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ANTIBIOTIC GUIDELINES, TRAFFIC LIGHT SYSTEM AND VETERINARY ANTIBIOTIC USE CARDS FOR ANIMALS IN BHUTAN

PRESERVING THE EFFICACY OF ANTIBIOTICS

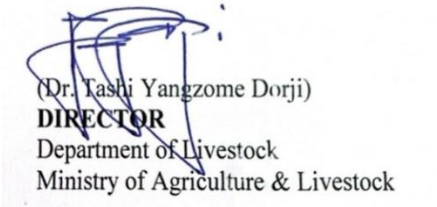
FOREWORD

Throughout history, infectious diseases have been a major threat to human and animal health and was a prominent cause of morbidity and mortality. The introduction of antimicrobial agents in the 1930s and 1940s revolutionized human medicine by substantially reducing morbidity and mortality rates from bacterial diseases. However, it was soon observed that bacteria became resistant to antibiotics, and resistant strains emerged shortly after the introduction of every new antimicrobial. The emergence and spread of antimicrobial resistance associated without the discovery of novel antimicrobial agents has resulted in a major medical challenge and a serious public health problem.

The spread of antimicrobial resistance does not respect phylogenetic or ecological borders. Animal-to-human transmission of resistant pathogenic bacteria can occur by various means including food and water supply as well as direct contact with animals or manure. Mobile genetic elements harbouring resistance genes can be easily transferred between bacteria from terrestrial animals, fish and humans. Furthermore, resistance genes and resistant bacteria can spread across geographical boundaries through movement of people, animals and food.

Antimicrobial resistance in human and 'non-human' environments are interdependent on a global scale and growing scientific evidence indicates that it is negatively impacted by both human and animal antimicrobial usage. Consequently, when addressing the problems of antimicrobial resistance, one has to take a global and holistic approach that embraces different sectors and ecological niches. Recognizing the importance of antimicrobial agents in both human and animal health and the need to preserve their efficacy being an important aspect in the veterinary profession, the Antibiotic Guideline for Animals was prepared adopting the principles of evidence-based medicine. This guideline and veterinary antibiotic use cards can be used in conjunction with National veterinary formulary and Standard Treatment Guidelines.

We are hopeful that this guideline will provide the required information for prescribing the antimicrobials to the veterinarians and para-professionals in their routine animal health activities.



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Contents

1. Introduction

Antibiotic treatment guidelines for veterinary medicine provide essential recommendations to ensure the responsible and effective use of antibiotics in animals. These guidelines aim to optimize therapeutic outcomes, safeguard animal health and welfare, and mitigate the risk of antimicrobial resistance. They emphasize accurate diagnosis, the selection of appropriate antibiotics, correct dosing, and adherence to withdrawal periods in animals. By promoting evidence-based practices, these guidelines support sustainable veterinary care while protecting public health.

Antibiotics, also called antibacterial, are a type of antimicrobial medicines used in the treatment and prevention of bacterial infections. Antibiotics can be individually administered to animals to treat (therapy) or prevent (prophylaxis) disease. At therapeutic doses, antibiotics which prohibit the bacterial growth are classified as “bacteriostatic drugs”, and those that directly kill bacteria are classified as “bactericidal drugs”.

Antibacterial can also be administered to clinically healthy animals belonging to the same flock, pen or herds and animals with clinical signs (metaphylaxis) and is typically used during disease outbreaks in animals including aquaculture and poultry. In metaphylaxis, infections are treated before their clinical appearance and the treatment period is usually shorter than for therapeutic treatment.

Systemic antibiotics treatment can be administered orally, (through medicated feed or water) or by parenteral injections as an initiation of antibiotic treatment.

Local antibiotic treatment includes intramammary infusion, intrauterine treatment and topical treatment such as skin, ear and eye treatment.

With regard to farmed fish, antibiotic treatment is almost always administered by medicated feed, although some brood stock may be treated individually by injection or immersion.

2. Antibiotics in food-producing animals

Antibiotics are widely used in food-producing animals and this has contributed to the emergence of antibiotic-resistance in bacteria in food-producing animals. These resistant bacteria can contaminate the foods that come from those animals, and persons who consume these foods can develop antibiotic-resistant infections.

There is substantial evidence that antibiotic use in food-producing animals can have an adverse impact on public health through the following sequence of events:

- Inappropriate use of antibiotics in food-producing animals allows antibiotic-resistant bacteria to thrive while judicious use of antibiotics suppresses Antimicrobial Resistance (AMR) development. Resistant bacteria can be transmitted from food-producing animals to humans through consumption of animal products.
- Resistant bacteria from food producing animals can cause infections in humans; and
- Infections caused by resistant bacteria can result in adverse human health consequences.

Because of the link between antibiotic use in food-producing animals and the occurrence of antibiotic-resistant infections in humans, it is encouraged to put the following basic principles to minimize inappropriate use of antibiotics in animals:

1. *Herd management and size:* Small, closed breeding and finisher herds, tend to perform better in terms of disease control and overall animal health compared to larger farms. This is primarily due to the increased focus on individual animal care and stricter biosecurity measures, which help reduce the need for antibiotic use. Encouraging such practices can minimize the risk of inappropriate antibiotic use;

2. *Mixing of animals from different sources should be avoided:* animals from different sources should not be mixed. Implementing a three-site production system—separating breeder sites, nursery sites, and finishing sites into distinct facilities—can enhance biosecurity and improve health outcomes.

3. *Population density:* Increased density in pens or barn is linked to increased stress and disease transmission resulting in higher mortality and reduced growth;

4. *Weaning age*: Weaning age plays a significant role in minimizing the development of antibiotic resistance in animals by influencing their overall health, immune system development, and disease susceptibility.

5. *Housing environment:* Appropriate housing and environmental management for disease prevention; and

6. *Herd/population immunity:* Protection via natural or induced immunity to control disease via vaccination.

7. *Biosecurity measures:* Improved biosecurity measures to prevent disease.

8. *Community engagement:* Raising awareness among farmers and animal owners about the judicious use of antibiotics, adherence to withdrawal periods, proper record-keeping of antibiotic usage, controlled use of antibiotics for prophylaxis and improved biosecurity to minimize the antibiotic resistance.

9. *Adhere to prescribed withdrawal periods.* Strictly following the antibiotics withdrawal periods in food animals.

3. Antibiotics as growth promoters in food-animals

For over 30 years, supplementing animal feed with antibiotics to promote growth has been a widespread practice, accounting for more than half of global antimicrobial use. These antibiotics helped improve feed conversion, boost animal growth, and reduce morbidity and mortality from both infectious clinical and subclinical diseases. However, growing evidence has shown a clear link between the use of antibiotics in animals and the development of resistance in both animals and humans. As a result, the use of antibiotics as growth promoters is increasingly discouraged in animal production, given the significant public health risks posed by antibiotic resistance. This shift underscores the need for alternative methods, such as improving animal welfare, nutrition, and disease prevention strategies, to ensure sustainable and safe livestock production without relying on antibiotics for growth enhancement.

4. Rational use of Antibiotics

In order to minimize the possible impact of antibiotic usage on public and animal health, various international organizations such as the WHO, WOAH, FAO and the EU Commission have in recent years emphasized the importance of prudent and rational antibiotic use in animals.

These organizations have emphasized to a greater extent that the prudent antibiotic use is important, not only to safeguard the efficacy of antibacterial drugs in veterinary medicine but, even more so, to prevent the emergence and spread of undesirable antibiotic-resistance phenotypes of zoonotic bacteria as well as in commensal bacteria that can be transmitted between animals and humans.

Following guidelines should be followed for the responsible use of antibiotics in animals

4.1 Efficient management

Antibiotics are not a substitute for good management and hence, it should be aimed to reduce infection in farms and pet animals.

Encourage vaccination to prevent disease in the first place and involve hygiene and Infection Prevention Control (IPC) procedures, biosecurity measures, management improvements including stocking density, nutrition, record keeping, etc.

4.2 Avoid inappropriate use

Antibiotics should only be used when it is known or suspected that an infectious agent is present which is susceptible to the antibiotics selected. Limit antibiotic treatment to ill or at-risk animals only. Successful treatment relies on the correct administration of antibiotics. The competent user should follow the manufacturers' instructions or guideline on the route of administration, dose, dose frequency, duration of treatment, handling, storage, withdrawal periods and labelling etc. Above all, emphasis should also be in avoiding under-dosing and also completing the course of treatment.

4.3 Choose the right antimicrobials

Wherever possible, antibiotic use should be guided by an accurate diagnosis preferably based on microbial identification. While treatment may initially be commenced based on clinical diagnosis, the sensitivity of the suspected causative organisms should be determined. This ensures that, if the initial treatment fails, it can be adjusted according to the results of susceptibility testing.

4.4 Monitor antimicrobial sensitivity

Clinical diagnosis is often the initial basis for treatment; however, bacterial culture and sensitivity tests must be performed whenever possible to change to the most sensitive antimicrobials.

4.5 Minimise use

The prophylactic use of antibiotics is never a substitute for good management. Use antibiotics only when animals are at risk and or when there is evidence that usage reduces morbidity and/or mortality in the animals.

4.6 Good Record keeping

Proper records of treatment and the outcome of treatment are also essential to evaluate the effectiveness of treatments. Historical information, including laboratory sensitivity data, is valuable in deciding on future treatments. Hence, a proper and accurate record of the antibiotic usages should be maintained.

4.7 Report of treatment failures

Treatment failure may be the first indication of resistance to an antibiotic. It is essential therefore, that each and every suspected failure be reported to the concerned focal persons/agency.

4.8 Restriction of use of Fluoroquinolones and third/fourth generation Cephalosporins

These two classes of antibiotics are considered to be critically important both for human and animal health and hence should be used as recommended below:

- Not to be used as preventive treatment applied by feed or water in the absence of clinical signs in the animals to be treated.
- Not to be used as a first line treatment unless technically justified.
- Since these antibiotics are last-resort antibiotics for combacting the severe bacterial infections and infections caused by multi-drug resistant bacteria, over use and misuse of these antibiotics will lead to selection of the resistant bacterial strain.
- *Extra label use* of Fluoroquinolones and Cephalosporins should be limited and used only when no alternatives are available.

5. Specific antibacterial

5.1 Aminoglycosides

Aminoglycosides are amongst the most rapid bactericidal medicines available for treatment of aerobic gram-negative sepsis. They have demonstrated safety as empirical treatment in severe infection. Gentamicin is the aminoglycoside of choice where approximately 95% or more of aerobic gram-negative isolates are susceptible.

Aminoglycosides are administered IM or SC for systemic infections as they are not absorbed from the GI tract.

All aminoglycosides are potentially ototoxic and nephrotoxic. Clinically significant adverse effects are more likely with advancing age, pre-existing renal impairment or hearing loss.

Aminoglycosides like Gentamicin shall not be recommended in dairy cattle due to its extremely long withdrawal periods.

Preparations available in EVDL: Gentamicin, Amikacin and Streptomycin.

5.2 Beta-lactams

Beta-lactams are broad spectrum antibiotics highly effective against both gram-positive and gram-negative bacteria. They are widely used in the treatment of various infections, including respiratory, skin, and soft tissue infections. Penicillin are beta-lactam of choice for infections caused by *Streptococcus* and other susceptible gram-positive bacteria, while broader-spectrum agents, such as cephalosporins and carbapenems, are utilized for more resistant infections.

Beta-lactams are primarily administered orally or intravenously, depending on the drug and the severity of the infection, as they are well absorbed from the GI tract. The efficacy is dependent on maintaining drug concentrations above the minimum inhibitory concentration (MIC) for a sufficient duration.

While generally well-tolerated, beta-lactams can cause allergic reactions, ranging from mild rashes to severe anaphylaxis. Cross-reactivity may occur among subclasses, particularly penicillins and cephalosporins. Beta-lactams are not used in certain species (e.g., small herbivores like rabbits and guinea pigs) due to the risk of subsequent enterotoxemia.

Preparations available in EVDL: Cephalosporins and Penicillins

5.3 Cephalosporins

Most cephalosporins are unstable in gastric acid and must be given IM or IV except for Cephalexin and cefadroxil, cefachlor, and cefixime. Cephalosporins are distributed in the extracellular fluid and penetrate body tissues except the cerebrospinal fluid (CSF). Cephalosporins are considered among the safest antibiotics in veterinary medicine but may still cause some adverse effects. Hypersensitivity reactions, including cross-reactivity with penicillins, occur in less than 10% of cases, and anaphylaxis is rare. Gastrointestinal side effects such as diarrhea, nausea, and abdominal discomfort may occur. Renal toxicity is uncommon but requires caution in animals with pre-existing renal impairment. Prolonged use may lead to

reversible hematologic effects like neutropenia or thrombocytopenia. Ceftriaxone, a commonly used cephalosporin, can occasionally cause biliary sludging, especially in neonates. While these side effects are rare, careful monitoring and appropriate dosing are essential to ensure safe and effective use in veterinary practices.

5.3.1 First generation cephalosporins

They are effective against gram-positive aerobes and ineffective against many gram-negative aerobes.

Preparations available in EVD: Cephalexin

5.3.2 Second generation cephalosporins

This group has a broader spectrum of activity than the first generation and has good coverage for gram-negative bacteria compared to gram-positive bacteria. However, they are not widely used in veterinary medicine.

Preparations available in EVDL: Cefuroxime

5.3.3 Third generation cephalosporins

They have an extended spectrum of action against gram-negative organisms, and have limited activity against gram positive cocci. The third generation cephalosporins are resistant to β-lactamases, and penetrate the blood–brain barrier.

Preparations available in EVDL: Cefotaxime and Ceftriaxone

5.4 Penicillins

Penicillins are a widely used class of beta-lactam antibiotics in veterinary medicine due to their broad efficacy and low toxicity. Many Penicillins are broken down by gastric HCl and are thus poorly absorbed orally. The distributions of Penicillins are confined mostly to the extracellular spaces, but clinically effective concentrations in most tissues occur except for the CNS, bones, prostate, and eye.

Penicillins are generally administered IM except for the acid-stable Penicillins which are administered orally.

Penicillin allergies, though uncommon in animals, can be severe, causing symptoms like skin eruptions, angioedema, and anaphylaxis, especially in cattle. Cross-reactivity with other beta-

lactams may occur. Procaine penicillin should be avoided in poultry due to their sensitivity to procaine, which can lead to neurotoxicity or fatal reactions. Other adverse effects include gastrointestinal upset in small animals and superinfections caused by overgrowth of resistant organisms during prolonged use. Resistance to penicillins is commonly due to beta-lactamase enzymes that degrade the antibiotic, reducing its efficacy. The details of different formulations are described in table 1.

5.4.1 Narrow spectrum Penicillins

These are mainly active against gram-positive organisms but are inactivated by beta-lactamases. Benzathine penicillin is given IM and provides low levels of Benzyl penicillin for up to 4 weeks. Benzyl penicillin (Penicillin G) is administered parenterally and remains the treatment of choice for susceptible infections.

Procaine penicillin is an IM preparation designed to extend the half-life of Benzyl penicillin. It provides blood levels for up to 24 hrs, but these are effective only against highly susceptible organisms.

Table 1 Various formulations of Penicillin with use

Formulation	**Duration of Action**	**Clinical Use**	**Limitations**
Benzyl Penicillin (Penicillin G)	Short (hours)	Treatment of acute gram-positive infections (e.g., mastitis, pneumonia)	Inactivated by beta-lactamases, must be administered parenterally
Benzathine Penicillin	Up to 4 weeks	Long-term treatment of chronic infections or prophylaxis	May not reach effective concentrations in some tissues
Procaine Penicillin	Up to 24 hours	Treatment of acute infections	Not suitable for poultry, limited duration of action

5.4.2 Moderate spectrum Penicillins

These Penicillins have greater activity against some gram-negative organisms than narrow spectrum but are destroyed by beta-lactamase producing strains. They have no anti-pseudomonal activity.

Preparations available in EVDL: Benzathine penicillin, Strepto-penicillin, Amoxycillin, Ampicillin, Ampicillin-cloxacillin and Procaine penicillin G.

5.5 Chloramphenicol group

Chloramphenicol is a broad-spectrum antibiotic with a range of activity that includes Gram-positive and Gram-negative bacteria, rickettesiae and chlamydiae. Chloramphenicol is not allowed for use in food-producing animals because of the potential danger of residue-induced toxicity in humans.

Chloramphenicol is rapidly absorbed from the GI tract and widely distributed to all tissues including the CNS and eye. Chloramphenicol is administered orally, IM, IV, or SC every 6–8 hrs to dogs, birds, or horses and every 12 hrs to cats.

Dose-related anaemia may occur in animals. Anorexia and diarrhoea may occur especially in cats with high or prolonged dosage. Chloramphenicol use is restricted to topical application.

Preparations available in EVDL: Chloramphenicol ointment

5.5 Macrolides

Macrolides are bacteriostatic agents. They are active primarily against gram-positive aerobes and anaerobes and Mycoplasma spp.

Macrolides are effectively absorbed when administered orally. Oral preparations are protected from gastric acid destruction through enteric-coated formulations or the use of stable, esterified salts. As weak organic bases, macrolides exhibit wide distribution throughout the body, except in the central nervous system (CNS). Macrolides tend to concentrate in acidic environments, such as respiratory secretions, milk, and leukocytes.

Common side effects of oral dosing include mild GI upset, and pain and irritation at IM injection sites.

Preparations available in EVDL: Erythromicin

5.6 Nitrofurans

They are broad spectrum and bacteriostatic agents. Nitrofurans may not be used in food-producing animals (including topically) because they have been shown to be potential carcinogens in laboratory animals.

Preparations available in EVDL: Nitrofurazone

5.7 Nitroimidazoles

Nitroimidazoles are bactericidal agents and act against most obligate anaerobes and are active against protozoa, including Giardia and Trichomonas Spp. Metronidazole is well absorbed orally and widely distributed, including the CNS.

Metronidazole is administered orally twice a day in dogs, cats, and horses. High or prolonged dosage may produce neurotoxicity with signs that include nystagmus, ataxia, and seizures.

Preparations available in EVDL: Metronidazole

5.8 Quinolones

Quinolones are broad-spectrum antibacterial agents that exert their bactericidal activity by inhibiting bacterial DNA topoisomerase II (also known as DNA gyrase). This enzyme is essential for DNA replication, transcription, and repair, making quinolones highly effective against a wide range of bacterial pathogens

Preparations available in EVDL: Enrofloxacin and Ciprofloxacin.

5.9 Sulfonamides and trimethoprim

Sulfonamides are bacteriostatic agents that inhibit bacterial growth by interfering with folic acid synthesis. Sulfonamide competitively inhibits the enzyme dihydropteroate synthase, which is essential for folate production. This disruption leads to folic acid deficiency, impairing critical cellular processes and ultimately causing damage to bacterial cells

Trimethoprim is synergistic with sulphonamides.

Preparations available in EVDL: Sulfadimidine, Sulfadiazine and trimethoprim, Sulfanilamide and Sulphamethoxazole

5.10 Tetracyclines

Tetracyclines have a broad-spectrum activity, which includes Gram positive and Gram negative bacteria, Chlamydia, Rickettsia, Mycoplasma, Spirochetes, some non-tuberculous mycobacteria and some protozoa. They are usually bacteriostatic. They have good tissue penetration but do not enter CSF.

Tetracyclines are administered orally or IV every 8–24 hrs. IM injections produce pain, irritation, and sterile abscesses unless special buffered solutions are used. Oral therapeutic doses should be avoided in adult ruminants and used with caution in horses because of the danger of disrupting ruminal or colonic microflora, respectively. Side effects include permanent staining of unerupted teeth in young animals. Oral Tetracyclines should not be used with herbivores because of serious effects on ruminant digestion.

Preparations available in EVDL: Tetracycline, Oxytetracycline and Doxycycline

5.11 Peptides

Peptides are antibacterial agents which exert action by inhibiting bacterial cell wall synthesis. Clinical use of this drug is limited by their toxicity. The toxicity of peptide-based antibiotics significantly limits their systemic use in animals, particularly in food-producing species, due to the potential impact of residues on human health. Polymyxins, such as colistin, are known to cause nephrotoxicity and neurotoxicity, especially when administered at higher doses, making careful dosing essential to minimize these adverse effects. Additionally, the topical application of peptide antibiotics can lead to local tissue reactions, including irritation or hypersensitivity at the application site. In food animals, residue issues are a critical concern, necessitating strict adherence to withdrawal periods to ensure that harmful residues do not remain in meat, milk, or eggs intended for human consumption.

Preparations available in EVDL: Colistin, Vancomycin

6. Ideal Antibiotic & Choice of Antibiotics

For the treatment of a bacterial infection, the antibacterial agent selected must have activity against the causative pathogenic microorganism and must attain effective concentrations at the site of infection.

An Ideal Antibiotic

1. Bacteria should not develop resistance to that drug.
2. Should be effective in presence of body fluids and exudates.
3. Bactericidal levels of the drug should reach blood, tissue and CSF immediately and remain maintained for a long period of time.
4. Should be non-toxic.
5. Should be excreted in urine.
6. Should exhibit selective and effective antimicrobial activity.

7. Should be bactericidal rather than bacteriostatic.

Choice of Antibiotic

When an antibacterial is indicated, the choice should be based on factors such as

1. Identification of the infecting organism and its known or potential susceptibility
2. Host factors
3. Age – especially be cautious of extremes of age
4. Species – different species will have different dose and administration requirements.
5. History of previous antibiotic exposures and hypersensitivities
6. Genetic or metabolic abnormalities
7. Pregnancy
8. Hepatic and renal functions
9. Immune status
10. Site of infections
11. Safety including adverse reactions and drug interactions,
12. Previous clinical experience,
13. Cost
14. The potential for selection of resistant organisms and
15. The associated risk of super-infection.

An adequate history of previous adverse reactions to drugs may prevent the inadvertent administration of an antimicrobial drug to which the animal is allergic. A failure to do so can have serious (and sometimes fatal) consequences.

7. Correct Dosage and Route of Administration

The dose selected should result in adequate therapeutic concentrations at the site of infection without causing side effects or toxicity. In practice, the recommended dose should be used. In veterinary practice, there are two common drug routes: oral administration and parenteral (Intravenous, Intramuscular and subcutaneous). Other less common routes are topical (ointment/spray) or intra-mammary/ intra-uterine insertion.

7.1 Recommended dose is one that will give blood and tissue levels, which will be effective against very susceptible organisms, with minimal side effects to the host.

7.2 Intravenous route administered antibiotics attain high and immediate blood and tissue levels and this route should be used in the treatment of septicemia and other life threatening/chronic diseases. The concentrations obtained are much higher than those obtained with equivalent doses of the same drug given intramuscularly or orally, and consequently greater diffusion concentrations are achieved at sites of infection. The intravenous route is used for low-concentration high volume antimicrobial agents such as Sulphamethazine and Oxytetracycline. Drugs specifically formulated for intravenous administration use should be used. Severely toxemic terminal cases may die immediately following injections.

7.3 Intra-muscular route Intra muscular injection is the most commonly used method in large animals. Where possible this route should be avoided in meat-producing animals, especially with irritant preparations.

Advantages: Easy to treat individual animals. High absorbance rates and therefore are suitable in cases that drugs need to exert their effects early and fast. Absorbance rates depend on injection methods, usually IV (intravenous) > IM (intramuscular) > SC (subcutaneous).

Disadvantages: The application is more complicated than oral administration. It requires proper techniques for animal restraint and injection. Criteria such as hygiene or sterilization are necessary to ensure that infection or inflammation does not occur due to the injection process.

7.4 Oral route is generally restricted to pre-ruminant animals, young foals and pigs. Thus, this method is the easiest method for administration and where the cost of revisits is a significant consideration; this route is often chosen for continuing medication, as it is within the capability of any owner. In general, systemic infections are better treated by parental route.

Advantages: This is an easy and safe drug application route. In addition, it is the most convenient way when animals are raised in large numbers, such as in industrial farms.

Disadvantages: Slow effects, and therefore not suitable in acute diseases.

Note: Orally administered antibiotics are particularly used as prophylactic to prevent diseases for ruminants. Microbial activities play an important role in their digestion and oral antibiotics might affect the microbial ecology and cause digestive disorders. Therefore, this route is usually applied only when ruminants are milk-fed, such as for cattle that are less than six months old.

8. Duration of Treatment

As a rule of thumb, antibiotic therapy should be continued for 3-5 days and the treatment should continue for 1-2 days after the resolution of clinical signs. Chronic infections, skin infections, osteomyelitis, infections in immuno-suppressed animals, and infections with intracellular pathogens often require longer treatment periods and as a general rule treatment should continue for 1-2 weeks beyond resolution of clinical signs. Recommendations on treatment duration are given in more detail in the disease-specific and species specific treatments. It is also important that treatment is not continued longer than necessary to avoid unnecessary use of antibiotics.

9. Antibiotics in pregnant animals

There is no drug or medicine that can be called safe during pregnancy. Hence, the use of antibiotics should be done cautiously in pregnant animals especially metronidazole. However, Penicillins, Cephalosporins and Erythromicins are considered safe to be used in pregnant animals. Certain antibiotics are considered unsafe during pregnancy due to potential risks to the developing fetus. Metronidazole should be avoided, especially during the first trimester, as it can have teratogenic effects in species like dogs and cats. Tetracyclines (e.g., doxycycline, tetracycline) are unsafe, particularly during the second and third trimesters, as they can cause tooth discoloration and inhibit bone growth in the fetus. Aminoglycosides (e.g., gentamicin, amikacin) are also unsafe due to the potential for ototoxicity and nephrotoxicity in the developing fetus. Fluoroquinolones (e.g., enrofloxacin, ciprofloxacin) may damage cartilage and adversely affect fetal development, particularly during early pregnancy. Lastly, sulphonamides (e.g., sulfadiazine, trimethoprim-sulfamethoxazole) can cause folic acid deficiency, which negatively impacts fetal development, especially when used in high doses or during early pregnancy. These antibiotics should only be used in pregnant animals if absolutely necessary and under strict veterinary supervision to prevent the congenital malformations.

10. Anti-Microbial Resistance (AMR)

Antimicrobial resistance (AMR) is resistance of a microorganism to an antimicrobial medicine to which it was originally sensitive. Resistant organisms (bacteria, fungi, viruses and some parasites) are able to withstand the attack by antimicrobial medicines. Hence, the standard treatments become ineffective, infections persist increasing risk of spread to others. The evolution of resistant strains is a natural phenomenon that happens when micro-organisms are exposed to antimicrobial drugs, and exchange of resistant traits occurs between certain types of bacteria. Over-use and misuse of antimicrobial medicines accelerates this natural phenomenon. Poor infection control practices encourage the spread of AMR. The misuse of antibiotics in veterinary practice can occur in several ways, including buying, selling, and using antibiotics without proper prescriptions or instructions. Additionally, antibiotics are sometimes used for inappropriate purposes, such as for growth promotion or disease prevention, rather than for treating specific infections. Misuse also involves using antibiotics to treat viral infections, administering incorrect doses, applying the wrong administration routes, and failing to observe proper withdrawal periods for animal products, leading to the collection of products earlier than allowed. Furthermore, antibiotics may be wrongly prescribed, such as when they have no effect on the pathogenic bacteria involved, or when they are improperly combined or overused when not necessary. Such practices contribute to the development of antibiotic resistance, and resistant bacteria can spread through the environment, particularly in farms with poor biosecurity measures.

10.1 Mechanism of resistance

- Production of inactivating enzymes. Eg., b-lactamase enzyme hydrolyses Penicillins and renders it inactive.
- Transferase enzymes inactivate amino-glycosides.
- Changes in permeability or drug uptake.
- Changes in structure of receptors or the target molecules. Such changes include ribosomal components with which the antibiotics interact. Eg., Erythromicin
- Development of alternative metabolic pathways. Eg., Sulphonamides inhibit dihydrofolate synthetase enzyme thus dihydrofolic acid is inhibited.
- Changes in structure of target enzymes may decrease the drug affinity.
- Exchange of antimicrobial resistance genes among the organisms.

10.2 How to avoid resistance

- Avoiding indiscriminate use.
- Start the therapy as early as possible.
- Follow the recommended dosage, route of administration and length of treatment even if the animal seems to get better.
- Avoid Concurrent therapy with two or more antibacterial agents.
- Store unused antibiotics as recommended by producers and adhere to expiry dates.
- Ensure appropriate disposal of unused antibiotics avoiding any potential environmental contamination with residue.
- Treatment should be based on culture and sensitivity as far as possible, especially in cases of suspected treatment failure or multiresistant organisms.

11. Withdrawal Period (WP)

Withdrawal periods is the time necessary for an animal to metabolize an administered drug and the amount of time necessary for the drug concentration level in the tissues to decrease to a safe, acceptable level. The normal range of withdrawal period for food animals for meat ranges from 0-60 days. There are different withdrawal periods for different drugs and are mentioned in the table against each antibiotic.

The withdrawal period in food animals is necessary to curb the antibiotic residues in food which might result in adverse health effects for humans and antimicrobial resistance development. Withdrawal periods should be strictly followed in food animals. The antibiotic residues on food products are being regulated by Bhutan Food and Drug Authority (BFDA) for the public safety concerns.

12. Uses of Antibiotics in animals

With the recent development of AMR, the use of antibiotics in animals should be prudent and judicious. The use of antibiotics can be minimized by good management practices like vaccination and good biosecurity. However, the antibiotics are used for following reasons in animal:

12.1 Therapeutic use Antimicrobials are used for treatment of diseases. The infected animals receive a course of antibiotics, which usually involves high doses for a relatively short period of time.

12.2 Non-therapeutic use

12.2.1 Growth promoters The use of growth promoters is characterized by administration of very low-dose of antibiotics on a regular basis, mostly over a lifetime of the food-producing animal and is given through feed to increase growth-rate and productivity. Studies have revealed that use of antibiotics in feed as growth promoters is one of the sources of AMR and hence, **Bhutan doesn't permit the use of antibiotics in feed.**

12.2.2 Prophylactic and metaphylactic use The use of antibiotics in animals that are not clinically ill but are at high risk of getting infection. For example, animals are administered antibiotics before surgery, during viral infections, transportation of animals and dry cow therapy to combat infection. Prophylactic use of antibiotics can be a substantial aid in the control and prevention of diseases in animals, however, the use of antibiotics should never be a replacement for good management practices, as the use will eventually lead to resistant development. Surgical prophylaxis should only be used in documented high risk scenarios and not to replace good surgical sterility.

13. Usage of Antibiotics in Post-operative care in animals

The use of antibiotics after surgery should not be a substitute for a poor surgical environment. Hence, the recommendation is to use the antibiotics prior to surgery and continue after surgery. However, antibiotics are recommended for the surgical procedure which takes more than 90 minutes. For elective orthopaedic surgeries, bowel surgeries and periodontal surgeries; the recommended antibiotics are Penicillin G, Ampicillin, and Amoxicillin and if anaerobes are suspected metronidazole can be administered. However, the use of post-operative antibiotics should not be a substitute for a poor surgical environment.

14. Regulation

Use of antibiotics in the animal feed and also food products of animal origin are regulated by Bhutan Food and Drug Authority (BFDA). Antibiotics for therapeutic purposes are regulated by BFDA under the Bhutan Medicines Act 2003 and Bhutan Medicines Rules and Regulations 2019.

15.Traffic light system and veterinary antibiotic use cards

Development of antimicrobial resistance (AMR) in infectious organisms such as bacteria, fungi, viruses and parasites is a complex global health challenge. AMR is largely driven by use of antimicrobials in human health, animal health and up to some extent agriculture. The cause of AMR is mainly through non-judicious use of antimicrobials by the end users. Efforts to safeguard the precious antimicrobials have become ever so important as there is fewer discovery of new antimicrobial agents. The ideal solution to combat AMR is through adoption of various antimicrobial stewardship (AMS) programmes. One of the important AMS strategies is the development and implementation of standard treatment guidelines which are aimed at reducing the irrational prescription of antimicrobials by guiding best practices. The Centre for disease control and prevention (CDC), US department of Health and Human services has recommended 12 critical steps to prevent AMR in a healthcare setting, one among which is also through implementation of treatment guidelines. In Bhutan, the prescription of veterinary drugs including antimicrobials is guided by the Standard Treatment Guidelines (STG) and the Antimicrobial Guidelines for Livestock (AGL). These guidelines were developed in 2017 by the department of Livestock and distributed freely to all the relevant stakeholders. Generally, it is found that hard bound and bulky guidelines are not ideal for end users due to various issues that come with it. Therefore, in recent times, more focus has been given to simplify the guidelines along with inclusion of infographics as much as possible. Prescription cards or booklets provide a condensed and to-the-point reference, focusing on the most critical aspects of antimicrobial prescribing. This brevity ensures that healthcare professionals can quickly access the necessary information without getting lost in lengthy documents. They are more user-friendly and can be easily carried in the pockets or kept in accessible places for quick reference thus leading to greater uptake by the end-users.

With the help of the Fleming fund project, we have developed the antimicrobial prescription cards for selected livestock species and pet dogs. For Bhutan, these animals are priority species since they receive frequent antimicrobial treatment compared to other species. They also have greater significance in terms of the risk through which residues and resistant pathogens can spread through the food chains and direct contact with their human owners. The antimicrobials in the guideline cards are based on the WHO (AWaRe and traffic light system) and WOAH classification and mostly follow standard recommendations. The guideline cards have been adopted from the Australian Veterinary Prescribing Guidelines but based on the existing regulations, resource availability and practices in Bhutan.

16. Scope

This document is intended to guide the field veterinary clinicians (veterinarians and Para veterinary professionals) in the selection and prudent use of veterinary antimicrobials especially, the critically important antimicrobials for human health. It can also be used as reference for teaching or training of veterinary students in the country who will be engaged in prescribing antibiotics in the future. Relevant information on the WHO and WOAH (previously OIE) classification of antimicrobials, are also included in this document to provide the basic concept required to understand the importance of such classifications and the need to safeguard the critically important antimicrobials.

17. Objective

- Provide easily accessible guide on important antimicrobials used in animals to field veterinarians and para-veterinary professionals in Bhutan to encourage judicious prescription of antibiotics.
- Prevent use of certain antimicrobials in food animals that are known to carry risks of transmission of resistance and antibiotic residues to humans through the animal food sources.
- Limit the use of important antimicrobials for human health which are also used in animals in order to safeguard their efficacy.

18. WHO antimicrobial classification system

(Ref: List of critically important antimicrobial for human medicine, 6th revision, 2018)
https://apps.who.int/iris/bitstream/handle/10665/312266/9789241515528-eng.pdf

In order to enhance the adoption of antimicrobial guidelines, it's essential that individuals possess sufficient understanding of antimicrobial agents and their significant categorizations. The WHO and WOAH systems for classifying antimicrobials represent the established standards for assessing the significance of these agents in human and animal applications respectively. This compilation identifies the specific antimicrobial categories employed in animals that could pose increased threats to human populations, along with strategies to mitigate the emergence of antimicrobial resistance (AMR) with medical significance. The antimicrobials are classified into Critically important, High Important and Important for human medicine based on the following criteria:

Critically important: Antimicrobial classes which meet both C1 and C2 are termed critically important.

Highly important: Antimicrobial classes which meet either C1 or C2 are termed highly important.

Important: Antimicrobial classes used in humans which meet neither C1 nor C2 are termed important.

Criterion 1 (C1): The antimicrobial class is the sole, or one of limited available therapies, to treat serious bacterial infections in people.

Criterion 2 (C2): The antimicrobial class is used to treat infections in people caused by either:
(1) bacteria that may be transmitted to humans from non- human sources, or (2) bacteria that may acquire resistance genes from non- human sources.

19. WHO AWaRe Classification system

The WHO's Expert Committee on the selection and proper use of essential medicines introduced the AWaRe antibiotic classification in 2017. This framework was designed to assist antibiotic stewardship initiatives on a local, national and global level. Antibiotics are categorized into three groups: **Access, Watch, and Reserve**. This classification system considers the varying effects of antibiotics and their classes on antimicrobial resistance, underscoring the need for their responsible application. The AWaRe classification serves as a valuable resource for policymakers, healthcare practitioners, and researchers, aiding them in enhancing antibiotic prescription practices, monitoring, and stewardship efforts. A summary of the AWaRe groups is provided below:

Access group

- No restrictions on their use. They may be prescribed without approval.
- First- or second-line empiric therapy for many common indications.
- They are generally narrower-spectrum with low risk of toxicity and low potential to induce resistance.
- They are generally narrow-spectrum antimicrobials.
- These should be readily available at all hospitals with the appropriate quantity, quality, formulation and at a reasonable price.
- Examples: amoxicillin and cefazolin.

Watch group

- Lower level of restriction.

- Generally, have an associated toxicity risk or the potential to induce resistance.
- Recommended as first- or second-line agents in the hospital's recommended guidelines.
- May be prescribed without restrictions for certain defined indications or clinical conditions but must be approved prior to use for other conditions that are not listed, or for extended duration of therapy, per the highly restricted 'red' antimicrobials.
- These agents should have prioritized targets for AMS programs to limit their use to only recommended indications.
- Examples: vancomycin, ceftriaxone and piperacillin-tazobactam.

Reserve group

- Highly restricted. Last-resort options, e.g., for serious or life-threatening infections due to multi-drug resistant bacteria and may have a high toxicity risk or cost.
- Very broad spectrum of activity or may be seen as a 'last-resort' treatment option.
- These antibiotics should be accessible, but their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable.
- These medicines should be protected and prioritized as key targets of national and international stewardship programs to preserve their effectiveness.
- Can only be prescribed by an expert, or require expert approval.
- Examples: colistin and linezolid.

20. WOAH antimicrobial classification system

(Ref: OIE list of antimicrobial agents of veterinary importance)

https://www.woah.org/app/uploads/2021/03/a-oie-list-antimicrobials-may2018.pdf

The vital lists of antimicrobials maintained by WHO and WOAH for both human and veterinary medicine can complement and offer valuable insights, enabling a judicious balance between animal health requirements and public health concerns. Therefore, a separate list for veterinary antimicrobials were developed by WOAH concurrently with WHO list in 2005[6].

The WOAH also classified the veterinary antimicrobials as *Veterinary Critically Important Antimicrobial Agents (VCIA), Veterinary Highly Important Antimicrobial Agents (VHIA) and Veterinary Important Antimicrobial Agents (VIA)* based on the following two criteria:

Criterion 1. Response rate to the questionnaire regarding Veterinary Important Antimicrobial Agents: - This criterion was met when a majority of the respondents (more than 50%) identified the importance of the antimicrobial class in their response to the questionnaire.

Criterion 2. Treatment of serious animal disease and availability of alternative antimicrobial agents: - This criterion was met when compounds within the class were identified as essential against specific infections and there was a lack of sufficient therapeutic alternatives.

Veterinary Critically Important Antimicrobial Agents (VCIA) - meet both criteria 1 and 2.

Veterinary Highly Important Antimicrobial Agents (VHIA) - meet either criterion 1 or 2.

Veterinary Important Antimicrobial Agents (VIA) - meet neither criterion 1 nor 2.

21. Traffic light system

The traffic light system of antimicrobial classification was developed by WHO for WHO Essential Medicine listed antimicrobials. It is basically giving the AWaRe groups colour codes (Green, Orange and Red) as used in the traffic lights to guide vehicular traffic. Green corresponds to Access (no restriction/ to use freely), Orange to Watch (to take caution before use/ some form of restriction) and Red to Reserved/ Restricted (Stop/ not permitted/ highly restricted).

The traffic light system not only guides healthcare professionals in selecting the most appropriate antimicrobial treatment for infections but also helps in curbing the development and spread of AMR. By promoting responsible usage, minimizing overuse or misuse, and ensuring that the most effective treatments are reserved for serious infections, the traffic light system contributes significantly to the preservation of antimicrobials for both current and future generations. The justifications as to why critically important antimicrobials for human health needs to be protected is provided in table 3.

Different countries have different antimicrobials classified under the traffic light system depending on the manner in which they are being used and prevailing local regulations.
For Bhutan, the traffic light system of classification of veterinary antimicrobials listed in the Essential Veterinary Drug List has been developed to guide the veterinary clinicians while prescribing antimicrobials (annexure antibiotic guide cards). It is adapted from the antimicrobial classifications of WHO, WOAH and Australian Antimicrobial Stewardship guidelines. It shall be subject to review and amendment whenever new evidences are presented.

A comparative traffic light system of veterinary antimicrobials listed in the EVDL is provided against the WOAH, WHO AWaRe and Human Health of Bhutan in the Table 2.

Table 2: Classification of antimicrobials as Traffic light system per WOAH, WHO AWaRe, Human Health Bhutan and Animal Health, Bhutan.

Sl. No	List of antibiotics	WOAH	WHO AWaRe	Human Health, Bhutan	Animal health, Bhutan	
					Companion animal	Food animal
1	Amoxycillin trihydrate bolus	*VCIA*	*Access*	*Access*	*Access*	*Access*
2	Ampicillin + Cloxacillin Inj.	*VCIA*	*Access*	*Access*	*Access*	*Access*
3	Benzathine Penicillin Inj.	*VCIA*	*Access*	*Access*	*Access*	*Access*
4	Cephalexin bolus	*VHIA*	*Access*	*Access*	*Access*	*Access*
5	Oxytetracycline LA Inj.	*VCIA*	*Watch*	*X*	*Access*	*Access*
6	Strepto-penicillin Inj.	*VCIA*	*Access*	*X*	*Access*	*Access*
7	Sulphadimidine Inj.	*VCIA*	*Access*	*X*	*Access*	*Access*
8	Trimethoprim + Sulphadiazine bolus	*VCIA*	*Access*	*X*	*Access*	*Access*
9	Ceftriaxone Inj.	*VCIA*	*Watch*	*Watch*	Reserve	Reserve
10	Enrofloxacin inj.	*VCIA*	*Watch*	*Watch*	*Access*	Reserve
11	Benzathine penicillin LA Inj.	*VCIA*	*Access*	*Access*	*Access*	*Access*
12	Enrofloxacin tab	*VCIA*	*Watch*	*Watch*	*Access*	Reserve
13	Doxycycline hyclate tab	*VCIA*	*Access*	*Access*	*Access*	*Access*
14	Cefotaxime Inj.	*VCIA*	*Watch*	*Watch*	Reserve	Reserve
15	Gentamicin inj.	*VCIA*	*Access*	*Access*	*Access*	Reserve
16	Metronidazole inj.		*Access*	*X*	*Access*	*Watch*
17	Oxytetracycline SA	*VCIA*	*Watch*	*X*	*Access*	*Access*
18	Sulphadiazine + Trimethoprim powder	*VCIA*	*Access*	*X*	*Access*	*Access*
19	Tetracycline Hcl W/S	*VCIA*	*Access*	*X*	*Access*	*Access*
20	Gentamicin Cream	*VCIA*	*Access*	*X*	*Access*	Reserve
21	Chloramphenicol eye ointment/applicaps		*Access*	*Access*	*Access*	*Access*
22	Ciprofloxacin ear/eye drops	*VCIA*	*Watch*	*Watch*	*Access*	Reserve
23	Cefoperazone sodium I/mammary	*VCIA*	*Watch*	*Watch*	Reserve	Reserve
24	Strepto-penicillin I/mammary	*VCIA*	*Access*		*Access*	*Access*

Safeguarding critically important antimicrobials of human medicines used for treatment in animals have been tabulated with justifications (table 3).

Table 3 Justification for safeguarding critically important antimicrobials (reserved category) of human medicines used for treatment in animals.

Sl. No.	Antimicrobial class	Justification
1.	3/4/5 generation cephalosporins - Cefotaxime - Ceftriaxone - Cefoperazone	- High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. - Transmission of Enterobacteriaceae, including *E. coli* and *Salmonella*, from non-human sources. - High frequency of use in human medicine.
2.	Aminoglycosides - Amikacin - Streptomycin - Gentamicin	- High frequency of use in human medicine. - Transmission risk of *Enterococcus* spp., *Enterobacteriaceae* (including *E. coli*), and *Mycobacterium* spp. from nonhuman sources. - One of few alternatives available in some countries because of resistance.
3.	Quinolones - Ciprofloxacin - Enrofloxacin	- High frequency of use in human medicine. - Transmission risk of *Campylobacter* spp. and *Enterobacteriaceae,* including *E. coli* and *Salmonella,* from non-human sources. - One of few alternatives available in some countries because of resistance.
4.	Polymyxins - Colistin	- High frequency of use in human medicine. - Colistin resistant bacteria and the *mcr* family genes can be transmitted via the food chain. - One of few alternatives available in some countries because of resistance.

22. Antibiotic use guide cards for various livestock and pets

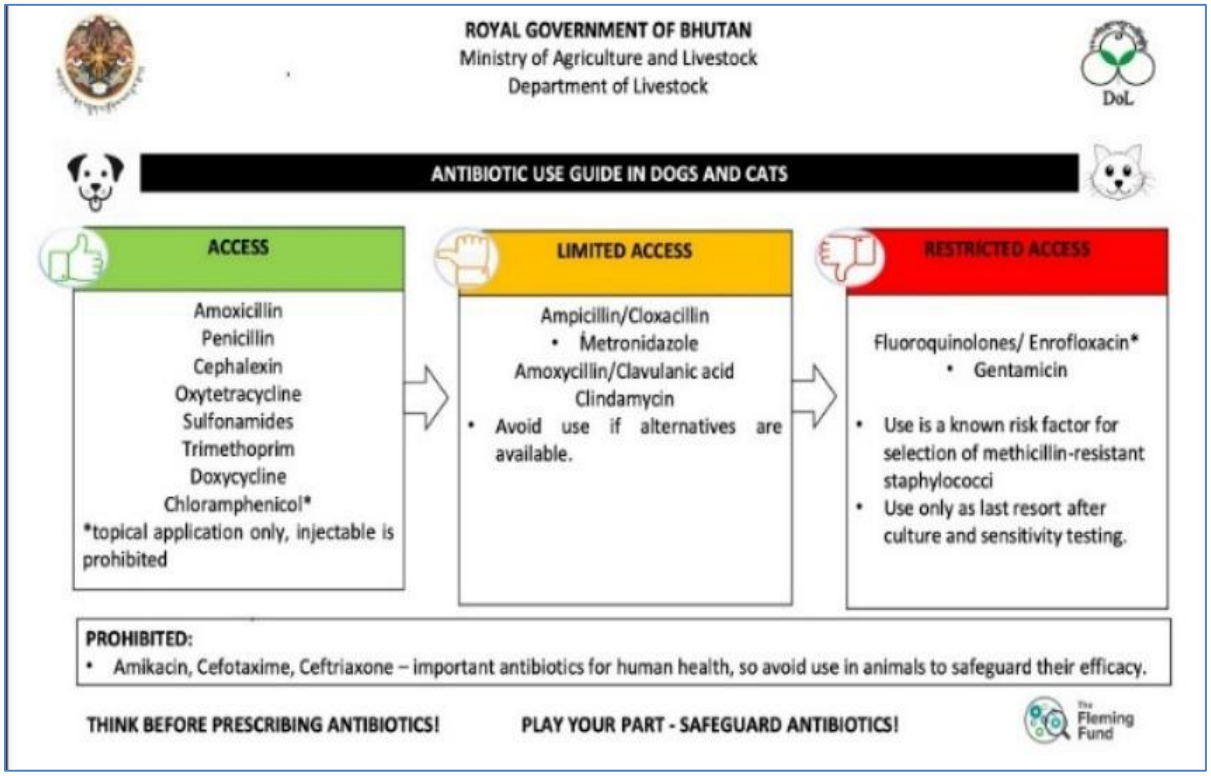

Figure 1. Antibiotic use card for dogs and cats

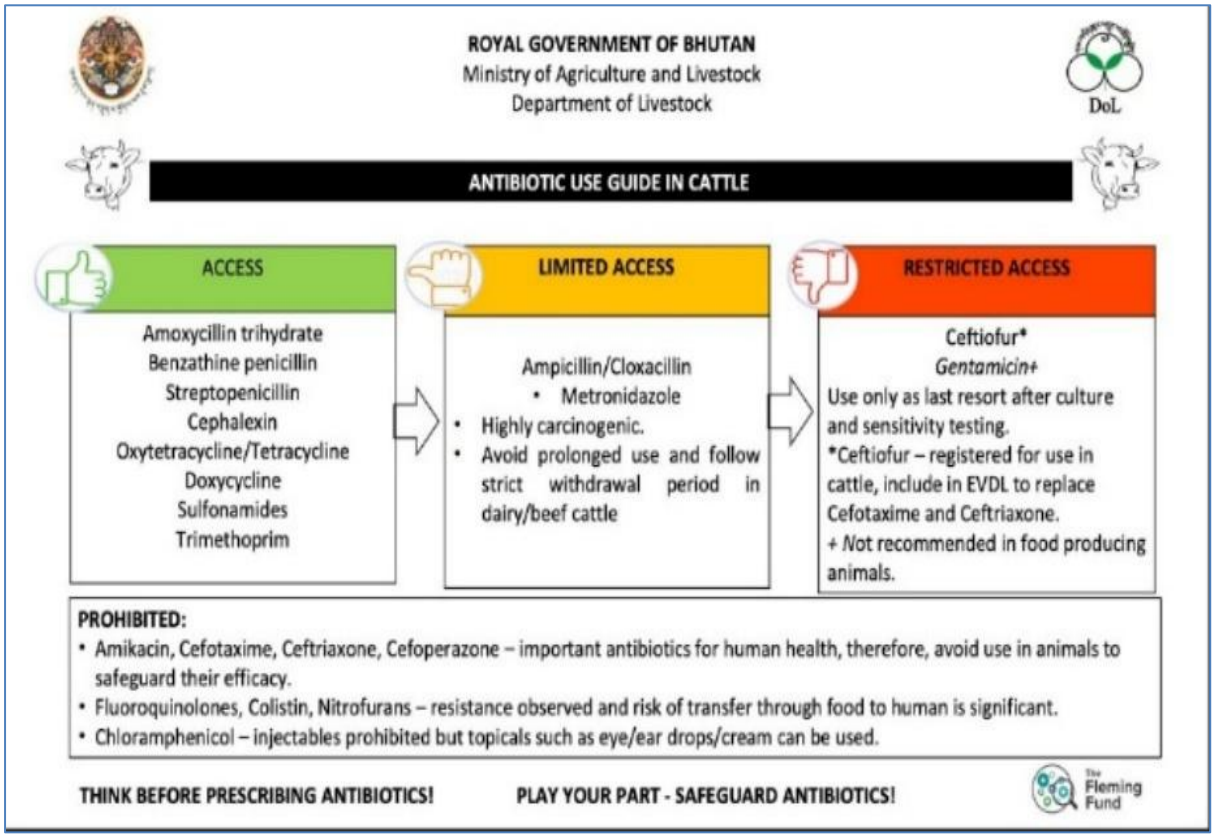

Figure 2. Antibiotic use card for cattle

2. Antibiotic use card for cattle

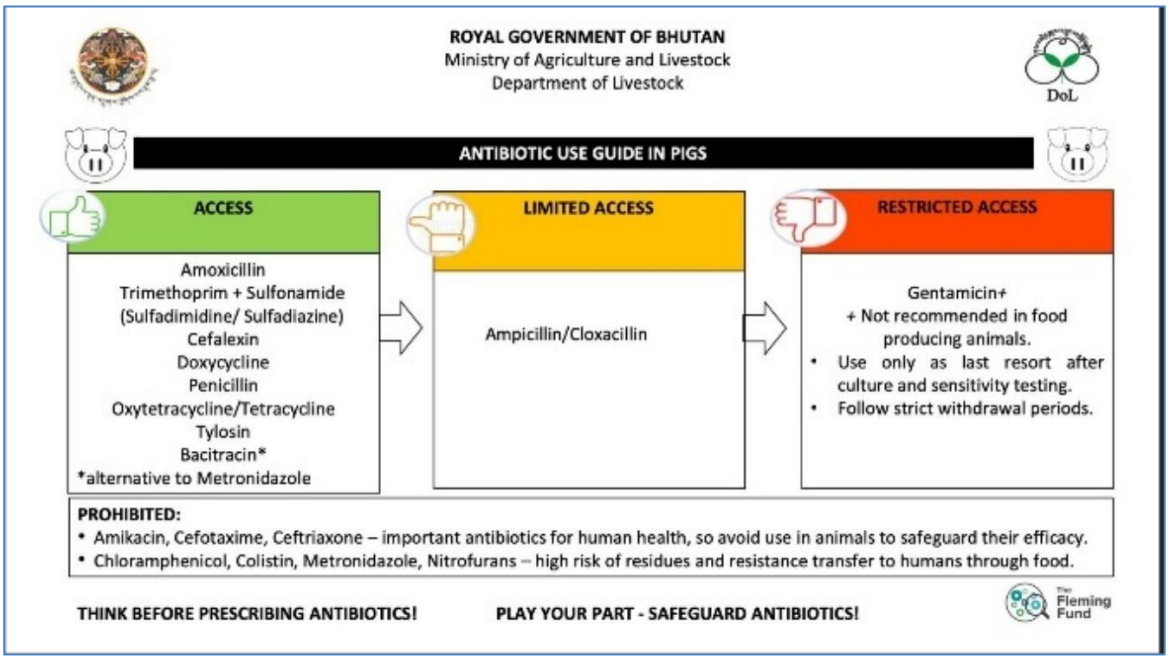

Figure 3 Antibiotic use card for pigs

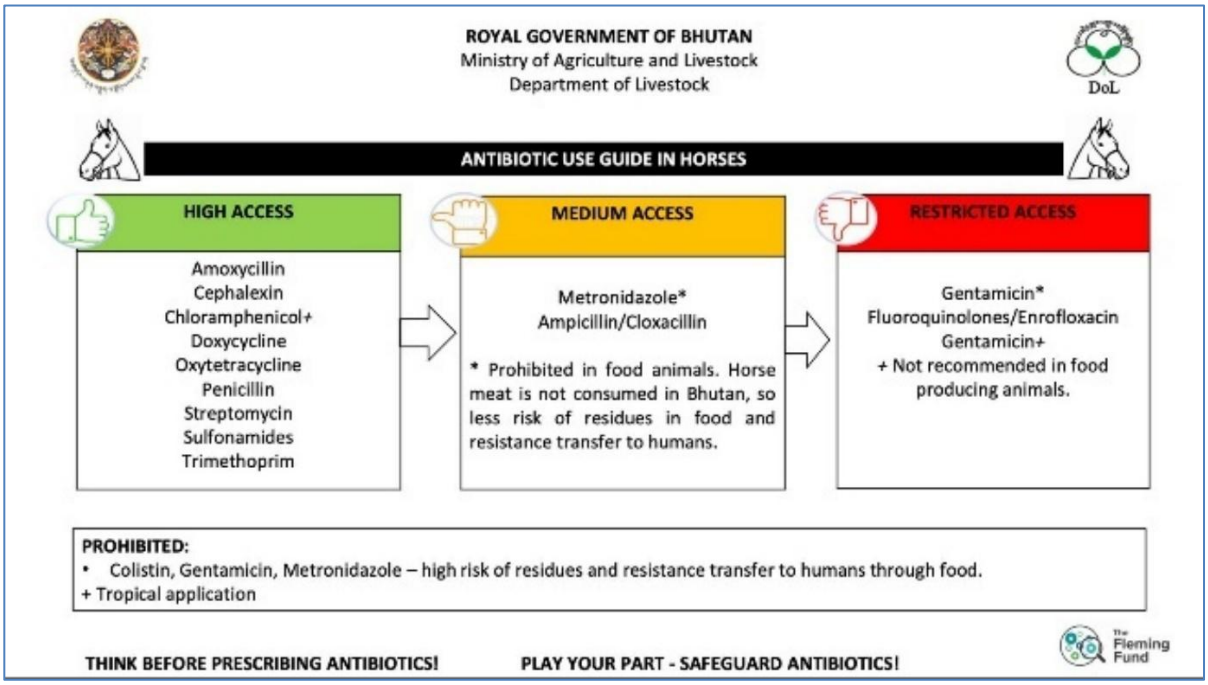

Figure 4 Antibiotic use card for horses.

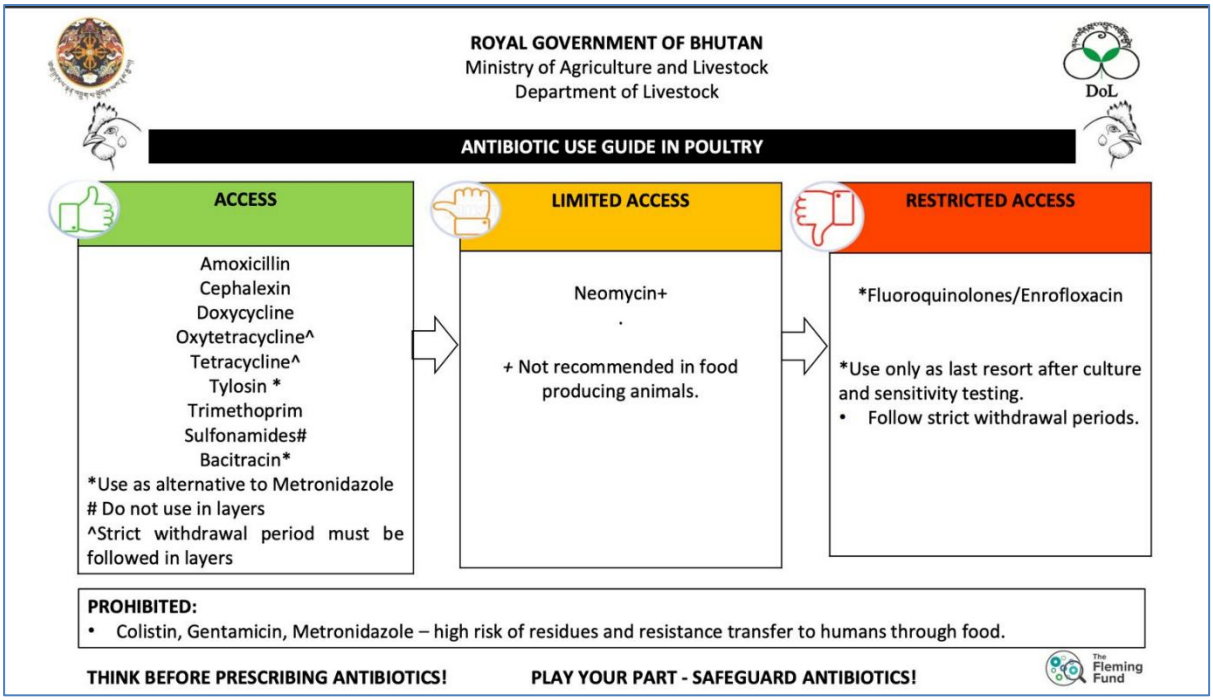

Figure 5 Antibiotic use card for poultry birds

23. Glossary

Abbreviation Expansion

ABST:	Antibiotic sensitivity test
BW:	Body weight
BFDA:	Bhutan Food & Drug Authority
CNS:	Central nervous system
CST:	Culture & Sensitivity Test
EVDL:	Essential Veterinary Drug List
GI:	Gastrointestinal
Hrs:	Hours
IM:	Intramuscular
IV:	Intravenous

24. Definitions:

1. **Antibiotics**: Antibiotics are substances produced naturally by microorganisms, such as bacteria or fungi, that have the ability to inhibit the growth of or kill other microorganisms.
2. **Antimicrobial**: Antimicrobial is any substance of natural, semi-synthetic or synthetic origin that kills or inhibits the growth of microorganisms but causes little or no damage to the host. Antimicrobials include all agents that act against all types of microorganisms – bacteria (antibacterial), viruses (antiviral), fungi (antifungal) and protozoa (antiprotozoal).
3. **Narrow Spectrum:** The antibiotic having limited action and the action is towards a particular organism.
4. **Board Spectrum:** The antibiotic is effective against both gram positive and negative organisms.
5. **Bacteriostatic:** The antibiotic which inhibits the growth and replication of the bacteria is called bacteriostatic.
6. **Bactericidal:** The antibiotic which kills an organism is called bactericidal.
7. **Long acting antibiotics:** These are depository preparations such as procaine Penicillin, benzathine Penicillin or Oxytetracycline LA. They are used for longer duration of action and are always given Intramuscular. These preparations are then released slowly into the blood.
8. **Withdrawal Period:** Withdrawal periods is the time necessary for an animal to metabolize an administered medicine and the amount of time necessary for the medicine concentration level in the tissues to decrease to a safe, acceptable level.
9. **Off label Use:** Use of antimicrobials other than for intended use

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