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Antimicrobial Resistance (AMR) Multi-Stakeholder Partnership Platform

Antimicrobial Prophylaxis in Animals

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Summary

- Prophylaxis (also known as prevention) is the administration of antimicrobials with an aim to prevent a disease that is not already present.
- Prophylaxis encompasses a wide range of uses in animals, with different risks, benefits and concerns. This includes group or individual treatments, and use in food or non-food (e.g. companion, working)animals.
- Reducing the use of prophylaxis, particularly in groups of food animals, is an important stewardship goal. However, some use of antimicrobial prophylaxis is necessary to address for health and welfare concerns in situations where the risk and implications of a specific disease are high.
- Antimicrobial stewardship efforts should discourage routine antimicrobial prophylaxis in groups of animals; antimicrobial use in the absence of evidence of need; the use of higher tier drugs (especially HPCIAs and CIAs) and the use of antimicrobial prophylaxis in lieu of proper management or preventive medicine..

Antimicrobial prophylaxis in animals is a topic of increasing scrutiny. A general principle of antimicrobial stewardship is to avoid using antimicrobials in individuals that do not have a bacterial infection. However, appropriate prophylaxis that is applied in a targeted manner for high-risk situations where the risk of bacterial infection is great can reduce morbidity, mortality and welfare concerns. It can also potentially decrease overall antimicrobial use (AMU) if it prevents the need for therapeutic courses of antimicrobials, which may involve longer treatment courses and/or the use of higher tier antimicrobials. However, with large scale use, use that is poorly targeted, use that is not based on proper risk assessment and when antimicrobials are used in lieu of improvements in animal management and preventive medicine, the negative aspects of AMU (particularly on selection and spread of antimicrobial resistance) are more difficult to justify. Accordingly, efforts to assess, reduce and optimize prophylaxis are warranted, especially under the FAO global initiative of Reducing the Need for Antimicrobials on Farms for Sustainable Agrifood System Transformation (RENOFARM). However, a proper understanding of the complexity of antimicrobial prophylaxis is required to avoid misunderstanding and over-simplification of a complex issue, and diversion of attention from high impact areas.

Note: This document is the product of a collaborative process undertaken within the AMR Partnership Platform, with contributions from some of its members. The content reflects the collective input and discussions and represents the views of the authors. These views do not necessarily reflect the positions of all Platform members. The article has been reviewed and endorsed by the Platform's Steering Committee, which supports the collaborative nature of this process.

Prophylaxis (or 'prevention') is a very broad categorization of AMU. It is also lacking in a consistent definition. Various agencies and governments have used similar but somewhat different definitions (Table 1). However, a consistent component of definitions is *administration of antimicrobials to animals that are deemed to be at increased risk of bacterial infection and where prophylaxis is assumed to be able to reduce the risk of disease.*

Beyond broad definitions, the appropriateness and potential impacts (both positive and negative) vary with the circumstances of use. This can include scenarios such as:

A) Routine administration of antimicrobials to groups of animals in the absence of evidence of need, largely because of historical practices.
B) Routine administration of antimicrobials for a prolonged period of time to a group of animals because of a high endemic rate of a specific disease in the group.
C) Routine administration of antimicrobials to most or all animals at a specific stage in life or production to reduce a specific disease or syndrome (e.g. tetracycline treatment of pigs at the time of weaning to prevent post-weaning diarrhea, administration of intramammary antimicrobials to dairy cattle at the end of lactation to prevent mastitis, tetracycline with ITM vaccination for prevention of East Coast fever).
D) Targeted administration of antimicrobials to a group of animals in response to a specific, defined disease threat that is known to be mitigated by antimicrobial prophylaxis.
E) Administration of antimicrobials to a specific animal at a specific and well, defined high-risk time (e.g. peri-operative antimicrobial prophylaxis for prevention of surgical site infection).

The appropriateness of use varies between these categories. "A" represents poor antimicrobial use (misuse/ overuse) and is a not an acceptable form of prophylaxis. "B" represents a situation where improved animal health and management practices are likely required and where antimicrobials are being used to compensate for suboptimal animal care. "C" is a situation where targeted antimicrobials might be important to reduce disease burden and improve animal welfare, but only if animal health and management has been optimized. Further, it is unlikely that it is actually necessary for all animals (either all animals in a group or all groups over time) and that more targeted approaches could be used. "D" is an uncommon scenario but one where a short prophylaxis regimen could represent an appropriate intervention. "E" represents a situation where antimicrobial prophylaxis can clearly reduce morbidity and the potential need for longer therapeutic courses of antimicrobials.

Prophylaxis vs Metaphylaxis

Also referred to as 'disease control' metaphylaxis is administration of an antimicrobial to an animal that is thought to have subclinical infection based on history, clinical judgement, presence of disease in other animals in the group or knowledge of disease patterns in the group, in order to reduce the likelihood that clinical disease develops. This differs from prophylaxis in that metaphylaxis assumes animals are already infected but have not yet developed overt disease, and is designed to both prevent development of overt disease infected individuals and to reduce transmission within a group. There is potentially overlap between these two categories as the difference between prophylaxis and metaphylaxis may be difficult to discern.

Prophylaxis vs Non-Veterinary Medical Use

Prophylaxis is a medical use of antimicrobials to prevent disease. In contrast, antimicrobials are used in a minority of countries for non-veterinary medical use, namely growth promotion. Use of antimicrobials for growth promotion typically involves low doses of antimicrobials to improve growth and production (e.g. feed conversion). The mechanism(s) for these are not well elucidated but may involve impacts on the critical bacterial population (the 'microbiota' or 'microbiome') in the animal's gut. While dosing is sometimes described as 'sub-therapeutic' as it involves antimicrobial doses lower than those used for treatment or prophylaxis, this can still exert pressure for selection for antimicrobial resistance. Many antimicrobials that are used for growth promotion are from different drug classes than those used therapeutically or prophylactically, reducing potential harms. However, use of medically important antimicrobials is still currently allowed in some countries. It is important to avoid combining or confusing growth promotion and prophylaxis because the relevant issues are very different.

Table 1: Examples of definitions of antimicrobial prophylaxis in animals

Agency/ Group	Definition	Reference
Codex	Administration or application of antimicrobial agents to an individual or a group of plants/crops or animals at risk of acquiring a specific infection or in a specific situation where infectious disease is likely to occur if the antimicrobial agent is not administered or applied	https://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCXC%2B61-2005%252FCXC_061e.pdf
EU	Administration of a medicinal product to an animal or group of animals before clinical signs of a disease, in order to prevent the occurrence of disease of infection	https://eur-lex.europa.eu/eli/reg/2019/6/oj
WHO	Use of antimicrobials in healthy animals considered to be at risk of infection or prior to the onset of clinical 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 been diagnosed clinically.	https://iris.who.int/bitstream/handle/10665/258970/9789241550130-eng.pdf?sequence=1#:~:text=Disease%20prevention%20use%20(or%20prophylactic,onset%20of%20clinical%20infectious%20disease
WOAH	To administer an antimicrobial agent to an individual or group of animals at risk of acquiring a specific infection or in a specific situation where infectious disease is likely to occur if the drug is not administered.	https://www.woah.org/en/what-we-do/standards/codes-and-manuals/terrestrial-code-online-access/?id=169&L=1&htmfile=chapitre_antibio_monitoring.htm
AVMA	Administration of an antimicrobial to an individual animal to mitigate the risk for acquiring disease or infection that is anticipated based on history, clinical judgement, or epidemiological knowledge. On a population basis, prevention is the administration of an antimicrobial to a group of animals, none of which have evidence of disease or infection, when transmission of existing undiagnosed infections, or the introduction of pathogens, is anticipated based on history, clinical judgement or epidemiological knowledge.	https://www.avma.org/resources-tools/avma-policies/avma-definitions-antimicrobial-use-treatment-control-and-prevention
	To prevent means to administer an antimicrobial agent to an individual or a group of animals at risk of acquiring a specific infection or in a specific situation where infectious disease is likely to occur if the antimicrobial agent is not administered	Simjee *et al*., 2022 https://pubmed.ncbi.nlm.nih.gov/35030247/

AVMA: American Veterinary Medical Association
EU: European Union
WHO: World Health Organization
WOAH: World Organization for Animal Health

The following scenarios provide examples of different types of prophylaxis.

Scenario 1
A swine farmer has been increasing his production because of increased market demand. They have not hired more personnel and have a barn that is overstocked and in need of upgrades. Their use of vaccines is sporadic as they do not use a veterinarian regularly. They have recurrent problems with infectious respiratory and intestinal disease and routinely use antibiotics in the feed of all pigs after weaning.

While this practice may indeed reduce disease and could potentially reduce overall AMU if the incidence of disease would be high and many animals would receive longer therapeutic courses, this is an undesirable approach because of the routine, ongoing use and large number of treated animals. It is of further concern when antimicrobials are used to compensate for suboptimal farm practices such management problems (e.g. stocking density, ventilation, nutrition) or inadequate use of preventive medicine strategies (e.g. vaccination). Improvements in farm management, veterinary care and farm infrastructure would have a greater impact on disease, welfare and production.

Scenario 2
A dog with an abdominal obstruction from ingestion of a foreign body (e.g. a dish towel). Surgery is required to remove the obstruction, which will require making an incision into the intestine. This creates a high potential for bacterial contamination so antimicrobial prophylaxis is provided. A single dose of an antimicrobial is administered shortly before the surgical procedure. This is an appropriate use of antimicrobials since, if antimicrobials were not used, the risk of infection would be higher, leading to animal health and welfare concerns, and the need for a longer therapeutic course of antimicrobials, which would usually be higher tier drugs.

Scenario 3a
A dairy farmer routinely treats all cattle with a dose of intra-mammary antimicrobials at the end of its lactation cycle, to reduce the risk of mastitis. This is known to reduce the incidence of mastitis but has also been shown to increase antimicrobial resistance. However, it is suboptimal as it represents an approach based on convenience versus one that targets animals that are more likely to benefit from antimicrobials.

Scenario 3b
The farmer switches to a targeted approach using 'selective dry cow treatment'. This involves antimicrobial administration only to a subset of cows that is determined to be at higher risk of infection at the end of lactation or that has subclinical mastitis. This approach bridges therapy, prophylaxis and metaphylaxis, but has been shown to reduce the incidence of antimicrobial use without any increase in disease risk.

Background: Antimicrobial stewardship efforts directed at antimicrobial use (AMU) in animals are important parts of National Action plans and other activities. Antimicrobial prophylaxis is used widely in humans and animals, and is an important target for reduction and improvement in AMU. However, there is often lack of consideration of the breadth of prophylaxis in animals and the complexity of the area, which can lead to ineffective or harmful responses. Antimicrobial prophylaxis is an important target for AMU reduction in animals, but some aspects of prophylaxis are important for animal health and welfare purposes, particularly individual-animal prophylaxis. It is important for decision-makers to understand these issues to help maximize stewardship efforts while negative consequences, which are often unintended consequences based on inadequate understanding of the topic.
Objectives: To increase understanding of the breadth of issues pertaining to prophylaxis in animals.
Scope: The document is focused on antimicrobial prophylaxis in animals. It is intended to be a concise, focused document that just deals with prophylaxis, to ensure that the specific area is highlighted adequately.
Target audience: The main target audience is individuals that may be involved in discussions about antimicrobial prophylaxis as part of national action plans or other activities that aim to address antimicrobial prophylaxis. A secondary audience in individuals in human medical, public health and environment fields that have an interest in AMR, particularly those involved in discussions around antimicrobial stewardship. However, given the widespread interest in prophylaxis in various individuals, the overall audience would be very broad and include anyone with an interest in AMU or AMR, including the general public.
Development process: The document was developed after discussions at a Global Leaders Group meeting, because of ongoing confusion or lack of broad understanding regarding prophylaxis in animals. Side discussions at the GLG meeting lead to an effort by Scott Weese and representatives from WOAH and FAO, to draft a document. Based on a change in personnel, the document was ultimately created by WOAH and Dr. Weese. It was approved by WOAH, prior to submission to other quadripartite members for comment. It was then submitted to the MSPP Veterinary Education Action Group for comment, discussions and approval.

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