial meeting to assess the human health risks of antimicrobial use in food-producing animals, followed by a meeting to consider the options available for managing the identified human health risks. Accordingly an expert workshop, Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific Assessment, was jointly convened in Geneva in 2003 by FAO, OIE, and WHO to perform a scientific assessment of antimicrobial risks arising from non-human usage of antimicrobials and to formulate recommendations for future risk management actions. (12). The expert group concluded that there is clear evidence of adverse human consequences due to resistant organisms resulting from non-human usage of antimicrobials.

In 2004, the second stage of the process, an expert workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Management Options, was convened by FAO,

OIE and WHO in Oslo, Norway to consider risk management options, given the conclusions of the scientific assessment *(13)*. The workshop recommended that WHO should pursue the concept of "critically important" classes of antimicrobials for human medicine, while the OIE should develop a list of critically important antimicrobials for veterinary medicine.

The WHO list of critically important antimicrobials (WHO CIA List)

In 2005, WHO convened an expert committee in Canberra, Australia, to develop a process for defining and prioritizing medically important antimicrobials (i.e. antimicrobials important to human medicine). The expert committee established the criteria for classification of antimicrobials used in humans as important, highly important, or critically important for human medicine *(14)*. These criteria were then used to establish a WHO CIA List. The expert committee also advised that these criteria, and therefore the WHO CIA List, should be updated at regular intervals.

In 2007, WHO convened a multi-disciplinary expert WHO CIA List committee in Copenhagen, Denmark, to update the criteria for classifying antimicrobials used in humans and to revise the WHO CIA List, using the newest information. Such information included the emergence of extended-spectrum beta lactam resistance among *Salmonella* and *Escherichia coli* in food-producing animals, and plasmid-mediated fluoroquinolone-resistance determinants *(15)*. In this first revision of the WHO CIA List, the experts provided additional criteria for prioritizing the human health importance of antimicrobials judged critically important for human medicine. These criteria were used to identify the highest priority classes of antimicrobials among the critically important antimicrobials for humans.

In 2007, a Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials was convened in Rome to review the WHO CIA List and the OIE List *(16).* The OIE List was developed using a survey of veterinarians and categorized the importance to animal health of antimicrobials used in food-producing animals. It was adopted in 2006 with contributions from veterinary services and international organizations working with OIE. The experts concluded that because the two lists were developed for different purposes, and only the WHO CIA List considered the human health implications of use of antimicrobials in food-producing animals, it would not be possible to combine them. However, comparison of the two lists and consideration of relevant criteria (e.g. frequency and severity of human infection caused by resistant foodborne bacteria and preferred treatment for the infection) indicated that three classes of antimicrobials - fluoroquinolones, cephalosporins, and macrolides – should be top priority when considering action on use of antimicrobials in food-producing animals.

In 2008, WHO established the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) to support efforts to minimize the public health impact of antimicrobial resistance associated with use of antimicrobials in food-producing animals. WHO AGISAR comprises more than 20 experts in a broad range of disciplines relevant to antimicrobial resistance, including human infectious diseases, animal health, and environmental health, appointed following a public call for advisors and a transparent selection process. In 2009, during the first WHO AGISAR meeting in Copenhagen, Denmark, the expert WHO CIA List committee was also convened to develop the second revision of the WHO CIA List *(17)*. The revision provided recommendations on how the WHO CIA List could be used to prioritize specific risk management strategies for the antimicrobials judged critically important to human medicine, and thereby help to preserve their continued effectiveness in humans.

The third and fourth revisions of the WHO CIA List were created, respectively, by the expert WHO CIA List committee during the WHO AGISAR meetings in Oslo, Norway in 2011 *(18)* and Bogota, Colombia in 2013 *(19)*. At the WHO AGISAR meeting in Oslo, WHO AGISAR provided recommendations

on the food-producing animal use of selected antimicrobials, taking into account the WHO CIA List *(18)*. For example, WHO AGISAR recommended that the antimicrobials classified on the WHO CIA List as critically important for humans that have not been used in food-producing animals yet, should not be used in food-producing animals.

The WHO AGISAR meeting in Bogota recommended that WHO develop guidelines on the use of antimicrobials in food-producing animals that would take into account the WHO CIA List *(19)*. Such WHO guidelines could include recommendations on potential restrictions of antimicrobials in food-producing animals that, taking into account the WHO CIA List and previous recommendations made by earlier WHO expert consultations, could contribute to the preservation of the effectiveness in humans of medically important antimicrobials, particularly antimicrobials judged critically important to human medicine. The fifth revision of the WHO CIA List was created by the expert WHO CIA List committee during the WHO AGISAR meeting in Raleigh, United States of America in 2016 and is available on the WHO website[l].

Previous WHO recommendations relevant to these guidelines

Recommendations on use of antimicrobials in food-producing animals from the World Health Assembly and from WHO meetings and consultations include:

1	In 1997, the WHO Consultation on Medical Impact of the Use of Antimicrobials in Food Animals in Berlin recommended that antimicrobials for growth promotion in animals should be terminated if the antimicrobial is used in humans *(7)*.
2	In 1998, the Fifty-first World Health Assembly adopted a resolution (WHA51.17) urging Member States to encourage the reduced use of antimicrobials in food-producing animals *(20).*
3	In 1998, the WHO consultation on the Use of Quinolones in Food-Producing Animals and Potential Impact on Human Health in Geneva recommended that fluoroquinolones should be used only under the close supervision of a veterinarian and preferably based upon culture and susceptibility testing; and that treatment with other efficacious antimicrobials would be preferable to treatment with fluoroquinolones *(21).*
4	In 2000, the WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food recommended that *(8)*: a. use of antimicrobials for growth promotion that belong to classes of antimicrobials used in humans should be terminated, b. use of antimicrobials in food-producing animals judged to be essential to human medicine should be restricted and justified by culture and susceptibility results, and c. disease prevention use of antimicrobials in food-producing animals should not be a substitute for good animal health management.
5	In 2003, a joint FAO, OIE, and WHO report, Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific Assessment recommended that WHO appoint an expert group of physicians to define the antimicrobials that are considered critically important in humans *(12)*.
6	In 2004, a joint FAO, OIE, and WHO report, Non-Human Antimicrobial Usage and Antimicrobial Resistance: Management Options recommended that WHO should develop a list of antimicrobials critically important for humans with a view to enabling specific resistance-prevention actions for these antimicrobials in the context of non-human use. The workshop also recommended that the OIE should develop a list of critically important antimicrobials in veterinary medicine *(13)*.

[l] http://www.who.int/foodsafety/areas_work/antimicrobial-resistance/cia/en/

7	In 2009, WHO AGISAR recommended that the WHO CIA List should be used for prioritizing specific risk management strategies for medically important antimicrobials, particularly antimicrobials judged to be critically important to human medicine *(17)*.
8	In 2011, WHO AGISAR recommended that the antimicrobials classified on the WHO CIA List as critically important for humans but which have not been used in food-producing animals yet, should not be introduced into food-producing animal usage *(18)*.
9	In 2015, the World Health Assembly adopted the global action plan on antimicrobial resistance which called on Member States to *(22)*: a. develop policies on use of antimicrobials in food-producing animals including implementation of guidelines on use of antimicrobials critically important in humans, b. phase out the use of antimicrobials for growth promotion in food-producing animals, and c. reduce the non-treatment use of antimicrobials in food-producing animals.
10	In 2015, the WHO/FAO Codex Alimentarius published Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance, stating that foodborne antimicrobial resistance risk analysis should consider relevant international documents, including the WHO CIA List *(10)*.

Relevant recommendations by external organizations

A number of external organizations, countries, and private companies have reviewed the human health consequences of use of antimicrobials in food-producing animals. Although the scope and dates of these reviews vary, there is consensus among the scientific community that use of antimicrobials in food-producing animals can cause adverse human health consequences. There is no consensus, however, as to the proportion of antimicrobial resistance in bacteria isolated from humans caused by use of antimicrobials in food-producing animals. Nevertheless, given the public health risk posed by use of antimicrobials in food-producing animals, a number of external organizations have recommended, and a number of countries and private companies have imposed, restrictions on use of antimicrobials in food-producing animals, particularly on antimicrobials important for human medicine. These restrictions and recommendations include:

1	In 1969, the United Kingdom Swann Commission recommended prohibition of the use for animal growth promotion of antimicrobials used in human medicine *(4)*.
2	In 1986, Sweden prohibited the use of antimicrobials for growth promotion in food-producing animals *(23)*.
3	In 1997, the European Union prohibited the use of avoparcin (a glycopeptide closely related to vancomycin) for growth promotion in food-producing animals *(24)*.
4	In 1997, the United States of America prohibited the extra-label use of fluoroquinolones and glycopeptides in food-producing animals, due to their importance for use in humans *(25)*.
5	In 1998, an expert committee for the Ministry of Agriculture, Fisheries and Food in the United Kingdom recommended that key antimicrobials in humans should be identified, with the aim of reducing the use of such antimicrobials in food-producing animals *(26)*.
6	In 1998, the European Union Chief Medical Officers recommended that the use of antimicrobials in food-producing animals for growth promotion should be stopped whenever there was clear evidence of a significant risk to human health from such usage *(27)*.
7	In 1999, producers in Denmark voluntarily discontinued the growth promotion use of antimicrobials in food-producing animals *(11)*.

8	In 1999, the European Union prohibited the growth promotion use of four classes of antimicrobials in food-producing animals, followed in 2006 by a discontinuation of all growth promotion use of antimicrobials in food-producing animals *(24)*.
9	In 1999, an expert committee for the Ministry of Health in Australia recommended taking a conservative regulatory approach towards approval of antimicrobials in food-producing animals, to enable severe limitations or prohibitions on use in food-producing animal of antimicrobials important for use in humans *(28)*.
10	In 2002, Demark imposed severe limitations on the use of fluoroquinolones in food-producing animals such that fluoroquinolones were only available for use by veterinarians in food-producing animals following demonstrated need based upon antimicrobial susceptibility testing and following specific approval by national authorities *(29)*.
11	In 2002, the Infectious Disease Society of America recommended a multi-pronged approach to limit the impact of antimicrobial resistance including limits on the use of antimicrobials in food-producing animals *(30)*.
12	In 2002, the Alliance for Prudent Use of Antibiotics recommended that the use of antimicrobials for economic purposes such as growth promotion should be discontinued, and that, because of their critical role in treating human disease, fluoroquinolones and third-generation and fourth-generation cephalosporins should not be used in food-producing animals except to treat refractory infections in individual animals *(31)*.
13	In 2005, the United States of America prohibited the use of fluoroquinolones in poultry *(32)*.
14	In 2011, the Netherlands used the WHO CIA List to place severe limitations on use in food-producing animals of antimicrobials listed as critically important for humans *(33)*. For example, use of fluoroquinolones and third and fourth generation cephalosporins in food- producing animals is only permitted upon demonstrated need based on antimicrobial susceptibility testing and following specific approval by national authorities. Following implementation of this restriction, use of such antimicrobials in food-producing animals fell to almost zero (validated via a national surveillance programme on use of antimicrobials in food-producing animals) and no adverse animal health consequences were identified.
15	In 2012, the United States of America prohibited the extra-label use of third-generation and fourth-generation cephalosporins in food-producing animals, due to their importance for use in humans *(25)*.
16	In 2012, the OIE recommended that antimicrobials listed on the WHO CIA List as critically important for humans should not be used as a first line treatment in food-producing animals unless justified based on the results of bacteriological tests *(34)*.
17	In 2015, a government-commissioned review of antimicrobial resistance in the United Kingdom recommended global restrictions on use of antimicrobials in food-producing animals, particularly antimicrobials important for humans *(35)*. The committee acknowledged the WHO CIA List as an important step towards identifying and prioritizing the antimicrobials that should be more restricted in food-producing animals.
18	In 2015, the McDonalds Corporation announced their endorsement of the WHO CIA List, prohibiting their supplying producers from treating their food-producing animals with antimicrobials listed as critically important to humans on the WHO CIA List and not presently approved for veterinary use, and prohibiting the growth promotion use of any antimicrobial on the WHO CIA List *(36)*.

Rationale for, and objectives of, these guidelines

Minimizing the adverse human health impact of the use of medically important antimicrobials in food-producing animals will require action. WHO facilitated the creation of the WHO CIA list to enable prioritization of public health interventions aimed at preserving the effectiveness of medically important antimicrobials, such as restrictions on some uses of medically important antimicrobials in food-producing animals. Building on the creation of the WHO CIA List, there is a need to develop best practice statements and recommendations on the use of medically important antimicrobials in food-producing animals.

A number of groups, including WHO Member States have requested that these guidelines be developed. Some actors interpret the current WHO CIA List as *de facto* WHO guidelines, not realizing that there is a need to go through a rigorous, transparent process to search the evidence and use this to make recommendations contained in WHO guidelines. Therefore, there is clear need for, and anticipation of, WHO guidelines on the use of medically important antimicrobials in food-producing animals that takes into account the WHO CIA List.

The goal of these guidelines is to help preserve the effectiveness of medically important antimicrobials, particularly those judged to be critically important to human medicine. These guidelines will also help preserve the effectiveness of antimicrobials for veterinary medicine. These goals will be attained when there are reductions in use of medically important antimicrobials in food-producing animals. Such reductions in use of medically important antimicrobials in food-producing animals will contribute to a reduced prevalence of antimicrobial resistance in bacteria isolated from food-producing animals, and a reduced prevalence of antimicrobial resistance to medically important antimicrobials in bacteria isolated from humans. By helping to preserve the effectiveness of antimicrobials used in human medicine, these guidelines support the WHO global action plan on antimicrobial resistance. Specifically, these guidelines present evidence-based recommendations on use in food-producing animals of medically important antimicrobials that should help preserve their effectiveness for human medicine with minimal or no harms (e.g. to animal health, welfare, production, food safety and economy).

Taking into account the WHO CIA List, the objective of these WHO guidelines is to provide recommendations for limitations of specific uses of medically important antimicrobials in food-producing animals, particularly antimicrobials judged to be critically important for humans. These recommendations specifically address the overall use of medically important antimicrobials in food-producing animals and specific uses for growth promotion, disease prevention, and treatment in food-producing animals.

Who should use these guidelines?

The primary audience of these guidelines is policy makers and regulatory officials overseeing the use of antimicrobials in food-producing animals in WHO Member States. The target audience also includes veterinarians, food-producing animal organizations, food producers, pharmaceutical companies, animal health officials, public health officials, physicians and other healthcare providers, and consumers.

METHODS

These guidelines were developed by using methods and procedures described in the WHO handbook for guideline development (second edition)[I].

In summary, the process included:

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

Priority questions

The WHO Steering Group, in consultation with the GDG and GRADE methodologists, formulated two questions using the population, intervention, comparison, outcome, time, setting (PICOTS) format with time [T] being contained within the Intervention [I] and setting [S] into the population [P]). These PICOTS questions were:

I. For human populations of any age in any setting, does a limitation compared to not having that limitation of use of antimicrobial(s) in food-producing animals reduce the presence of antimicrobial-resistant genetic elements and/or antimicrobial-resistant bacteria in human populations?

2. For food-producing animals of any age in any setting, does a limitation compared to not having that limitation of use of antimicrobial(s) in food-producing animals reduce the presence of antimicrobial-resistant genetic elements and/or antimicrobial-resistant bacteria in food-producing animals?

Identification of critical and important outcomes

The WHO Steering Group, with input from the GDG, systematic review teams, and guideline methodologists considered potential outcomes discussed at the first GDG meeting and drafted a list of potentially important outcomes related to use of antimicrobials in food-producing animals. A questionnaire with these potential outcomes was then distributed to GDG members who were asked to rank the relative importance of each potential outcome on a nine-point scale ranging from I (least important) to 9 (most important). The median score was calculated for each outcome based on the GDG members' responses, to determine outcomes that are "critical" (median score ≥7) and "important but not critical" (median score 4–6) for making decisions about the recommendations. To ensure consistency, the WHO Steering Group reviewed the final list of critical and important outcomes for each guideline question (see Annex 3 for the final list of outcomes).

Systematic review search strategies

Specific inclusion and exclusion criteria were defined. Systematic review teams searched the following databases with no language

[I] http://apps.who.int/medicinedocs/en/d/Js22083en/

restrictions or other limits: Ovid MEDLINE, including In-Process and Other Non-Indexed Citations, 1964 to current; Ovid EMBASE, 1964 to current; CINAHL Plus with Full Text, 1964 to current; and Cochrane Database of Systematic Reviews, 1998 to current. The searches consisted of selected subject headings and keywords related to the use of antimicrobials. The searches also used IndMED, using the same keywords, and LILACS, using a combination of the keywords in English and some of their Spanish and Portuguese equivalents. The searches reviewed reference lists from retrieved articles and journals, conference proceedings and the websites of the US Centers for Disease Control and Prevention, the International Centre for Infectious Diseases, FAO, OIE and WHO. Also searched were proceedings of relevant scientific conferences over the past two years, and unpublished data submitted to the US Food and Drug Administration and the European Medicines Agency as part of drug registration applications. Additionally, review teams performed manual searches of clinicaltrials.gov and the WHO International Clinical Trials Registry Platform to identify studies that have not yet been published but are potentially eligible for inclusion. A WHO information specialist reviewed and endorsed the search strategy to ensure no major procedures had been overlooked.

Both systematic review teams addressed both PICOTS questions and worked independently of each other. The WHO Steering Group provided regular guidance and feedback on the protocol for the systematic reviews and the evidence tables. The systematic review team from Bond University provided a narrative report of their findings (Scott AM, Beller E, Glasziou P et al., unpublished data, 2016). The systematic review team from the University of Calgary provided a full quantitative report of their systematic review *(37).* This included an assessment of the quality of the primary studies, categorized by study design with the highest quality studies listed first in this order: systematic review, randomized trials, prospective cohort studies, retrospective cohort studies, case-control studies, time series studies, before and after studies, and ecological studies. The systematic review team from the University of Calgary also assessed the quality of each study within each category according to their judgement on likelihood of bias, robustness, and appropriateness of conclusions. Finally, the systematic review team from University of Calgary conducted a meta-analysis of the risk differences for reductions in the prevalence in antimicrobial resistance reported with various restrictions on antimicrobial use in food-producing animals. WHO then commissioned a supplemental analysis of the University of Calgary systematic review that updated the literature, stratified the findings by types of antimicrobial use in food-producing animals, and summarized the evidence of unintended consequences of restricting antimicrobial use in food-producing animals. Summaries of the systematic review reports, including the supplementary report from the University of Calgary, are available at Annex 4.

In addition to the systematic reviews, WHO also commissioned narrative literature reviews by topic-experts on the following:

1. illustrative examples of transfer of antimicrobial resistance determinants from food-producing animals to humans *(38)*;
2. biological plausibility of associations between use of antimicrobials in food-producing animals and selection for resistance in zoonotic pathogens and commensal bacteria, and transfer of resistance determinants from food-producing animals to humans; and
3. potential unintended consequences associated with restrictions on antimicrobial use in food-producing animals.

The resulting reviews were presented and discussed at the GDG meetings. Summaries are available at Annex 5, and full reports are available in Web Annex A.

Assessment of the evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to assess the quality of

the evidence and to determine the strength of the recommendations. The GRADE approach defines the quality of the evidence as the extent to which there is confidence that an estimate of effect or association reported in the available evidence is correct. Under the GRADE system, randomized clinical trials are initially ranked as high quality evidence, while observational studies as low quality evidence. Five domains are then considered (study limitations, inconsistency, indirectness, imprecision and publication bias) which may lead to rating down the quality of evidence and three (magnitude of effect, dose-response and effect of plausible residual confounding) to potentially raise the quality assessment.

Ratings	Meaning
High ●●●●	The GDG is very confident that the true effect of the intervention is close to the estimate of the effect presented to the group. Evidence with this quality rating provides a very good basis to support a decision for a recommendation. Starting point for randomized clinical trials.
Moderate ●●●○	The GDG is moderately confident that the true effect of the intervention is close to the estimate of the effect presented to the group. The true effect is likely close, but it could be substantially different. Evidence with this quality rating provides a good basis to support a decision for a recommendation.
Low ●●○○	The GDG has limited confidence that the true effect of the intervention is close to the estimate of the effect presented to the group. The true effect may be substantially different. Starting point for observational studies.
Very Low ●○○○	The GDG has very little confidence that the true effect of the intervention is close to the estimate of the effect presented to the group.

It should be noted that GRADE was developed to assess clinical and public health interventions in which quantitative studies are used to measure an effect size. It therefore had to be adapted for use in complex questions regarding environmental exposures and multi-component interventions (such as the prevalence of antimicrobial resistance associated with use of medically important antimicrobials in food-producing animals), which is challenging. Such questions often require the consideration of indirect evidence from intermediary endpoints, mechanistic data and several types of observational studies performed under field conditions.

It is not practical, and in some cases not ethical, to conduct randomized clinical trials to investigate the impact of restricting antimicrobial use in food-producing animals on the prevalence of antimicrobial resistance. Therefore, under the GRADE approach a body of evidence in this domain is bound to be rated as "low" given that GRADE mandates an initial rating of all studies that are not randomized controlled trials as "'low quality".

Formulation of recommendations

The synthesized evidence was used to formulate each recommendation, using the GRADE approach (as summarized in the evidence profiles, summary of findings tables, and the narrative summaries of the systematic reviews provided in Annex 4 and 5). Evidence-to-recommendation tables, which include the assessment and judgments on quality of evidence, balance between benefits and harms, values and preferences of affected populations, resource implications, equity, human rights, gender and social determinants of health, and acceptability and feasibility for each outcome, were developed for each question.

Draft recommendations, evidence summaries, the corresponding GRADE tables and other related documents were provided to the GDG who were then asked to comment on the document in tracked mode. The GDG members discussed and finalized recommendations at two meetings, one in Raleigh, United States of America, in October, 2016 and the second at WHO headquarters in Geneva, Switzerland, in March 2017.

Determining strength of the recommendations

The strength of a recommendation can be either strong or conditional. A strong recommendation is one for which the GDG is confident that the desirable effects of adherence to the recommendation clearly outweigh the undesirable effects. For public health policy, this means that in most situations the recommendation should be adopted as policy. A conditional recommendation is one for which confidence in the evidence supporting the recommendation may be low or may apply only to specific groups or settings. In these cases, the GDG may conclude that the desirable effects of adhering to the recommendation outweigh the undesirable effects, but the trade-offs are not clear in all situations. Furthermore, the determination of the strength of a recommendation also involves considerations of the balance between benefits and harms, the values and preferences of affected populations, resource implications, equity, human rights, gender and social determinants of health, and acceptability and feasibility.

The strength of each recommendation was determined by the GDG based upon the quality of the evidence, the balance of benefits versus harms, values and preferences, and resource implications. Information on the values, preferences, acceptability and views of those likely to be affected by the recommendation was not explicitly collected or assessed, rather the knowledge, opinions and experience of GDG members on these matters were relied upon. Cost evaluations were based on reported estimates obtained during the evidence retrieval process as well as the experiences and opinions of members of the GDG. Evidence-to-recommendation tables were used to note and synthesize these considerations and record the reasons for changes made to the strength of the recommendations.

The GDG deliberations are summarized in the evidence-to-recommendation tables (summarized in Annex 6 and available in full in Web Annex B). The evidence profiles, summaryof-findings tables, and the systematic review narrative evidence summaries, are also available in Web Annex B.

Decision-making during GDG meetings

GDG meetings were structured to allow participants to discuss each of the drafted recommendations, and where necessary, revise recommendations through group discussion. Agreement on final recommendations was reached by group consensus, which was unanimous for each recommendation. WHO staff, external technical experts involved in the collection and grading of the evidence, and observers did not participate in GDG decisions.

Peer review and finalization of these guidelines

Following the evidence-to-recommendation meetings, the full guidelines were drafted by the writing committee to reflect GDG members' deliberations and decisions. The draft document was then circulated to all GDG members and the WHO Steering Group for further comments and preliminary approval before it was sent to the External Review Group (ERG) for peer review. The ERG comments were used to revise the document, which was then circulated to GDG members for their final approval.

RECOMMENDATIONS AND BEST PRACTICE STATEMENTS

The GDG formulated the following recommendations and best practices using the body of evidence established via the two systematic reviews (including the supplementary report to one of the systematic reviews), the three narrative literature reviews, and other scientific sources.

Recommendations

The systematic evidence reviews yielded a large number of studies demonstrating a consistent decrease in the prevalence of antimicrobial resistance in bacteria isolated from food-producing animals or humans following restrictions in use of medically important antimicrobials in food-producing animals. However, the GDG acknowledged that there were limitations to this body of evidence. Chief among these was that the evidence was derived mostly from observational studies which, according to the GRADE approach, meant the quality of evidence for any recommendation in these guidelines will be rated as "low". Additionally, the systematic reviews found few studies that included small-scale food-producing animal operations; almost all of the studies involved moderate or large-scale food-producing animal operations. The reviews also found few studies from low and middle-income countries. Despite these limitations, the GDG determined that there was sufficient evidence to conclude that selection of antimicrobial resistance and transmission to humans will occur with antimicrobial use in all food-producing animal settings, including in small-scale production settings and in low and middle-income countries. Furthermore, the GDG concluded that the observed decreases in prevalence of antimicrobial resistance in bacteria isolated from food-producing animals and humans in reviewed studies would equally be expected to occur in small-scale food-animal production settings and in low or middle-income countries. Therefore, to ensure that people in all countries benefit from effective antimicrobials, the GDG concluded that these recommendations in these guidelines should be applied in all countries and settings, not just larger-scale animal production settings or high-income countries.

A summary of the evidence, justification, and implementation considerations is provided for each recommendation below. Further detail is provided in Annex 6 and in the Web Annex B. Users of these guidelines should refer to these remarks for the basis of any of the recommendations and how best to implement them. To facilitate implementation, derivative products such as policy briefs and other implementations tools will be developed.

Recommendation I: 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 shows 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 on antimicrobial resistance.

Remarks

Reductions of overall use of antimicrobials in food-producing animals may include any level of reduction of use of antimicrobials in food-producing animals, including reductions of a single antimicrobial, reductions of multiple antimicrobials, or combinations of reductions of use of antimicrobials. Such reductions may include complete restriction of use, restriction of selected uses such as growth promotion use, voluntary limitations, and/or limiting use to that done with oversight by a veterinarian.

Summary of the evidence

Of the two reviews commissioned, one provided a narrative review and the other a quantitative meta-analysis with, where appropriate, a supporting supplemental narrative. The quantitative analysis identified 179 studies describing antimicrobial resistance outcomes in animals, of which 80 were included in a meta-analysis measuring reduction in prevalence of antimicrobial resistance in bacteria isolated from animals following restriction of antimicrobial use. Pooled absolute risk reduction of the prevalence of antimicrobial resistance in bacteria isolated from animals varied across different antimicrobial classes, bacteria, and sample types, but ranged from 0-39%. The prevalence of antimicrobial resistance was 10-20% lower where antibiotic use was restricted (intervention groups) compared to those where it was not (comparator groups). The pooled prevalence of multidrug resistance was 24-32% lower in bacteria isolated from intervention groups. These findings were consistent, regardless of stratification, including stratification by intervention type. Twenty-one studies described antimicrobial resistance outcomes in humans (19 of which also reported antimicrobial resistance in bacteria isolated from animals), of which 13 were meta-analyzed. In humans, the pooled prevalence of antimicrobial resistance was 24% lower in intervention groups (where interventions to reduce

antimicrobial use in food-producing animals were implemented) compared to comparator groups. The effect was stronger among humans with direct contact with livestock animals (i.e. farm workers). The results were similar with multiple types of stratification in the systematic review, adding to the robustness of the findings.

Narrative literature reviews supported the conclusions of the systematic reviews, describing evidence of transfer of resistance determinants from food-producing animals to humans. A narrative literature review also described a clear association between antimicrobial use in food-producing animals and increased risks of human exposures to, and infections by, antimicrobial-resistant bacteria. Finally, another review found that any adverse consequences of restricting antimicrobial use in food-producing animals appear to be limited and temporary (see Annexes 4 & 5 for more detail).

Implementation considerations

A variety of measures can be used to achieve overall reduction of antimicrobial use. These include implementation of all recommendations in these guidelines and adopting measures that reduce the need for antimicrobials.

Implementing growth promotion and disease prevention strategies that do not involve use of antimicrobials, including improved hygiene, improved biosecurity, and better use of appropriate vaccines, will enable effective restriction of antimicrobial use in food-producing animals. Several countries have achieved substantial reductions by monitoring the quantities of antimicrobials dispensed by veterinarians and used on farms, then providing incentives to reduce excess use. Other interventions that have been successful include reducing profits for antimicrobial dispensing, removing over-the-counter availability, and altering prescriber behavior. Some countries may need support for implementation. FAO and OIE may assist countries that need support with implementation (e.g. alternatives to use of antimicrobials for growth promotion, governance models, considering needs of smallholders). FAO and OIE may also assist with tools for improving veterinary oversight of antimicrobial use. Countries should monitor antimicrobial use in animals in order to identify overuse and document reduction activities.

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 (see Annexes 4 & 5). Finally, many countries have successfully achieved complete restriction of growth promotion use of antimicrobials in food-producing animals, demonstrating the feasibility of this recommendation.

Evidence search question

Does complete restriction of classes of antimicrobials on the WHO CIA List used in food-producing animals for purposes of growth promotion, compared to no such restriction, reduce the presence of antimicrobial-resistant genetic elements and/or antimicrobial resistance in bacteria isolated from humans?

Summary of the evidence

The quantitative analysis identified 27 relevant studies. Of these 15 were meta-analyzed to measure the outcome "animal resistance". The pooled absolute risk reduction of prevalence of antimicrobial resistance in bacteria isolated from animals, with interventions that restricted use of antimicrobials for growth promotion ranged from 19-40%. Seven studies described the prevalence of antimicrobial resistance in humans, of which six underwent meta-analysis for the outcome "human resistance". The pooled prevalence of antimicrobial resistance was 6-20% lower in intervention groups (where interventions to restrict use of antimicrobials for growth promotion in food-producing animals were implemented) compared to comparator groups (where no interventions to restrict use of antimicrobials for growth promotion were implemented).

The narrative literature reviews supported the conclusions of the systematic reviews. Studies of use of antimicrobials in food-producing animals for growth promotion indicated transfer of resistance determinants

from food-producing animals to humans. There was a clear association between antimicrobial use in food-producing animals and increased risks of human exposures to, and infections by, antimicrobial-resistant bacteria. Finally, any adverse consequences of restricting use of antimicrobials for growth promotion in food-producing animals appear to be limited and temporary (see Annexes 4 & 5 for full detail).

Implementation considerations

Non-antimicrobial options for promoting optimal growth of food-producing animals, including improved hygiene, housing, biosecurity, animal husbandry practices, and better use of appropriate vaccines, should be implemented. Particular care is needed to avoid compensatory increases in antimicrobial use for disease prevention or treatment purposes, especially medically important antimicrobials. Experience gained from prohibition of the use of antimicrobials for growth promotion in Europe should be provided to other regions. A detailed WHO report on the effects of the prohibition in Denmark on antimicrobial resistance, animal production, food safety, national economy and other parameters can be found online *(I0)*. Developing regions should be assisted with implementation, including implementation and follow-up monitoring in AGISAR country pilot projects (e.g. Bangladesh, India, Kenya, Rwanda, and Tanzania). FAO and OIE may assist countries that need support with implementation (e.g. alternatives to use of antimicrobials for growth promotion, governance models, considering needs of smallholders). FAO and OIE may also assist with tools for improving veterinary oversight of antimicrobial use.

National antimicrobial resistance and antimicrobial use surveillance programmes, should evaluate, taking an integrated "One Health" approach, the effects of implementation of prohibition. The quantities of antimicrobials used in food-producing animals for disease prevention and treatment should be monitored to identify trends.

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 medical 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.

Evidence search question

Does complete restriction of the routine use of antimicrobials on the WHO CIA List for prevention of infectious diseases that have not yet been clinically diagnosed in food-producing animals, compared to no such restriction, reduce the presence of antimicrobial-resistant bacteria and/or genetic elements in humans?

Summary of the evidence

The systematic review identified 36 studies for quantitative analysis of which 26 underwent meta-analysis to measure the outcome "animal resistance", and 2 studies for the outcome "human resistance" for which a risk difference could be determined. The pooled absolute risk reduction of the prevalence of antimicrobial resistance in bacteria isolated from animals, with restricted nontherapeutic use of antimicrobials, ranged from 6-11%.

The narrative literature reviews supported the conclusions of the systematic reviews, finding evidence of transfer of resistance determinants from food-producing animals to humans and clear association between antimicrobial use in food-producing animals and increased risks of human exposures to, and infections by, antimicrobial-resistant bacteria. A review found that adverse consequences of restricting antimicrobial use in food-producing animals appear to be limited and temporary (see Annexes 4 & 5 for detail).

Implementation considerations

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.

Conditional recommendation, very low quality evidence

Justification

The GDG concluded that, based upon evidence from the systematic reviews and additional studies, this recommendation will achieve human health benefits of lowered antimicrobial resistance in bacteria in humans, but should be conditional due to the very low quality evidence for the outcomes of interest. 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 their environment, and to humans. Furthermore, 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 can be made when veterinary professionals judge that culture and sensitivity tests demonstrate that the selected drug is the only treatment option.

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.

Conditional recommendation, very low quality evidence

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 their 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 can be made when veterinary professionals judge that culture and sensitivity tests demonstrate that the selected drug is the only treatment option.

The question and evidence summary provided below pertain to both recommendation 4a and recommendation 4b.

Evidence search question

Does complete restriction of the critically important antimicrobials on the WHO CIA List for disease control and treatment in food-producing animals, compared to no such restriction; reduce the presence of antimicrobial-resistant bacteria and/or genetic elements in humans?

Summary of the evidence

Two systematic reviews were performed for this question, one providing a narrative summary of the evidence and the other a quantitative assessment. Both found there was a reduction of resistance transfer from food-producing animals to humans when antimicrobial use was restricted in food-producing animals. The quantitative analysis found 179 animal studies describing antimicrobial resistance outcomes in animals of which 80 underwent meta-analysis. The pooled absolute risk reduction of prevalence of antimicrobial resistance in bacteria isolated from animals, following interventions that restricted antimicrobial use, ranged from 0% to 39%, varying across different antimicrobial classes, bacteria, and sample types. The prevalence of antimicrobial resistance was 10-20% lower in groups with restrictions on antimicrobial use versus groups with no restrictions. The pooled prevalence of multidrug resistance was 24-32% lower in bacteria isolated from groups with restrictions. These findings were consistent through many different levels of stratification including stratification by type of restriction. Twenty-one studies described antimicrobial resistance outcomes in humans (19 of which also reported antimicrobial resistance in bacteria isolated from animals) and 13 of these underwent meta-analysis. In humans, the pooled prevalence of antimicrobial resistance was 24% lower in groups with restrictions on antimicrobial use when compared with groups with no restrictions. The effect was stronger in humans with direct contact with livestock animals (i.e. farm workers).

The narrative literature reviews supported the conclusions of the systematic reviews. One narrative review described evidence of transfer of resistance determinants from food-producing animals to humans and a clear association between antimicrobial use in food-producing animals and increased risks of human exposures to, and infections by, antimicrobial-resistant bacteria. Finally, another narrative literature showed that any adverse consequences of restricting antimicrobial use in food-producing animals appear to be limited and temporary (see Annexes 4 & 5).

Implementation considerations

Antimicrobials classified as critically important in human medicine on the WHO CIA List should only be used when recent culture and sensitivity testing results indicate that the critically important antimicrobial is the only treatment option. Feasibility of this recommendation is therefore dependent on access to culture and sensitivity testing. The obligation to do culture and sensitivity testing has been implemented in some countries including the Netherlands. This requirement may introduce inequity in countries currently lacking the capacity to perform such testing, but this would be marginal compared to the gains. Veterinarians should have access to culture and sensitivity testing. Countries lacking capacity should be assisted with implementation, which could include implementation and follow-up monitoring in AGISAR country pilot projects (e.g. Bangladesh, India, Kenya, Rwanda, and Tanzania). National antimicrobial resistance and antimicrobial use surveillance programmes should evaluate the effect of implementation.

The GDG acknowledges that use of critically important antimicrobials for humans might be justified if a veterinary professional judges it necessary, based on 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 only be used 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 possible treatment option. National antimicrobial resistance and antimicrobial use surveillance programmes should evaluate the effects of implementation.

Best practice statements

Best practice statements represent recommendations that guideline panels 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 I

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)."

CONTRIBUTORS AND THEIR ROLE IN THE DEVELOPMENT OF THESE GUIDELINES

WHO Steering Group

The WHO Steering Group comprised nine WHO staff members and two special members (a representative each from FAO and OIE). The special members provided comments on these guidelines, but were neither responsible for, nor endorsed, its contents. WHO staff serving on the WHO Steering Group were from five regional offices and from four of the WHO AMR technical work streams at WHO headquarters (Rational Use, National Action Plans and Surveillance, Infection Prevention and Control, and One Health). The WHO Steering Group guided the guideline development process, endorsed the draft of the initial scope of these guidelines, including the key systematic review questions for the systematic review teams, and endorsed the nominations of guideline methodologists, members of the GDG and members of the External Review Group. The names of the WHO Steering Group members are provided in Annex I.

Guideline Development Group

To constitute the GDG, the following criteria were considered: (i) diverse expertise required such as in clinical human medicine, veterinary medicine, microbiology, antimicrobial resistance, agricultural economics and veterinary ethics, (ii) geographic and gender balance, (iii) involvement of major groups affected by the recommendations and (iv) absence of significant conflict of interests. The names and profiles of fifteen candidates identified by the WHO Steering Group to become GDG members were posted on the WHO website for public comments. No comments were received. At this stage, two individuals withdrew due to their unavailability. The remaining individuals were requested to declare interests in writing. Declared interests were assessed by the WHO Secretariat according to processes described in the WHO handbook for guideline development (second edition) . No individuals were deemed to have any significant conflict of interests (a summary and management of declared interests is available in Annex 2). The final membership of

the GDG comprised thirteen individuals (the members' names and affiliations are listed in Annex I). One member of the GDG was a GRADE methodologist. Members of the GDG provided input into the drafting of the guideline scope and the PICOTS questions, and participated in prioritizing outcomes that guided the evidence reviews. The GDG appraised the evidence from the systematic reviews, advised on the interpretation of this evidence, formulated the final recommendations based on a draft prepared by the WHO Steering Group, and reviewed and approved the final guideline document.

Systematic review teams

During the scoping phase, the WHO Steering Group identified a need for systematic reviews of the evidence on the effectiveness of restrictions on use of antimicrobials in food-producing animals for lowering the prevalence of antimicrobial resistance in bacteria isolated from food-producing animals and humans. Two systematic review teams were chosen by the WHO Steering Group, one of them from Bond University, Queensland, Australia, led by Chris Del Mar and the other, from the University of Calgary, Canada, led by William Ghali. The members of both systematic review teams are listed in Annex I. Summaries of the systematic reviews are available in Annex 4 and full reports are available in the Web Annex A.

Narrative literature reviewers

The WHO Steering Group also identified topic expert scientists to conduct three narrative literature reviews. Summaries of these reviews, including the list of authors, are available in Annex 5.

External Review Group

An External Review Group (ERG) was set up to ensure that the guideline decision-making processes considered and incorporated the contextual values and preferences of potential users of the recommendations, health care professionals and policy-makers. The group was comprised of II experts and stakeholders with an interest in use of antimicrobials in food-producing animals. ERG members included veterinarians, microbiologists, and physicians, selected to ensure geographical- and gender-balance. All ERG members were asked to declare potential competing interests and three of them declared interests. The WHO Steering Group reviewed the declared interests and determined that none of them posed serious conflicts precluding participation in the guideline development process. The group reviewed the final guidelines document to identify any factual errors and commented on the clarity of the language, contextual issues and implications for implementation. It was not within the group's remit to change the recommendations formulated by the GDG. Names and affiliations of the ERG are provided in Annex I.

Management of conflicts of interests

All members of the GDG, ERG, systematic review teams, narrative reviewers, and other external contributors were required to submit a completed standard WHO declaration of interest (DOI) form.

The WHO Steering Group reviewed all information gathered before finalizing external experts and contributors' invitations to participate in guideline development. Potential candidates for the GDG underwent a public consultation process whereby the secretariat posted a short biography of each potential GDG member online prior to confirmation of their membership of the panel. In addition, the secretariat performed a focused internet search for each proposed GDG member, to identify any obvious public controversies or interests potentially in conflict with the guideline objectives.

When a potential conflict of interest (COI) was identified (for any external expert), the WHO Steering Group assessed the conflict to determine whether it would affect the objectivity of the external expert's judgment during the guideline development process. The assessment and management of potential conflicts were based on the WHO Office for Compliance, Risk Management and Ethics (CRE) 2014 Guidelines for declaration of interests (WHO experts) and criteria for assessing the severity of COI in the WHO Handbook for Guideline Development (2nd Edition) and were undertaken in consultation with CRE. Where COI were identified but were assessed as not posing a risk to the objectivity of the guideline development process, the external experts were required to disclose these COI at the beginning of the GDG meeting. At each GDG meeting, members were updated with a summary of all identified COI. See Annex 2 for a summary of all DOI statements provided by external experts, and an explanation of management of any identified COI.

DISSEMINATION AND 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 antimicrobial sensitivity testing. 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.

Dissemination

The recommendations made in these guidelines will be disseminated through WHO regional and country offices, ministries of health, ministries of agriculture, professional organizations, WHO collaborating centres, other United Nations agencies including FAO, and nongovernmental organizations including OIE. These guidelines will also be available on the public WHO website. To increase awareness of the recommendations, a summary of these guidelines will be published in a peer-reviewed journal. Derivative products of these guidelines, such as policy briefs and implementation tools will be developed by the WHO Department of Food Safety and Zoonoses. These guidelines will also be disseminated during meetings or scientific conferences attended by WHO staff. A summary will be translated into the six official UN languages and disseminated through WHO Regional Offices.

Monitoring and evaluation

The WHO Department of Food Safety and Zoonoses will monitor use and implementation of these guidelines as part of monitoring and evaluation of the WHO global action plan on antimicrobial resistance. The metrics for these monitoring and evaluation efforts are currently being developed by working groups of the WHO global action plan. WHO will utilize AGISAR to assist in the evaluation process on the uptake of these guidelines, placing uptake of these guidelines on the AGISAR annual meeting agenda. Member States will be encouraged to implement antimicrobial usage monitoring to document reductions in antimicrobial use in food-producing animals resulting from implementation of these guidelines.

RESEARCH GAPS

The GDG identified several research gaps in current evidence concerning use of antimicrobials in food-producing animals. Appropriate research would help identify practical approaches for reducing use of medically important antimicrobials in food-producing animals. Areas needing research identified during the guideline development process include:

- Identification of the most effective methods for implementing antimicrobial stewardship programmes in food-producing animals, and better understanding of values and preferences of those affected by these programmes.
- Cost-effectiveness studies of interventions aimed at reducing antimicrobial use in food-producing animals.
- Effects of restriction of antimicrobial use for disease control and treatment in food-producing animals on antimicrobial resistance in bacteria isolated from animals and humans.
- Development of rapid diagnostic and antimicrobial sensitivity tests.
- Effects of restriction of antimicrobial use in food-producing animals in low and middle-income countries on antimicrobial resistance in bacteria isolated from animals and humans, and on unintended consequences.

UPDATING THESE GUIDELINES

These guidelines will be updated five years after publication unless significant new evidence emerges, necessitating earlier revision. The WHO Steering Group will continue to follow research development in the area of antimicrobial resistance associated with use of antimicrobials in food-producing animals, particularly where new recommendations or a change in the published recommendation may be warranted.

As these guidelines near the end of its proposed five-year validity period, the WHO secretariat and the WHO Steering Group, will assess the currency of the recommendations and the need for new guidance on the topic. Where there are concerns that new evidence challenges the validity of a particular recommendation, the systematic review addressing the primary question will be updated. Any new questions identified following review at the end of five years will be used to guide evidence search and assessment, applying the WHO guideline development process. WHO welcomes suggestions regarding additional questions to be considered in updated guidelines.

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ANNEX 1

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ANNEX 2

Summary and management of declared interests

Members of the Guideline Development Group			
Name	**Declared interest(s)**	**Conflicts of interest**	**Management plan**
Hanan Balkhy	None declared	None	Full participation
Peter Collignon (Co-chair)	Travel costs received from his employer (Canberra hospital) to attend a WHO meeting	Not significant	Full participation
John Conly	1. Attendance of a meeting in 2013 on the use of linezolid in humans for nosocomial pneumonia and skin and soft tissue infections. Honorarium and travel costs covered by Pfizer, a pharmaceutical company that produces a wide range of medicines including antimicrobials. 2. Attendance of a meeting in 2014 on monoclonal antibodies (a potential replacement to certain antibiotics) for *Clostridium difficile* infection in humans. Honorarium and travel costs covered by Merck Canada, a pharmaceutical company that produces a wide range of medicines including antimicrobials. 3. Consulting role by affiliated institution to Sanofi-Pasteur for scoping review of *Clostridium difficile* infections. Review was ultimately not conducted. Travel costs covered by Sanofi-Pasteur to attend a meeting in 2014. 4. Travel costs covered by BioMerieux for attending a meeting on antimicrobial stewardship in 2015. 5. Attended a meeting as a guest speaker about antibiotic resistance in 2015. Honorarium and travel costs covered by BioMerieux. 6. Affiliated institution, University of Calgary, was commissioned to conduct a multi-centre randomized controlled trial for a *Staphylococcus aureus* vaccine to prevent post-operative infections in spinal fusion surgery patients. Travel and accommodation costs for work as local investigator covered by Pfizera	1. Minor (financial)* 2. Minor (intellectual)* 3. Not significant 4. Not significant 5. Not significant 6. Not significant * One-time engagement in a topic not directly related to the scope of the WHO guidelines (i.e. use of antimicrobials in animals).	Full participation as a Guideline Development Group member and methodologist. In addition to Dr Conly, a second methodologist who is neutral to the subject matter was invited to strengthen the methodological base.
Cindy Friedman	None declared	None	Full participation

Name	Declared interest(s)	Conflicts of interest	Management plan
Aidan Hollis	I. Provision of expert testimony to several generic pharmaceutical manufacturers (Teva, Sandoz, Apotex, Cobalt and Mylan) concerning the financial extent of the damages either to the generic company or to the patentee. 2. Consulting reports on the economic effects of tendering for generic drugs in Canada (2013) and the design of damages rules in Canada (2015) provided to the Canadian Generic Pharmaceutical Association.	I. Not significant 2. Not significant	Full participation
Samuel Kariuki	None declared	None	Full participation
Hyo-Sun Kwak	None declared	None	Full participation
Scott McEwen (Co-chair)	Research grants received by public institution	Not significant	Full participation
Gérard Moulin	None declared	None	Full participation
Antoinette Ngandjio	None declared	None	Full participation
Bernard Rollin	Served as an animal welfare expert in 2005-2008 on the few commissions to study the untoward effects of the industrialized animal agriculture	Not significant	Full participation
Flavia Rossi	None declared	None	Full participation
David Wallinga	Employee of non-profit, tax-exempt membership organization (Natural Resource Defense Council) based in United States of America that primarily advocates for environmental protections including the messaging to reduce antibiotic use in livestock. No individual grants received.	Not significant	Full participation

Methodologists			
Name	**Declared interest(s)**	**Conflicts of interest**	**Management plan**
John Conly	Same as above	Same as above	Same as above
Mauricio Ferri	I. Spouse is a Bristol-Myers Squibb employee as a medical scientist at the Immunology Department. 2. Consultancy service provided to the Oxford University not on the related subject matter 3. Consultancy service provided to the WHO Guidelines Review Committee since 2016	I. Not significant I. Not significant I. Not significant	Full participation

Members of the External Review Group			
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Saeed Murie AL-Shahrani	None declared	None	Full participation
Linda Tollefson	Employed for governmental institution	Not significant	Full participation
Khadija Id Sidi Yahia	None declared	None	Full participation
Jan Vaartem	Research grant received by public institution	Not significant	Full participation
Dik Mevius	None declared	None	Full participation
Paturkar Ashish Motiram	None declared	None	Full participation
Hnin Thidar Myint	None declared	None	Full participation
Haruo Watanabe	None declared	None	Full participation

ANNEX 3

Critical and important outcomes for decision-making

Methods

The WHO Steering Group, with input from the GDG, systematic review teams, and guideline methodologists considered potential outcomes discussed at the first GDG meeting and drafted a list of potentially important outcomes related to use of antimicrobials in food-producing animals. A questionnaire with these potential outcomes was then distributed to GDG members who were asked to rank the relative importance of each potential outcome on a nine-point scale ranging from I (least important) to 9 (most important). GDG members were informed that critical outcomes are usually rated from 7-9, important outcomes 4-6, and unimportant I-3. The median score was calculated for each outcome based on the GDG members' responses, to determine outcomes that are "critical" (median score≥7) and "important but not critical" (median score 4–6) for making decisions about the recommendations. To ensure consistency, the WHO Steering Group reviewed the final list of critical and important outcomes for each guideline question (see Annex 3 for the final list of outcomes).

Results

The GDG gave very high ratings to desirable outcomes from restrictions on antimicrobial use in animals; it gave the highest value (median 9, with score of 9 judged of "most importance") to the consideration that when people were infected with antimicrobial-resistant bacteria, this leads to more severe health outcomes. The GDG also gave high ratings to outcomes related to decreases in the prevalence of antimicrobial-resistant bacteria and/or antimicrobial-resistant determinants in food-producing animals (median 8) and humans (median 7-8). Undesirable outcomes were rated of lower importance, including decreases in food-producing animal health and welfare (median 4), decreases in food security (median 2), food safety (median 4), increased antimicrobial treatment use in animals following restrictions on growth promoters (median 4), and increased costs to producers and loss of income to national economies (median 3). However, the GDG did value the need to protect animal welfare by ensuring availability of antimicrobials to treat sick animals.

Questionnaire of Outcomes (with median and range importance score)

General questions

A1.

Human infections with antimicrobial-resistant bacteria are associated with more clinically severe human health consequences compared to human infections with antimicrobial-susceptible bacteria.

1	2	3	4	5	6	7	8	9
Of least importance								Of most importance

Limited importance important → critically

Median: 9, Range: 6-9

Responses	9	9	9	9	9	9	7	9	8	9	9	9	6

A2.

Restrictions on the use of antimicrobial agent(s) in food-producing animals decreases the prevalence of antimicrobial-resistant bacteria and/or antimicrobial-resistant determinants in food-producing animals.

1	2	3	4	5	6	7	8	9
Of least importance								Of most importance

Limited importance important → critically

Median: 8, Range: 3-9

Responses	9	8	9	9	3	7	8	7	8	8	9	7	9

A3.

Restrictions on the use of antimicrobial agent(s) in food-producing animals decreases the prevalence of antimicrobial-resistant bacteria and/or antimicrobial-resistant determinants in humans.

1	2	3	4	5	6	7	8	9
Of least importance								Of most importance

Limited importance important → critically

Median: 7, Range: 4-9

Responses	7	8	9	9	7	7	7	8	4	8	9	7	6

Specific questions

B1.

Complete restriction of the use of antimicrobials on the WHO CIA list for growth promotion in food-producing animals reduces the presence of antimicrobial-resistant determinants and/or antimicrobial-resistant bacteria in humans.

1	2	3	4	5	6	7	8	9
Of least importance								Of most importance

Limited importance important → critically

Median: 8, Range: 5-9

Responses	6	8	9	9	8	8	8	8	9	8	9	8	5

B2.

Complete restriction of the use of antimicrobials on the WHO CIA list for disease prevention in food-producing animals reduces the presence of antimicrobial-resistant determinants and/or antimicrobial-resistant bacteria in humans.

1	2	3	4	5	6	7	8	9
Of least importance								Of most importance

Limited importance important → critically

Median: 7, Range: 6-8

Responses	6	8	8	6	7	8	7	8	7	8	8	7	7

B3.

Restriction of the highest priority critically important antimicrobials on the WHO CIA list in food-producing animals reduces the presence of antimicrobial-resistant determinants and/or antimicrobial-resistant bacteria in humans.

1	2	3	4	5	6	7	8	9
Of least importance								Of most importance

Limited importance important → critically

Median: 8, Range: 6-9

Responses	9	8	9	8	8	9	6	8	8	8	9	8	9

B4.

Undesirable outcomes on human health from restriction of antimicrobials from the CIA list used as growth promoters or disease prevention and highest priority antimicrobials from the CIA list in food-producing animals include:

Decreases in food-producing animal health and welfare

1	2	3	4	5	6	7	8	9
Of least importance								Of most importance

Limited importance important → critically

Median: 4, Range: 2-9

Responses	5	2	5	3	2	2	4	6	7	4	9	7	3

Decreases in food and protein availability to people

1	2	3	4	5	6	7	8	9
Of least importance								Of most importance

Limited importance important → critically

Median: 2, Range: 1-7

Responses	4	1	5	2	2	2	4	1	4	2	6	7	2

Increased transmission of human pathogens (e.g. *Salmonella*, *Campylobacter* etc.) because more carrier animals and/or less healthy animals sent to slaughter

1	2	3	4	5	6	7	8	9
Of least importance								Of most importance

Limited importance important → critically

Median: 4, Range: 1-9

Responses	7	4	4	1	6	3	4	4	4	4	4	9	2

Increased transmission of resistant bacteria from food-producing animals to people (due to increase in antimicrobial treatment use to compensate for loss of growth promoter use) (WHO 2002)

1	2	3	4	5	6	7	8	9
Of least importance								Of most importance

Limited importance important → critically

Median: 4, Range: 1-7

Responses	6	2	2	1	-	4	4	5	-	4	3	7	3

Increased costs to producers and loss of income to national economies related to decreases in health and productivity in food-producing animals

1	2	3	4	5	6	7	8	9
Of least importance								Of most importance

Limited importance important → critically

Median: 3, Range: 1-8

Responses	6	2	2	1	2	4	6	2	4	2	3	8	4

ANNEX 4

Summaries of systematic reviews including supplementary report

1. Bond University Team: Systematic Review
2. University of Calgary Team: Systematic review with meta-analysis
3. University of Calgary Team: Supplementary report

Summary of Systematic Review #1

Use in food-producing animals of critically important antimicrobial agents for human medicine: systematic review, May-October 2016

Bond University Team

Background

The contribution of antimicrobial administration to food-producing animals to antimicrobial resistance in bacteria in humans forms a potential risk to human health. WHO is embarking on guidelines to advise Member States. To support this, it commissioned a systematic review of the scientific literature to address the potential benefits of limiting antimicrobials for this purpose.

Questions

Do interventions for limiting use of antimicrobials in food-producing animals reduce antimicrobial resistance in bacteria in 1) other animals; and 2) humans?

Methods

Timeline: This was a rapid systematic review, undertaken in 4½ months.

Search strategy: This was built and tested with a validation set of already known relevant studies.

Screening: teams of trained personnel screened by title/abstract, and then by full-text; consistency between screeners was tested.

Data extraction: experienced teams extracted data into pre-designed and tested forms.

Synthesis: two experts undertook a narrative synthesis of the data. Heterogeneity (principally from different animals, settings, antimicrobial classes, interventions and sampling timeframes) precluded meta-analysis.

Results

One hundred and eleven studies were included in the review. One study provided good evidence that withdrawal of antimicrobial results in a reduction of identifiable resistance in potential pathogens in retail meat food for human consumption, and in humans, with credible effect sizes and time sequences. There is also adequate evidence to conclude that limiting antimicrobial supplementation in food-producing animals feed reduces the burden of antimicrobial resistance in bacteria in animals, but insufficient evidence to quantify this effect (which may be specific to different antimicrobials at different doses, food-producing animals and environments). Administration of one antimicrobial can induce resistance in an antimicrobial from a completely different class.

Conclusions

Limiting the use of antimicrobial supplementation for food-producing animals is likely to reduce the presence of antimicrobial resistance in bacteria in other food-producing

animals and humans. This may extend beyond the antimicrobial used to other antimicrobial classes. More primary studies are necessary to strengthen the research evidence. For more details, see Web Annex A.

Summary of Systematic Review and Meta-Analysis #2

Restriction in the use of antibiotics in food-producing animals and antibiotic resistance in food-producing animals and humans: systematic review and meta-analysis

University of Calgary Team

Background

Antibiotics are the cornerstone of therapy for bacterial infectious diseases in humans and animals. The "One Health" approach recognizes that the health of humans, animals, and the environment are intricately linked, that the use of antibiotics in animals selects for resistant bacteria, and that bacteria and their resistant genetic elements can be transmitted cross-species from animals to humans. The rise in resistance to antibiotics is therefore a threat to public health globally and there is growing recognition that we may need to use antibacterial agents in a more judicious way. In this systematic review and meta-analysis, commissioned by WHO, we sought to summarize the evidence on the effects interventions to reduce antibiotic use in food-producing animals have on the presence of antibiotic resistant bacteria and resistant genetic elements in animals and in humans.

Methods

We conducted a comprehensive search of electronic databases (including Agricola, AGRIS, BIOSIS Previews, CAB Abstracts, MEDLINE, EMBASE, Global Index Medicus, ProQuest Dissertations, and Science Citation Index) in July 2016. In addition, we reviewed conference proceedings of major scientific meetings on antibiotic resistance and conducted a thorough grey literature search that included governmental websites from a wide range of regions globally. Inclusion criteria were original studies that reported on any interventions that aimed to reduce antibiotic use in food-producing animals and compared presence of antibiotic resistant bacteria or genetic resistance elements between intervention and comparator groups in food-producing animals or in humans. Analysis was conducted and reported separately for animals and humans. We pooled studies that reported an absolute risk difference in the prevalence of resistance in bacteria isolated from intervention compared to control groups using DerSimonian and Laird random-effects models. Meta-analysis for animals was conducted separately for different antibiotic classes for six different bacteria and sample type combinations, while meta-analysis for humans was not stratified due to smaller numbers of studies. Studies reporting on genetic elements of resistance and studies that could not be meta-analyzed (because they reported on different units of analyses or did not provide risk differences) were described qualitatively.

Results

A total of 5,945 unique records were identified and screened. Of these, 386 were reviewed at the full-text stage. In total, 181 studies were included in the systematic review. Of these, 179 described antibiotic resistance outcomes in animals, of which 81 were meta-analyzed. Twenty-one studies described antibiotic resistance outcomes in humans (19 of which also reported antibiotic resistance in bacteria isolated from animals), of which 13 were meta-analyzed. The pooled absolute risk reduction of the prevalence of antibiotic resistance in bacteria isolated from animals, with interventions that restricted antibiotic use, varied across different antibiotic classes, bacteria, and sample types, but ranged from 0% to 39%; in general, the prevalence of

antibiotic resistance was commonly 10-20% lower in intervention compared to control groups. The pooled prevalence of multidrug resistance was 24-32% lower in bacteria isolated from intervention groups. These findings held through many different layers of stratification including by intervention type. Similarly, for humans, the pooled prevalence of antibiotic resistance was 24% lower in intervention groups (where interventions to reduce antibiotic use in food-producing animals were implemented) compared to control groups. The effect was similar, albeit weaker, when considering humans without direct contact with livestock animals, compared to farm workers.

Conclusion

There is a large body of evidence that, when pooled, consistently shows that interventions that restrict the use of antibiotics in food-producing animals are associated with a reduction in the presence of antibiotic resistant bacteria in these animals. Our analysis also suggests that there may be a reduction in the number of antibiotic resistant bacteria in human populations with these interventions, with the greatest effect for those in direct contact with animals. These findings are in keeping with One Health approach and the understanding that animals and humans share the same environment, and they suggest that the effects of restricting antibiotic use in animals on antibiotic resistance may extend beyond the animals themselves.

For more details, see Web Annex A. The results of this work can also be found in a journal publication *(37).*

Summary of supplementary report of systematic review and Meta-Analysis #3

Supplemental report to: restriction in the use of antibiotics in food-producing animals and antibiotic resistance in food-producing animals and humans: systematic review and meta-analysis

University of Calgary team

The full report to the WHO, titled "Restriction in the use of antibiotics in food-producing animals and antibiotic resistance in bacteria isolated from food-producing animals and humans—a systematic review and meta-analysis" was completed in October 2016. Findings from this completed review were used for development of the WHO guidelines on the use and restriction of antibiotics in food-producing animals. To assist further with development of recommendations, the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) requested further supplemental work. This was: *(1)* an update of the literature search, to identify studies published since the search strategy was last run in July 2016; *(2)* stratified analysis of the pooled reduction in antibiotic resistance, by the type of antibiotic use that is restricted or targeted by interventions three; and *(3)* data extraction of the studies included in the systematic review for unintended consequences or harms from interventions that restrict antibiotic use. This report presents the results of the requested supplemental work.

Update of the literature search

The search strategy described in the original systematic review was re-run in January 2017 in the following electronic databases, to capture studies published since our July 2016 search: Agricola – Ebsco Platform, AGRIS (http://agris.fao.org), BIOSIS Previews – Web of Knowledge Platform, CAB Abstracts – Ebsco Platform, MEDLINE – Ovid Platform (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R), EMBASE – Ovid Platform, Global Index Medicus (http://www.globalhealthlibrary.net/): The non-MEDLINE indices included: AIM (AFRO), LILACS (AMRO/PAHO), IMEMR (EMRO), IMSEAR (SEARO), WPRIM (WPRO), WHOLIS (KMS), and SciELO, ProQuest Dissertations – ProQuest Platform, and Science Citation Index – Web of Knowledge Platform.

A total of 1911 citations were identified. Two authors reviewed all abstracts for potential eligibility for inclusion into the systematic review. Any abstract that (a) reported on original research, (b) described an active intervention that aimed to limit antibiotic use in animals, and (c) described antibiotic resistance in bacteria isolated from animals or humans were selected for full-text review. Fifteen studies were selected for full-text review, of which four met the pre-specified criteria, as described in the original report, for inclusion into the systematic review. All four were animal studies, only one of which could be included into the main set of meta-analyses. We have updated the systematic review and meta-analysis to include these four studies. A revised full report, dated 7 March 2017, was provided to WHO. The findings and conclusions in the updated report are unchanged from those in the original report.

Stratified analysis by type of use

To conduct the stratified analysis by use type, it was necessary to classify interventions based on the type of antibiotic use targeted. The following classification scheme was thereby created, with input and feedback from WHO AGISAR: *(1)* restriction on the use of all antibiotics, *(2a)* antibiotic class-specific restriction, or restriction on the use of one or more, but not all, classes of antibiotics, for all indications of use, *(2b)* antibiotic-specific restriction, or restriction on the use of one or more individual antibiotics, for all indications of use, *(3)* restriction on the use of antibiotics for all non-treatment indications including growth promotion and disease prevention, (*4)* restriction on the use of antibiotics for the non-treatment indications of growth promotion and disease prevention, *(5)* restriction on the use of antibiotics for purposes of growth promotion only, and *(6)* undetermined. Of particular note, every study included into the systematic review assessed an intervention that restricted the use of antibiotics. Studies that did not specify the type of antibiotic use or indication targeted in this restriction were classified as "undetermined". This included studies, for example, that compared regions or farms using "more" versus "less" antibiotics with no indication that was specifically targeted or described, or studies that assessed the impact of reducing antibiotic use in a jurisdiction without delineating how this was achieved. Each category in the classification scheme is mutually exclusive. If a single study included more than one intervention, then each intervention was classified separately based on the above approach.

Of the 179 animal studies included in the systematic review, 69 restricted all uses of antibiotics, 36 studies restricted use of antibiotics for all non-treatment purposes, while 27 restricted the use of antibiotics for growth promotion only. A total of 39 studies could not be classified based on the type of antibiotic use targeted by the intervention. An index of the 179 animal studies, their corresponding references from the original report, and their assigned classifications of interventions is presented in a supplemental table in the appendix to this supplemental report. A table also presents the categorization of interventions by type of antibiotic use being targeted for restriction, for human studies. Of the 21 human studies, five restricted all uses of antibiotics, two restricted antibiotic use for all non-treatment indications, and seven restricted use of antibiotics for growth promotion only. Five studies could not be classified based on the type of antibiotic use targeted by the intervention. An index of the 21 human studies, their corresponding references from the original report, and their assigned classifications of interventions is presented in a supplemental table to this supplemental report.

Similar to the stratified analysis conducted in the original systematic review and meta-analysis, stratified meta-analysis was performed for all studies amenable to meta-analysis, ignoring specific bacterial species, sample types, units of analysis, and antibiotic classes. The supplemental report has a table that outlines the results from meta-analysis stratified by the type of antibiotic use targeted by interventions in animal studies.

Stratified meta-analysis must be interpreted with some caution, due to the lower numbers of studies that can be included and the overlapping confidence intervals in the pooled estimates across strata. With these caveats in mind, we would propose three high-level observations from the stratified analysis, which we summarize below, followed by further elaboration: 1) the type of antibiotic use targeted by interventions is not specified in many of the studies identified by our search. This finding underlines the need for better characterization of interventions in future research, and perhaps even more importantly, in the development of future policy and regulations. 2) There is some suggestion that the interventions that target only specific antibiotic classes or specific antibiotic drugs may have less effect on antibiotic resistance than do antibiotic restrictions covering all classes. 3) Among antibiotic restriction interventions that target all classes, there does not seem to be any advantage of complete bans preventing any use relative to restrictions that still permit treatment and disease prevention use.

Unintended consequence

Data were extracted from the studies included in the systematic review, regarding potential harms stemming from interventions that restrict antibiotic use. Categories of potential harms included: 1) increased use of antibiotics, 2) adverse effects on human health, 3) decrease in food and protein availability, 4) food safety, 5) adverse effects on animal health and welfare, 6) adverse effects on animal production, and 7) economic consequences. Only 48 studies in total (all animal studies, two of which also examined antibiotic resistance in bacteria isolated from humans) reported any data on the presence or absence of potential harms of interventions that restrict antibiotic use. Of these, 32 explicitly had at least one of the aforementioned potential harms as a primary research objective. One study examined animal production consequences as a secondary objective. The other 15 studies reported potential harms in the discussion section without pre-specifying these as objectives. No studies reported adverse effects on human health or on food and protein availability. A table in the report presents a summary of the extent to which information on harms is reported in the identified studies. Of note, a single study could report on more than one potential harm.

A. Antibiotic use

Five studies reported on potential unintended consequences with regard to the total amount of antibiotics used. One study reported that when one antibiotic growth promoter was banned, there tended to be an increased use of other permitted antibiotic growth promoters until the use of these, too, was restricted. The other four studies reported that when antibiotic use was restricted, this resulted in increased administration of antibiotics to individual animals for treatment purposes, but that the total amount or volume of antibiotics used nevertheless decreased.

B. Food safety

The most widely reported potential unintended consequence was in the domain of food safety, with 34 studies reporting on this outcome. Of these, 14 (41%) found that interventions that restricted antibiotic use resulted in increased contamination with bacteria (including *Salmonella spp*., *Campylobacter spp.*, and *Enterobacteriaceae*) in the retail meats produced. Fifteen of 34 studies (45%) reported no difference in contamination rates between food products from intervention and comparator groups. A smaller percentage of studies (12%) demonstrated either variable results within studies or a lower level of contamination of meats in intervention versus comparator groups. The clinical and public health significance of these findings are unclear, especially as to what extent adequate preparation and cooking can mitigate the risk of bacterial contamination of raw retail meat, and whether higher bacterial contamination translates into increased clinical and zoonotic disease.

C. Animal health

Only five studies reported potential adverse effects on animal health. Three such studies were specific to dairy herds, showing variable results. Two of the three reported higher prevalence of intra-mammary infections when the use of antibiotics is restricted (though one study indicated that the higher prevalence was significant only at parturition but not the dry-off period), while the third study showed no difference in the prevalence of mastitis between intervention and comparator groups. Berge et al. reported an increase in respiratory disease but decrease of diarrhoea in calves where antibiotics used for disease prevention and growth promoters were restricted. Lastly, Dorado-Garcia et al. reported no difference in mortality or mean mortality age in intervention versus comparator groups.

D. Animal production

Studies reporting on the effects of antibiotic restriction on animal production again demonstrated variable results. One study indicated that such interventions resulted in greater weight gain (from reduced diarrhoea) in intervention groups, while two studies indicated that animal production was adversely affected by antibiotic restriction, with increased feeding time (to achieve a target weight) or increased production cycle duration in intervention groups. There may also be effects on parity and milk yield, with antibiotic restriction being associated with increased parity but lower milk yield in one study.

E. Costs and economics

Only three studies reported potential economic consequences of antibiotic restriction interventions. One study showed that restriction in antibiotic use, in combination with restrictions in the uses of hormone implants and anti-helminthics, may increase feeding time to reach target weight in animals, leading to increases in the need for land for disposal of waste, and increases in energy consumption for animal food production. It is difficult to disentangle the extent to which these unintended consequences in animal production and costs are attributable to the antibiotic restrictions themselves, versus the co-interventions that were implemented in this study. Other studies show variable economic implications to treatment and veterinary costs, with one study showing an increase while another showing a decrease in such costs.

Conclusion

The supplemental analysis that has been requested sheds light on various policy-relevant questions. Specifically, in the bacteria studied, broad restrictions covering all antibiotic classes appear to be more effective in reducing antibiotic resistance compared to narrow restrictions of one antibiotic class or drug. Furthermore, complete restrictions on the use of all antibiotics do not seem to be more effective than interventions that allow for appropriate treatment use. Regarding potential unintended consequences, there appears to be a recurring finding of somewhat increased use of treatment antibiotic courses in individual animals (though an overall reduction in the volume of antibiotics used) with interventions that restrict antibiotic use, and possible implications for food safety given the possible higher prevalence of bacterial contaminants in these food products. These findings are likely to be important to explore further as future guidelines and recommendations on antibiotic use are developed.

For more details, see Web Annex A. The results of this work can also be found in a journal publication *(37).*

ANNEX 5

Summaries of the narrative literature reviews

1. Illustrative example of probable transfer of resistance determinants from food-producing animals to humans: streptothricins, glycopeptides, and colistin
2. Biological plausibility for associations between antimicrobial use in food-producing animals and increased risks of human exposures to, and infections by, antimicrobial-resistant zoonotic pathogens
3. Potential unintended consequences associated with restrictions on antimicrobial use in food-producing animals

Summary of Narrative Literature Review #1

Illustrative example of probable transfer of resistance determinants from food-producing animals to humans: streptothricins, glycopeptides, and colistin

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This review summarized the published evidence of probable transfer of resistance determinants for streptothricins, glycopeptides, and colistin from food-producing animals to humans.

Streptothricins

Nourseothricin, a streptothricin antimicrobial agent, was widely used as a growth promoter in the swine industry in the former German Democratic Republic from 1981-1988. In contrast, toxicity prevented use of streptothricin antimicrobial agents in humans. Less than one year after the introduction of nourseothricin in swine, a plasmid-borne streptothricin resistance *(sat)* seemingly emerged in *E. coli* isolated from swine administered nourseothricin. Subsequently, plasmid-borne streptothricin resistance was detected in the gut flora of humans with direct, indirect, and no contact to pig farms, but living in the same regions. Following reports of the plasmid-mediated streptothricin resistance demonstrates an illustrative example of the detection—and apparent emergence—of streptothricin resistant bacteria in swine as a result of antimicrobial use, and the dissemination of the resistant bacteria and mobile genetic elements conferring resistance to humans.

Glycopeptides

Avoparcin appears to have been widely used in food-producing animals, particularly in chickens and pigs, in parts of Europe, since before the mid-1970s. Vancomycin use in humans, in contrast, was very limited in Europe until the late 1990s. It appears likely that the use of avoparcin in food-producing animals selected for the emergence and dissemination of a resistance gene cluster (VanA), which was increasingly identified in animals and healthy people. Molecular subtyping of the VanA gene cluster has identified variants that are more likely to be associated with certain food-producing animal species. Subsequently, GRE were transmitted and found to colonize healthy humans, presumably via the food chain.

Therefore, evaluation of the VanA gene cluster variants provides an illustrative example of the probable emergence and selection of a genetic resistance determinant due to antimicrobial use in food-producing animals, and subsequent dissemination of the resistant bacteria to humans.

Colistin

Colistin has been widely used in food-producing animals—particularly poultry and swine—in areas of Europe and Asia for decades, perhaps since the early 1980s or earlier. Colistin use in humans, in contrast, has been extremely limited, at least until recently. It appears highly probable that the use of colistin in food-producing animals has selected for a novel resistance gene *(mcr-1)*, identified as far back as the mid-1980s in chickens in China, which has become increasingly identified in isolates from food-producing animals in many regions of the world since its discovery in 2015. This novel resistance gene has more recently been identified among isolates from humans; however, to date *mcr-1* has been more frequently associated with food-producing animal and meat isolates compared to human isolates. These chains of events, despite the data gaps, provide an illustrative example of the probable emergence, selection, and widespread dissemination of a resistance gene due to antimicrobial use in food-producing animals, and subsequent transfer of bacteria harboring that resistant gene to humans.

For more details, see Web Annex A. The results of this work can also be found in a journal publication *(38).*

Narrative Literature Review #2

Biological plausibility for associations between antimicrobial use in food-producing animals and increased risks of human exposures to, and infections by, antimicrobial-resistant zoonotic pathogens

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This review summarized the published evidence of the biological plausibility for associations between antimicrobial use in food-producing animals and increased risks of human exposure to and infections by antimicrobial-resistant zoonotic pathogens.

Background

Antimicrobial use in food-producing animals contributes to antimicrobial resistance in zoonotic pathogens that can be transmitted to humans. To assist in managing this public health risk, the WHO commissioned reviews of evidence on the health risks of antimicrobial use in food-producing animals. Our report focuses on the biological plausibility of associations observed between these uses and risks to human health.

Methods

We reviewed published papers on mechanisms of antimicrobial resistance in general and specifically in the context of antimicrobial use in food-producing animals and dissemination of resistant to humans. We adopted methods used by the US Task Force on Community Preventive Services. We also used a scoping review process to locate recent papers and we searched references for additional sources of information.

Findings
An extensive literature on molecular mechanisms supports observed associations between agricultural use of antimicrobials and emergence and dissemination of antimicrobial resistance determinants from food-producing animals to human populations.

Interpretation
This review adds to the evidence in other reviews in this series. In addition to supporting the biological plausibility of these observations, we find that the context and conditions of food-producing animal production are highly conducive to amplifying horizontal resistance gene transfer, persistence of resistance, and emergence of multidrug resistance. In addition, mechanistic information highlights the importance of environmental reservoirs and pathways as sources of human exposure.

For more details, see Web Annex A.

Narrative Literature Review #3

Potential unintended consequences associated with restrictions on antimicrobial use in food-producing animals

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This review summarized the published evidence that restriction of antimicrobial use in food-producing animals does or does not have effects (largely unintended) on several non-antimicrobial resistance outcomes. The most thoroughly studied restriction is termination of use of antimicrobial growth promoters (AGPs) in Europe.

Antimicrobial use
Following the AGP ban in Denmark, antimicrobial treatment use in poultry and cattle was unaffected by the ban, however in weaned pigs there were relative increases in treatment use of some antimicrobials important for use in humans (tetracyclines, penicillins, macrolides, aminoglycosides). Among *Salmonella* Typhimurium (but not *E. coli*) isolates from pigs and domestically acquired infections in humans, there was an increase in resistance to tetracyclines that may have been caused by increased tetracycline use in pigs. There was a decrease in macrolide resistance in *Campylobacter* from pigs. Use of cephalosporins and fluoroquinolones was unaffected by the AGP ban. Experience in other countries varied; treatment use decreased in Norway, was unaffected in Switzerland, and increased in Sweden and the Netherlands following their AGP bans.

Food safety and security
AGP termination in Denmark did not affect the incidence of antimicrobial residues in foods, domestically-acquired human salmonellosis,

campylobacteriosis or yersiniosis, nor were there effects on contamination of domestic meat and poultry with *Salmonella* and *Campylobacter*. From the perspective of global food security, likely decreases in poultry and pork production were estimated to be no more than 2% and average daily protein supply would likely decrease by no more than 0.1 g per person (or 0.2% of total protein intake).

Animal health and welfare

Some countries experienced temporary problems following their AGP bans, mainly diarrhoea in weaned pigs and necrotic enteritis in poultry. In Denmark, treatments for post-weaning diarrhoea increased from approximately 0.4 to 1.0 treatments per pig-month prior to and after AGP termination in weaners, respectively. Necrotic enteritis diagnoses were made in 25 of 1700 Danish broiler flocks in the year after the ban compared with 1-2 per 1700 flocks annually prior to the ban.

Environment

No evidence was found in Denmark of adverse environmental effects, including total nitrogen and phosphorus output in animal manure.

Animal production

Estimates of the magnitude of AGP adverse effects on production, mainly from experimental studies, vary widely, ranging from approximately 0-15%, however there is evidence that beneficial effects have declined over time, and since the early 2000s range from 0-5%. In Denmark, some temporary production losses (two years or less after the ban) were detected in weaned pigs, mainly through mortality (0.6% increase), growth rate (2.6% decrease) and feed efficiency (increase of 1-2% in feed units required per weaner produced). No effects on productivity or feed efficiency in finishers were identified. Production effects in Danish broilers were limited to decreased feed efficiency (-2.3%) that was largely offset by savings in the cost of AGPs. In a large U.S. study, removal of AGPs was associated with reduction in livability of 0.14%-0.2%, an average decrease in body weight of 0.03-0.04 lb., and an average increase in feed conversion ratio of 0.012-0.016.

Economic impacts

In Denmark, net costs due to productivity losses from AGP termination were estimated to be 7.75 DKK (1.04 €) per pig produced (1%) and no net cost for poultry. Findings from a general equilibrium model of the Danish economy indicated that AGP termination lowered pig production by about 1.4% per annum and increased poultry production by 0.4% per annum. Impact of AGP termination on the Danish economy was estimated to be a reduction of 0.03% (363 million DKK (48 million €) by 2010 at 1995 prices) in real Gross Domestic Product (GDP). A recent U.S. evaluation estimated that a 1-3% increased cost of production in pigs and broilers would lead to a 1% increase in wholesale prices and drop in output of less than 1%. Another study estimated the potential loss of production and meat value following an AGP ban under two scenarios: 1) effects of AGPs are high (using growth response data from the 1980s), and 2) effects of AGPs are low (using growth response data from the 2000s). They projected that a worldwide ban on AGPs would result in a decrease of global meat production by 1.3% to 3% from its current level (1980s vs. 2000s scenarios). This corresponds to a global loss of between USD 13.5 and USD 44.1 billion in the two scenarios.

In 2010, the Danish Veterinary and Food Administration introduced the "Yellow Card" system to place regulatory restrictions on pig farmers that used twice the average quantity of treatment antimicrobials. The impact of the programme on slaughter condemnations in pigs at slaughter was evaluated. There were increases in some lesions, but decreases in others.

The Netherlands recently undertook major reductions in antimicrobial consumption in food-producing animals, as well as further restrictions on critically important antimicrobials such as fluoroquinolones and

cephalosporins. The Dutch Animal Health Service reported some indications of increased disease problems in pigs, but some of the increases may have been related to feed changes.

Conclusions

Overall, the adverse consequences of AGP bans and other restrictions described in the literature appear to be limited and temporary. Based on European experiences with terminating AGPs, such adverse effects that may be encountered can be reduced by taking steps to minimize disease in vulnerable classes of animals, especially weaner pigs, and supporting producers in making a transition to more targeted, prudent antimicrobial use. Such steps include improvements in veterinary advice, animal housing, non-antimicrobial disease control strategies and antimicrobial use surveillance. For future AGP bans, particular care is needed to avoid compensatory increases in antimicrobial use for disease prevention or treatment purposes, particularly antimicrobials important for therapy in either humans or animals.

For more details, see Web Annex A.

ANNEX 6

Recommendations and summary of the judgments of the guideline development group of the criteria related to the strength of the recommendations for each intervention

Recommendation	1	2	3	4
Type of food-producing animal use	Overall use	Growth promotion use	Prevention use (in the absence of disease)	Control and treatment use (in the presence of disease)
Intervention	Restriction of medically important antimicrobials in food-producing animals	Complete restriction of medically important antimicrobials for growth promotion in food-producing animals	Complete restriction of routine use of medically important antimicrobials for prevention of infectious diseases that have not yet been clinically diagnosed in food-producing animals	Restriction of critically important antimicrobials for disease control and treatment in food-producing animals
Is the problem a priority?	Yes	Yes	Yes	Yes
Are a large number of people affected?	Yes	Yes	Yes	Yes
Are the desirable anticipated effects large?	Yes	Yes	Probably yes	Probably yes
Are the undesirable anticipated effects small?	Yes	Yes	Probably yes	Probably yes

Intervention	Restriction of medically important antimicrobials in food-producing animals	Complete restriction of medically important antimicrobials for growth promotion in food-producing animals	Complete restriction of routine use of medically important antimicrobials for prevention of infectious diseases that have not yet been clinically diagnosed in food-producing animals	Restriction of critically important antimicrobials for disease control and treatment in food-producing animals
What is the overall certainty of this evidence?	Low	Low	Low	Very low
How certain is the relative importance of the desirable and undesirable outcomes?	No important uncertainty or variability	No important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability
Are the desirable effects large relative to undesirable effects?	Yes	Probably yes	Probably yes	Probably yes
Are the resources required small?	Varies	Varies	Uncertain	Varies
Is the incremental cost small relative to the net benefits?	Varies	Varies	Probably yes	Varies
What would be the Impact on health inequalities?	Probably reduced	Probably reduced	Uncertain	Uncertain
Is the option acceptable to key stakeholders?	Yes	Probably yes	Varies	Varies
Is the option feasible to implement?	Yes	Yes	Probably yes	Uncertain

Intervention	Restriction of medically important antimicrobials in food-producing animals	Complete restriction of medically important antimicrobials for growth promotion in food-producing animals	Complete restriction of routine use of medically important antimicrobials for prevention of infectious diseases that have not yet been clinically diagnosed in food-producing animals	Restriction of critically important antimicrobials for disease control and treatment in food-producing animals
Balance of consequences?	Desirable consequences clearly outweigh undesirable consequences in most settings	Desirable consequences clearly outweigh undesirable consequences in most settings	Desirable consequences clearly outweigh undesirable consequences in most settings	Desirable consequences probably outweigh undesirable consequences in most settings
Type of recommendation?	Strong recommendation for the intervention	Strong recommendation for the intervention	Strong recommendation for the intervention	Conditional recommendation for the intervention
Recommendation	We recommend an overall reduction in use of all classes of medically important antimicrobials in food-producing animals	We recommend complete restriction of use of all classes of medically important antimicrobials in food-producing animals for growth promotion	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	a. We suggest that antimicrobials classified as critically important for human medicine should not be used for control of the dissemination of clinically diagnosed infectious disease identified within a group of food-producing animals b. We suggest that antimicrobials classified as highest-priority critically important for human medicine should not be used for the treatment of food-producing animals with a clinically diagnosed infectious disease

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ISBN: 978-92-4-155013-0