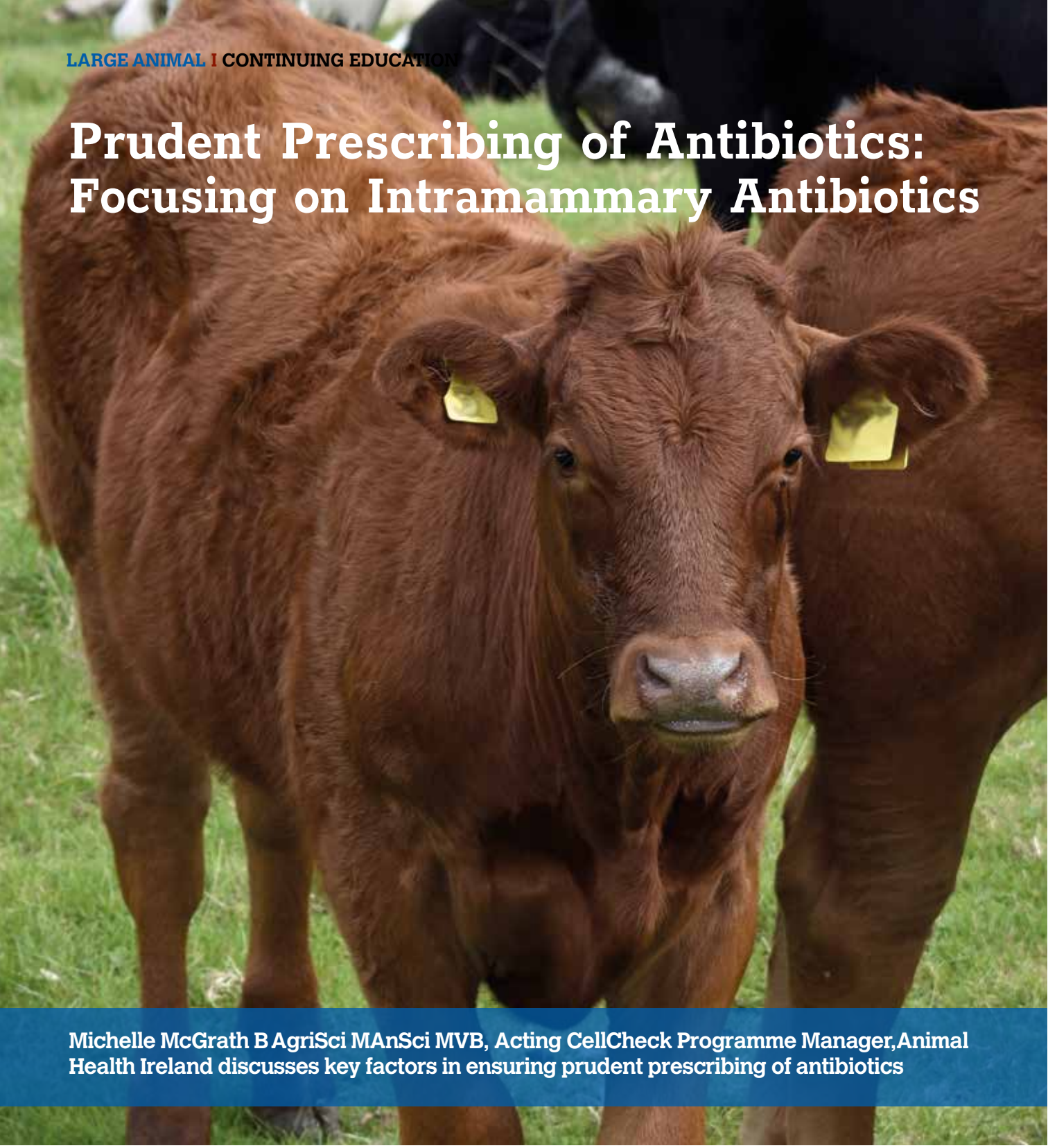
Prudent Prescribing of Antibiotics: Focusing on Intramammary Antibiotics



Michelle McGrath B AgriSci MAnSci MVB, Acting CellCheck Programme Manager,Animal Health Ireland discusses key factors in ensuring prudent prescribing of antibiotics

One of the main objectives of the new Veterinary Medicinal Products Regulation, EU 2019/6, is to address the growing issue of antimicrobial resistance (AMR). AMR is a global phenomenon and a well-recognised threat to public health, as well as animal health. The World Health Organisation estimates that if AMR is not addressed, it will be responsible for 10 million human deaths annually by 2050.

Putting this into context, that would be more deaths annually due to AMR than deaths caused by cancer. The risk of resistance increases if antibiotics are used: at too low a dosage; for too short a duration; too often; as a blanket measure in an untargeted manner; for the treatment of bacteria that are not susceptible to the particular antibiotic; for the treatment of diseases caused by viruses or other germs not susceptible to antibiotics; or for too long a period of time (Health Products Regulatory Authority Report, 2022).

The new regulation requires that antimicrobials are not used routinely or to compensate for poor hygiene, inadequate animal husbandry or poor farm management. Since January 2022, antimicrobials are only allowed for prophylaxis (as a preventative measure) in "exceptional cases" for administration to an individual animal or restricted number of animals when the risk of infection is

very high, and consequences are likely to be severe. A prescription for antimicrobials for metaphylaxis (treating animals that have been in contact with infected animals) may only be issued after diagnosis of infection, when the risk of spread of an infection is high and when no other appropriate alternatives are available (Department of Agriculture Food and the Marine, 2022).
Small quantities of medicines are allowed to be kept on a farm if a veterinary practitioner deems them necessary, where there may be an essential need for the administration to an individual animal or restricted number of animals when the risk for infection, or an infectious disease is very high or its consequences are likely to be severe (Department of Agriculture Food and the Marine, 2022). The new National Veterinary Prescription System will assist Ireland in meeting its annual EU regulatory requirement to report on antimicrobial usage, which is a critical aspect in the fight against anti-microbial resistance.

PRUDENT PRESCRIBING FOR IN-LACTATION AND DRY COW ANTIBIOTICS

In recent years the European Medicines Agency (EMA), acting at the request of the European Commission, has reviewed the indications and conditions under which a number of the more modern antimicrobial classes (fluoroquinolones, macrolides and cephalosporins) are used in veterinary medicine. They have categorised antimicrobial classes into four categories A (avoid – not to be used for veterinary use), B (for restricted use only), C (to be used with caution) and D (for prudent use) [See pages 271 and 272 for more details].
It is the view of the CellCheck Technical Working Group (TWG), that both animal and herd-level information are required for responsible prescribing of in-lactation and dry cow antibiotics.

ANIMAL-LEVEL INFORMATION NECESSARY FOR RESPONSIBLE PRESCRIBING

Cases of clinical mastitis, often in-lactation, are identified based on clinical signs of inflammation or systemic illness, or abnormal changes in the appearance of milk. Subclinical infection is diagnosed on the basis of individual cow somatic cell count (SCC) levels. However, there should also be ongoing collection and bacteriological testing of milk samples from animals with clinical or subclinical mastitis, both to guide individual clinical decisions and, equally importantly, as part of the broader assessment and monitoring of mastitis pathogen challenge(s) and antibiotic resistance patterns on the farm as outlined below.

ONGOING ASSESSMENT OF ALL LACTATING ANIMALS

The TWG recommends milk recording every four to six weeks as best practice, for prescribing decisions and mastitis monitoring, with a minimum of six recordings throughout the lactation, including one shortly prior to drying off and one shortly following calving.

- Milk recording results are currently accepted internationally as best practice in identifying cows at the end of their lactation with probable infected quarters, and for prescribing dry-cow antibiotic treatment. While it may be possible to improve the accuracy of diagnosing infection through the additional measures of clinical disease history, bulk tank SCC trends and milk culture results, milk recording is a mainstay of this decision-making process. This is because of the relative practicality of completing milk recording and its multiple additional benefits to farm management.
- Several recent studies from the Netherlands[1] and New Zealand[2], have shown that a single milk recording, taken within four to six weeks of drying off, can provide useful information about infection status at drying off. However, this is insufficient to guide mastitis control throughout the year and it should be noted that the composition of late lactation milk can cause sampling and testing difficulties. Care should also be taken when interpreting studies from other countries where prevalence rates and pathogen profiles may differ.
- CellCheck resources, including the Farm Summary Report, are available, highlighting the value of, and return from, milk recording data.

Alternatives to milk recording are available, but are currently of limited practical value:

- Individual cow bacterial culture or polymerase chain reaction(PCR)-based techniques are the gold standard for indicating presence of bacteria or bacterial DNA, respectively, and thus may be proposed as suitable individual cow information. However, in Irish farming systems with seasonal calving and hence block drying off, the logistics of aseptically sampling large numbers of cows shortly before drying off, as well as the time and direct costs, may render this proposal impractical for most herds.
- The California mastitis test (CMT) is a simple cow-side test that is quick, and low cost and may be used to define if the cow is likely to be infected in one or more glands at a point in time. The CMT should be performed by the prescriber on all cows shortly before drying off, which may be impractical and prohibitive but it may be a temporary solution in the absence of milk recording. However, interpretation of the results is subjective, and the test can be negative with SCC levels of less than 500,000 cells/ml. Further, according to UK[3] and US[4] studies, using a CMT to determine infection status at the point of drying off is known to be less accurate in high SCC herds infected with gram positive pathogens which are a significant cause of mastitis in Irish herds[5].

HERD-LEVEL INFORMATION TO SUPPORT RESPONSIBLE PRESCRIBING

In addition to individual cow information, each of the following factors are also needed to support responsible prescribing, both for dry-cow and in-lactation antibiotics:

- A bona fide relationship with the herd owner, which enables the veterinary practitioner to carry out clinical examinations and exercise clinical judgement. This forms the basis of a robust Client Patient Practice Relationship (CPPR).
- A sophisticated understanding of the farm in general, including the herd, the people, the facilities and farm management (in general, during lactation and at drying off). In the case of a new client, engagement with the farmer, along with farm visits, clinical examinations, and appropriate ancillary testing will establish the necessary baseline of knowledge for responsible prescribing. This ensures knowledge and oversight of all

antibiotics prescribed and used, and a holistic and coherent understanding of the rationale and strategy for antibiotic prescribing and use.

- A thorough knowledge of the milk quality patterns of the farm, including temporal trends in bulk tank SCC and milk recording results, and access to accurate clinical mastitis records. The latter should also include treatment details, including outcomes.
- A detailed knowledge of the mastitis pathogen challenge(s) on-farm, through regular milk culturing of individual cases (clinical and subclinical), and potentially also from the bulk tank (PCR testing). Antimicrobial susceptibility testing (AST) should also be performed regularly, to guide appropriate antibiotic selection, and identify existing or emerging antibiotic resistance. Antibiotic selection should be chosen using the EMA guidelines and first line of treatment should preferably be from the 'EMA Category D: Prudence.' Antibiotics from 'higher' categories (EMA Categories B: Restrict, C: Caution) should only be considered with supporting milk culture and antibiotic susceptibility results and only when there are no antibiotics in a lower category that could be clinically effective. To facilitate this, it is recommended to collect and analyse the following milk samples, (which may be frozen for up to three months if necessary):
  - A pre-treatment milk sample from all clinical cases to identify the pathogen causing mastitis.
  - Milk samples from cows with high SCC, ensuring a mixture of young and old cows, with evidence of both recent and chronic infections, based on sampling conducted at different points throughout lactation.
- Develop or conduct an annual review of a mastitis treatment plan for in-lactation cases. In-lactation mastitis incidence should be monitored. Instigate measures to gain a detailed knowledge of the mastitis pathogen challenge(s) and antibiotic resistance patterns on the farm. A standard operating procedure for the treatment of in-lactation cases should be agreed with the farmer and a review of treatment of in-lactation cases in the past season should be carried out before prescribing dry cow antibiotics while reassessing the procedure for treating in-lactation cases for the next season.
- When prescribing in-lactation antibiotics in high-risk herds, a detailed understanding of the factors (including cause[s] and driver[s]) contributing to suboptimal mastitis control is necessary, based on a detailed on- and off-farm investigation and plan developed and agreed with the farmer to robustly and sustainably address each of these factors, including agreed actions and timelines and objective measures to monitor progress. If not already milk recording, the farmer should immediately commence whole herd milk recording.
- Records of mastitis events, treatments administered and related outcomes, should be captured (preferably electronically), to facilitate monitoring and assessment, as well as improvement of treatment protocols.
- A detailed understanding of CellCheck resources, including the use of the CellCheck Dashboard as an investigative tool, to inform the farm assessment and prescribing decisions.
- A strong professional relationship between the prescriber and other professional farm service providers is important to ensure a holistic approach to milk quality and broader animal health and welfare.

When prescribing dry cow antibiotics, follow the current CellCheck Dry Cow Strategy and make prescribing decisions informed by:

- Individual animal information (as above), herd-level information (as above), and European Medicines Agency (EMA) guidelines.
- In the absence of milk recording data, the prescribing PVP should use the following to identify individual cows that have evidence of infection, and therefore require antibiotic treatment:
  - Milk samples from cows with high SCC, ensuring a mixture of young and old cows, with evidence of both recent and chronic infections, based on sampling conducted at different points throughout lactation.
  - A single milk recording from each cow shortly prior to drying off, or
  - Individual cow milk culture results, or
  - Individual CMT, as carried out by the prescriber.

If the prescribing veterinary practitioner considers that prophylactic use of dry-cow antibiotic is justified to protect cow welfare, in situations where the risk of new infection over the dry period is unacceptable, it is critical that these risk factors are addressed and resolved, prior to the next dry period.
In order to ensure the continued availability and effectiveness of antibiotics they must be used responsibly.

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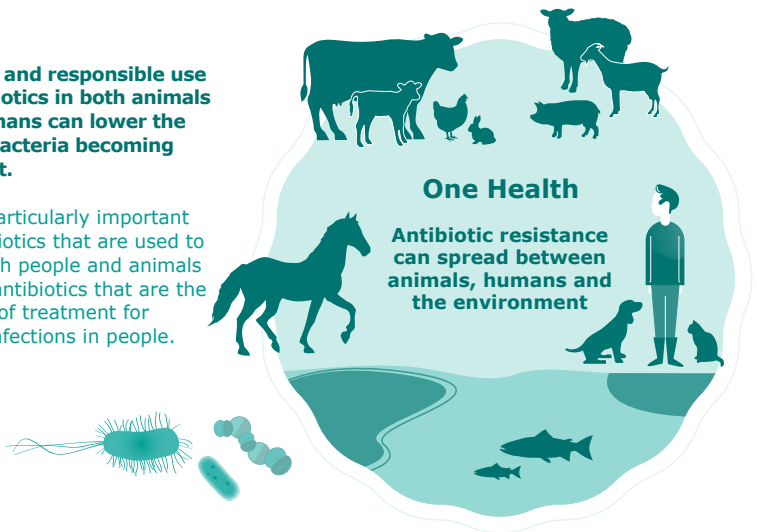
The following pages, 271 and 272, feature the European Medicines Agency (EMA) Categorisation of antibiotics for use in animals for prudent and responsible use. It includes examples of substances authorised for human or veterinary use in the EU. In addition, there is advice on the importance of taking the route of administration into account alongside categorisation when prescribing antibiotics.

Further Reading, References and the Reader Questions and Answers are on page 273.

EMA Categorisation of antibiotics for use in animals
for prudent and responsible use

Prudent and responsible use of antibiotics in both animals and humans can lower the risk of bacteria becoming resistant.

This is particularly important for antibiotics that are used to treat both people and animals and for antibiotics that are the last line of treatment for critical infections in people.



The Antimicrobial Advice Ad Hoc Expert Group (AMEG) has categorised antibiotics based on the potential consequences to public health of increased antimicrobial resistance when used in animals and the need for their use in veterinary medicine.

The categorisation is intended as a tool to support decision-making by veterinarians on which antibiotic to use.

Veterinarians are encouraged to check the AMEG categorisation before prescribing any antibiotic for animals in their care. The AMEG categorisation does not replace treatment guidelines, which also need to take account of other factors such as supporting information in the Summary of Product Characteristics for available medicines, constraints around use in food-producing species, regional variations in diseases and antibiotic resistance, and national prescribing policies.

Category A
Avoid

- antibiotics in this category are not authorised as veterinary medicines in the EU
- should not be used in food-producing animals
- may be given to companion animals under exceptional circumstances

Category B
Restrict

- antibiotics in this category are critically important in human medicine and use in animals should be restricted to mitigate the risk to public health
- should be considered only when there are no antibiotics in Categories C or D that could be clinically effective
- use should be based on antimicrobial susceptibility testing, wherever possible

Category C
Caution

- for antibiotics in this category there are alternatives in human medicine
- for some veterinary indications, there are no alternatives belonging to Category D
- should be considered only when there are no antibiotics in Category D that could be clinically effective

Category D
Prudence

- should be used as first line treatments, whenever possible
- as always, should be used prudently, only when medically needed

For antibiotics in all categories

- unnecessary use, overly long treatment periods, and under-dosing should be avoided
- group treatment should be restricted to situations where individual treatment is not feasible
- check out the European Commission's guideline on prudent use of antibiotics in animals: https://bit.ly/2s7LUF2

AMEG is the acronym for EMA's Antimicrobial Advice Ad Hoc Expert Group. It brings together experts from both human and veterinary medicine. They work together to provide guidance on the impact on public health of the use of antibiotics in animals.

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Full AMEG report: https://bit.ly/30ZEuRi

Categorisation of antibiotic classes for veterinary use

(with examples of substances authorised for human or veterinary use in the EU)

A — AVOID

Amdinopenicillins
mecillinam
pivmecillinam

Ketolides
telithromycin

Monobactams
aztreonam

Rifamycins (except rifaximin)
rifampicin

Carboxypenicillin and ureidopenicillin, including combinations with beta lactamase inhibitors
piperacillin-tazobactam

Carbapenems
meropenem
doripenem

Lipopeptides
daptomycin

Oxazolidinones
linezolid

Riminofenazines
clofazimine

Sulfones
dapsone

Streptogramins
pristinamycin
virginiamycin

Drugs used solely to treat tuberculosis or other mycobacterial diseases
isoniazid
ethambutol
pyrazinamide
ethionamide

Other cephalosporins and penems (ATC code J01DI), including combinations of 3rd-generation cephalosporins with beta lactamase inhibitors
ceftobiprole
ceftaroline
ceftolozane-tazobactam
faropenem

Glycopeptides
vancomycin

Glycylcyclines
tigecycline

Phosphonic acid derivates
fosfomycin

Pseudomonic acids
mupirocin

Substances newly authorised in human medicine following publication of the AMEG categorisation
to be determined

B — RESTRICT

Cephalosporins, 3rd- and 4th-generation, with the exception of combinations with β-lactamase inhibitors
cefoperazone
cefovecin
cefquinome
ceftiofur

Polymyxins
colistin
polymyxin B

Quinolones: fluoroquinolones and other quinolones
cinoxacin
danofloxacin
difloxacin
enrofloxacin
flumequine
ibafloxacin
marbofloxacin
norfloxacin
orbifloxacin
oxolinic acid
pradofloxacin

C — CAUTION

Aminoglycosides (except spectinomycin)
amikacin
apramycin
dihydrostreptomycin
framycetin
gentamicin
kanamycin
neomycin
paromomycin
streptomycin
tobramycin

Aminopenicillins, in combination with beta lactamase inhibitors
amoxicillin + clavulanic acid
ampicillin + sulbactam

Cephalosporins, 1st- and 2nd-generation, and cephamycins
cefacetrile
cefadroxil
cefalexin
cefalonium
cefalotin
cefapirin
cefazolin

Amphenicols
chloramphenicol
florfenicol
thiamphenicol

Lincosamides
clindamycin
lincomycin
pirlimycin

Pleuromutilins
tiamulin
valnemulin

Macrolides
erythromycin
gamithromycin
oleandomycin
spiramycin
tildipirosin
tilmicosin
tulathromycin
tylosin
tylvalosin

Rifamycins: rifaximin only
rifaximin

D — PRUDENCE

Aminopenicillins, without beta-lactamase inhibitors
amoxicillin
ampicillin
metampicillin

Tetracyclines
chlortetracycline
doxycycline
oxytetracycline
tetracycline

Aminoglycosides: spectinomycin only
spectinomycin

Anti-staphylococcal penicillins (beta-lactamase-resistant penicillins)
cloxacillin
dicloxacillin
nafcillin
oxacillin

Natural, narrow-spectrum penicillins (beta lactamase-sensitive penicillins)
benzathine benzylpenicillin
benzathine phenoxymethylpenicillin
benzylpenicillin
penethamate hydriodide
pheneticillin
phenoxymethylpenicillin
procaine benzylpenicillin

Sulfonamides, dihydrofolate reductase inhibitors and combinations
formosulfathiazole
phthalylsulfathiazole
sulfacetamide
sulfachlorpyridazine
sulfaclozine
sulfadiazine
sulfadimethoxine
sulfadimidine
sulfadoxine
sulfafurazole
sulfaguanidine
sulfalene
sulfamerazine
sulfamethizole
sulfamethoxazole
sulfamethoxypyridazine
sulfamonomethoxine
sulfanilamide
sulfapyridine
sulfaquinoxaline
sulfathiazole
trimethoprim

Cyclic polypeptides
bacitracin

Steroid antibacterials
fusidic acid

Nitroimidazoles
metronidazole

Nitrofuran derivatives
furaltadone
furazolidone

Other factors to consider

The **route of administration** should be taken into account alongside the categorisation when prescribing antibiotics. The list below suggests routes of administration and types of formulation ranked from the lowest to the highest estimated impact on antibiotic resistance.

- Local individual treatment (e.g. udder injector, eye or ear drops)
- Parenteral individual treatment (intravenously, intramuscularly, subcutaneously)
- Oral individual treatment (i.e. tablets, oral bolus)
- Injectable group medication (metaphylaxis), only if appropriately justified
- Oral group medication via drinking water/milk replacer (metaphylaxis), only if appropriately justified
- Oral group medication via feed or premixes (metaphylaxis), only if appropriately justified

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Full AMEG report: https://bit.ly/30ZEuRi

FURTHER READING

- https://animalhealthireland.ie/programmes/cellcheck/farm-guidelines/
- https://animalhealthireland.ie/assets/uploads/2022/01/CellCheck-Prudent-Prescribing-2022-FINAL.pdf?dl=1
- http://www.hpra.ie/homepage/veterinary/special-topics/antibiotic-resistance
- https://www.bva.co.uk/take-action/our-policies/responsible-use-of-antimicrobials/
- https://animalhealthireland.ie/assets/uploads/2022/01/CellCheck-Prudent-Prescribing-2022-FINAL.pdf?dl=1
- https://www.ema.europa.eu/en/documents/report/infographic-categorisation-antibiotics-use-animals-prudent-responsible-use_en.pdf

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2. McDougall S, Williamson J, Gohary K, Lacy-Hulbert J. Detecting intramammary infection at the end of lactation in dairy cows. J Dairy Sci. 2021;104(9):10232-10249. doi:10.3168/jds.2020-20036
3. Swinkels JM, Leach KA, Breen JE, *et al*. Randomized controlled field trial comparing quarter and cow level selective dry cow treatment using the California Mastitis Test. J Dairy Sci. 2021;104(8):9063-9081. doi:10.3168/jds.2020-19258
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5. Barrett, D.J., Healy, A.M., Leonard, F.C. *et al*. Prevalence of pathogens causing subclinical mastitis in 15 dairy herds in the Republic of Ireland. Ir Vet J 58, 333 (2005). https://doi.org/10.1186/2046-0481-58-6-333

Reader Questions and Answers

WHICH OF THE FOLLOWING STATEMENTS ARE FALSE?

1. PRUDENT PRESCRIBING IS:

- **A.** The practice of prescribing all medicinal products by a veterinary practitioner as evidenced by clinical records.
- **B.** Based on a diagnosis made following a clinical examination by a prescribing veterinary practitioner.
- **C.** Not taking into account either animal level or farm level information when a prescription is issued.
- **D.** The consideration of route of administration alongside categorisation to minimise the impact of antimicrobial resistance.

2. JUSTIFICATION FOR A VETERINARY PRESCRIPTION BY A VETERINARY PRACTITIONER CAN BE?

- **A.** Demonstrated following a clinical examination by the prescribing veterinary practitioner.
- **B.** Best outlined in a Client-Patient-Practice relationship (CPPR).
- **C.** Carried out by a referring or newly appointed veterinary practitioner clinically examining animals prior to advising on or prescribing a medicinal product.
- **D.** Carried out without establishing either a bona fide relationship with a farmer or sophisticated knowledge of individual animals on a farm.

3. ANTIMICROBIAL METAPHYLAXIS...

- **A.** Is the administration of a product at the same time to a group of clinically healthy (presumed non infected) animals in contact with sick animals?
- **B.** Is justified as a basis for treatment on a prescription.
- **C.** Can be used to prevent development of clinical signs and prevent further spread of disease.
- **D.** Can be justified on the basis of clinical examination of a group of animals where there is no need of treatment.

4. THE CATEGORISATION OF ANTIBIOTICS FOR USE IN ANIMALS

- **A.** Is based on consequences to public health of increased antimicrobial resistance.
- **B.** Is regularly reviewed by an expert group within European Medicine Agency (EMA), Antimicrobial Advice Ad Hoc Expert Group (AMEG).
- **C.** Examines critically important antibiotics only.
- **D.** Consists of four categories: Avoid, Restrict, Caution and Prudence.

5. RESPONSIBLE USE OF ANTIMICROBIALS

- **A.** Means as little as possible and only as much as necessary.
- **B.** Reduces spread of antimicrobial resistance in a One Health environment.
- **C.** Consists of the right diagnosis, right animal, right medicine, right amount and right duration with right storage and disposal.
- **D.** Involves treatment of an animal not in adherence with label instructions.

ANSWERS: 1C; 2D; 3D; 4C; 5D.