CONSERVING THE USE OF CRITICALLY IMPORTANT ANTIMICROBIALS IN FOOD-PRODUCING ANIMALS

Gaps and Possibilities in Global Guidance and Indian Policy Framework

AUGUST 2021

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Executive summary

Antimicrobial Resistance (AMR) is recognized as a silent pandemic that can cause huge cumulative damage. Antimicrobials, particularly antibiotics, are increasingly becoming ineffective. The ongoing Covid-19 pandemic has demonstrated the catastrophic consequences of an infectious disease that does not have effective medicines to treat. AMR can lead to prolonged hospital stays, costly diagnosis and treatments, increased morbidity and mortality as well as financial and economic burden. It can also significantly impact food and agriculture production, food safety, nutrition security and livelihood as well as Universal Health Coverage (UHC) and attainment of several Sustainable Development Goals (SDGs).

AMR accelerates by misuse and overuse of antimicrobials in human health, animal health, food-producing animals and crop production. In addition, environment and the way waste from key sources are managed play a role. In the case of food-animal production systems, antimicrobials are used for both therapeutic as well as non-therapeutic purposes in high quantities. This includes antimicrobials considered critically important for human health but are misused and/or overused for non-therapeutic purposes and as a substitute for good animal-rearing practices. Often these food systems are intensive and heavily dependent on chemicals such as antibiotics, which in turn have enabled the growth of intensive food-animal farming, though at a big cost. Such indiscriminate antimicrobial use is known to jeopardize their effectiveness in humans as well as in animals.

A 2021 World Health Organization (WHO) report on global antimicrobial resistance surveillance based on 2019 data from 70 countries also shows high resistance in bacteria causing common and serious infections against multiple critically important antimicrobials. WHO's 2017 "Priority Pathogen List" points towards the need to develop new antibiotics that are effective against bacteria otherwise becoming resistant to critically important antimicrobials. Its "AWaRe" classification of antibiotics revised in 2019 mentions several critically important antimicrobials in the "Watch" and "Reserve" categories. A recently released European Union report also shows positive associations between antimicrobial use in food-producing animals and AMR in animals and humans.

The need of the hour is to reduce overall antimicrobial use in food-producing animals and eliminate their misuse. But, most importantly, use of critically important antimicrobials must be conserved for human use. They are important for public health, and can save lives. With the development of new antibiotics a challenging task, the world cannot afford to lose these last-resort options. So far, other than action towards restricting use of certain critically important antimicrobials in a few European countries, the overall global action to minimize their use is yet to be in line with the urgency of AMR crisis.

The global momentum to fight AMR has been led by the Tripartite of WHO, FAO (Food and Agriculture Organization of the United Nations) and OIE (World Organisation for Animal Health). There is no one guidance collectively from the Tripartite, but each of the three organizations have their own guidance on antimicrobial use in food-producing animals. This guidance influences national action. National stakeholders, more so from developing countries, also look up to this guidance to formulate and sharpen their national action strategies.

This report analyses the global guidance of the Tripartite organizations with regard to critically important antimicrobials. In addition, it presents the on-the-ground situation in India, which also partly reflects the impact of global guidance.

The three main gaps (and possibilities) identified in the global guidance are:

- **Significant overlap in antimicrobials considered critical for humans and food-producing animals:** It was found that 47 antimicrobials (antibiotics) in the 2019 "OIE list of antimicrobial agents of veterinary importance" for food-producing animals were also part of the latest WHO list of critically important antimicrobials for human medicine developed in 2018. These 47 antimicrobials, which belong to nine WHO critically important antimicrobials, also include 28 antimicrobials from four out of five highest priority critically important antimicrobial classes as per the WHO list. These are third- and fourth-generation cephalosporins, macrolides and ketolides, quinolones and fluoroquinolones and polymyxins including colistin. In the OIE list, 38 antimicrobials are categorized as veterinary critically important antimicrobials and nine as veterinary highly important antimicrobials. There are 39 antimicrobials recommended for more than one and 28 for more than three species of food-producing animals.

- **Need for coherence in position on use of critically important antimicrobials in food-producing animals:** Assessment of guidance of individual Tripartite organizations (WHO-FAO-OIE) on antimicrobial use for treatment, control, prevention and growth promotion, and use of critically important antimicrobials revealed that there was need for coherence on certain aspects. Overall, greater degree of uniformity was observed on the issue of antimicrobials as growth promoters and phase-out of highest priority critically important antimicrobials for the same purpose. However, at the other extreme, positions vary on the use of antimicrobials for disease prevention and control as well as the use of highest priority critically important antimicrobials for treatment. Overall, more coherence was seen in the position of WHO and FAO. Clearly, there is need for more clarity, coherence and, most importantly, a uniform message from the Tripartite organizations. In the absence of this, chances of consensus among national-level animal- and human-health stakeholders are low and the possibility for misinterpretation remains high. This can result in limited action, leading to misuse and/or overuse of critically important antimicrobials in the food-producing animal sector.

- **Need for clarity and strong action on use of antimicrobials for disease prevention in food-producing animals:** Apart from the difference in position, the guidance of individual Tripartite organizations defines and categorizes differently the use of antimicrobials for disease prevention. Clearly, there is a need for review and consensus among the Tripartite organizations, which would in turn enable action against indiscriminate and unsafe use of antimicrobials for disease prevention at the global and national levels. Otherwise, the ongoing scenario will continue to impact the reduction goals of overall antimicrobial use as disease prevention is likely a big proportion among all antimicrobial use in food-producing animals. This severely impacts reduction of critically important antimicrobials as many are used for disease prevention—which is least regulated or supervised—and potentially in higher quantities. Of note, the European Union has planned to implement much stronger restrictions on antimicrobial use for both prevention and control starting 2022.

Considering the gaps (and possibilities) in the global guidance, it is recommended that the WHO-FAO-OIE Tripartite should consider developing a uniform and strong guidance for countries on the use of critically important antimicrobials across all food-animal sectors. This guidance should include a clear message for all critically important antimicrobials w.r.t. their use for treatment, growth promotion, disease prevention and control across different food-animal sectors. It should be specific about antibiotics that can be used (and conditions of use), and those that should be prohibited immediately or phased out in a particular sector. It should also consider stronger and specific guidance against antimicrobial use for disease prevention and control in different sectors. This uniform message collectively from the Tripartite organizations will reduce chances of misinterpretation and help generate consensus among national stakeholders, particularly of the low- and middle-income countries. It will also guide countries to develop their sector-specific targets and road maps to reduce overall use and conserve the use of critically important antimicrobials and help civil society stakeholders to push for much-needed change.

In addition, the Tripartite should focus on concerted intervention to develop a good understanding of global- and country-level use of critically important antimicrobials and resistance against them in animals and humans along with linkages.

In India, 27 critically important antimicrobials from seven classes were found to be used in dairy, poultry and aquaculture for both therapeutic and non-therapeutic purposes. Eighteen were from three highest priority critically important antimicrobial classes, i.e. macrolides and ketolides; third-, fourth- and fifth-generation cephalosporins; and quinolones and fluoroquinolones. Many of these are also part of the 2019 "OIE list of antimicrobial agents of veterinary importance".

While almost all these antimicrobials are recommended in India for treating infections in humans, a high degree of resistance was found in several common and severe infection-causing bacteria from humans against them. These include cefotaxime, ceftazidime, ciprofloxacin, levofloxacin, erythromycin, gentamicin, amikacin and ampicillin.

There were several gaps and possibilities identified in the Indian policy framework related to antimicrobial use in food-producing animals. Most Indian policies and guidelines do not target critically important antimicrobials except one against colistin in 2019 by the Ministry of Health and Family Welfare.

India clearly needs to focus on conserving the use of critically important antimicrobials. Apart from ensuring responsible use of critically important antimicrobials in human health, it should take concerted action to better regulate this valuable resource commonly and often indiscriminately used in food-animal sectors. This will also help animal health and food-animal production in the long-term. Apart from developed countries, a few developing countries have also begun to adopt required measures.

India should consider developing a roadmap and necessary policy framework to conserve the use of critically important antimicrobials. This should include developing and/or revising guidelines for antimicrobial use in all food-animal sectors, which aims to phase out use of critically important antimicrobials for all non-therapeutic purposes, with immediate priority given to highest priority critically important antimicrobials. Use of critically important antimicrobials for therapeutic purposes should not be resorted to in the presence of other effective antibiotic alternatives. The road map should recognize their use in disease prevention as non-therapeutic and discourage, restrict and gradually phase out such use in farms. Necessary focus should be placed on promoting and incentivizing use of non-antimicrobial alternatives, biosecurity and good animal-rearing practices to help phase out such use. It should consider amending the definition of "drug" in the

Drugs and Cosmetics Act, 1940 to help restrict antimicrobial use for disease prevention and bring antimicrobials in animal feed (and those used in crops) under its purview.

In addition, the policy framework should invest in setting up systems to collect data to understand critically important antimicrobial use and resistance against them in food-producing animals and its linkages with resistance in humans. It should also develop and implement a long-term research agenda for non-antimicrobial alternatives, and invest in training and creating awareness among farmers on good animal-rearing practices and responsible use and among veterinarians on stewardship of antimicrobials. Antimicrobial use in different food-animal sectors and residues in food from animals should be routinely monitored. The results of antimicrobial use and resistance surveillance should be made public.

Introduction

Antimicrobial Resistance (AMR) is recognized as a silent pandemic that can cause huge cumulative damage. Antimicrobials are becoming increasingly ineffective. The ongoing Covid-19 pandemic has demonstrated the catastrophic consequences of an infectious disease that does not have effective medicines to treat it.

AMR can lead to prolonged hospital stays, costly diagnosis and treatments, increased morbidity and mortality as well as financial and economic burden.[1] The global increases in healthcare costs are expected to reach up to US $1.2 trillion per year by 2050 in a high AMR impact scenario.[2] AMR is also likely to impact food and agriculture production, food safety, nutrition security and livelihood. It can negatively impact Universal Health Coverage (UHC) and attainment of several Sustainable Development Goals (SDGs). A 2017 World Bank report highlighted that in a high AMR-impact scenario, the world is expected to lose 3.8 per cent of its annual gross domestic product (GDP) by 2050 and witness a pronounced increase in extreme poverty.[3] Livestock production in low-income countries would decline the most by 2050 in this scenario.

AMR occurs when bacteria, viruses, fungi and parasites change over time and no longer respond to medicines, making infections harder to treat and thereby increasing the risk of disease spread, severe illness and death.[4] Antibiotic resistance, in particular, occurs when bacteria change in response to the use of antibiotics. Although it occurs naturally over time, it accelerates by misuse and overuse of antimicrobials in human health, animal health, and food-producing animals and crop production. In addition, environment plays a significant role. Waste from farms, factories, community and healthcare settings can contribute to the emergence and spread of AMR through environmental routes. Such waste may carry one or more of AMR determinants such as resistant bacteria, resistance-conferring genes and antibiotic residues.

After the Global Action Plan on AMR[5] in 2015, the global momentum to contain AMR was led by the Tripartite of the World Health Organization (WHO), Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE). Subsequently, the United Nations Environment Programme (UNEP) was involved to look into the environmental dimension of AMR and provide guidance to address it. In 2019, the United Nations ad-hoc Inter-Agency Coordination Group (IACG) on AMR also gave its recommendations to contain AMR, based on which the One Health Global Leaders Group on AMR was formed in 2020 to provide advocacy and advisory functions to ensure that action is taken to address the challenge of AMR.

Antimicrobials are used both in animal health as well as in food-animal production systems, which are often intensive and dependent on chemicals, including antibiotics. In fact, antimicrobials are believed to have significantly enabled the growth of chemical-dependent intensive farming, though at a big cost. They are used for both therapeutic as well as non-therapeutic purposes. The problem is that these antimicrobials, particularly antibiotics, which are also important for treating several infections in human health are overused and misused for non-therapeutic reasons in the food-producing animal sector. This is known to jeopardize their effectiveness in both humans and animals. The need of the hour is to reduce overall antimicrobial use and eliminate its misuse in the food-producing animals. Most importantly, use of antimicrobials that are critically important for human health are to be conserved.

At the national level, however, limited action is seen on use of critically important antimicrobials (CIAs) in food-producing animals. Part of the reason could be the global guidance on antimicrobial use in food-producing animals. While each of the Tripartite organizations—WHO, FAO and OIE—emphasize on responsible and prudent use of antimicrobials in the food-animal sector, their guidance on certain aspects of antimicrobial use requires more clarity and coherence. In such a scenario, national-level stakeholders find it difficult to have consensus on required action as different guidance can create confusion and lead to misinterpretation.

This report highlights the gaps and possibilities in the global guidance of the Tripartite organizations. It also presents current practices in India in the use of critically important antimicrobials in multiple food-animal sectors, which may have been partly influenced by the existing global guidance. This report is expected to inform the future global guidance on critically important antimicrobials in the food-animal sector towards conserving their use for humans and animals. It also intends to push for required change in the Indian policy framework on the same.

SECTION 1

GLOBAL GUIDANCE ON ANTIMICROBIAL USE IN FOOD-PRODUCING ANIMALS

1. Growing need to conserve the use of critically important antimicrobials

1.1 Critically important antimicrobials for human medicine

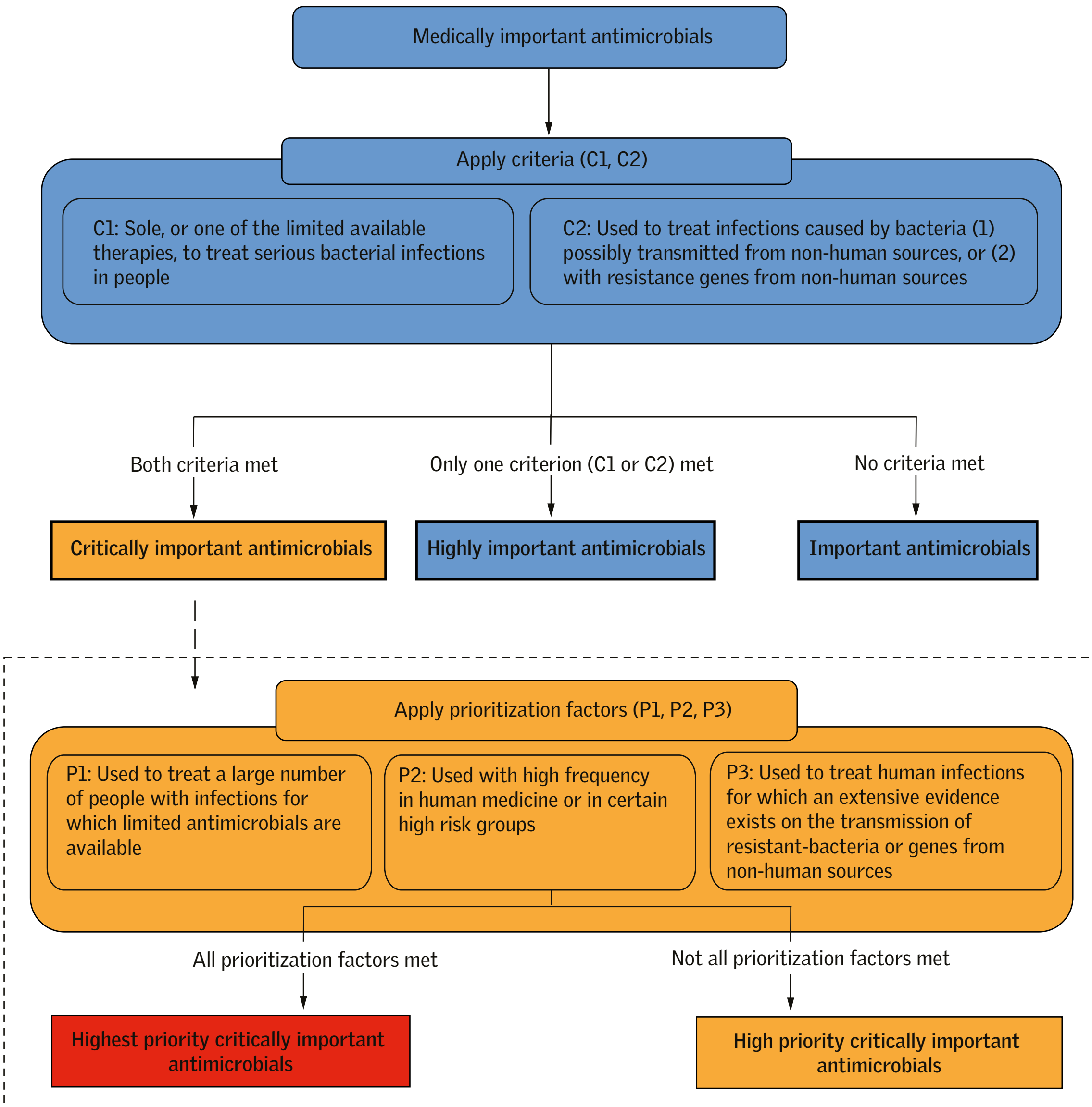
Recognizing the importance of antimicrobials to human medicine, the WHO has ranked all medically important antimicrobials (antimicrobials used in human medicine) for risk management of AMR due to non-human use of antimicrobials. Based on a criteria, antimicrobials are categorized into critically important antimicrobials, highly important antimicrobials and important antimicrobials.

As per the criteria, critically important antimicrobials are the sole or one of the limited available therapies to treat serious bacterial infections in humans. They are used to treat bacterial infections transmitted from non-human sources or infections from bacteria that may acquire resistance genes from non-human sources. Based on three additional factors, these are further categorized into highest priority critically important antimicrobials (HPCIAs) and high priority critically important antimicrobials. HPCIAs are antimicrobials that are used to treat large numbers of people with infections for which limited antimicrobials are available; used with high frequency in human medicine or in certain high-risk groups; and used to treat human infections for which extensive evidence exists on the transmission of resistant-bacteria or genes from non-human sources (see *Figure 1: Categorization of medically important antimicrobials and prioritization of critically important antimicrobials*).

The WHO list of "Critically important antimicrobials for human medicine", which is limited to antibiotics, has been developed by the Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) established by WHO to support its efforts to minimize the public-health impact of antimicrobial resistance associated with the use of antimicrobials in food-animals. The list is intended to ensure that all antimicrobials, especially critically important antimicrobials, are used prudently both in human and veterinary medicine.[6] It supports strategies to mitigate human health risks associated with antimicrobial use in food-producing animals and helps regulators and stakeholders know the types of antimicrobials used in animals that present a potentially higher risk to human populations and how use of antimicrobials could be managed to minimize AMR.

The list was originally developed following recommendations from two expert meetings organized by the FAO, OIE and WHO in 2003. The first version of the list was published in 2005, following which it was revised six times until 2018 (see *Table 1: Critically important antimicrobials as per the 2018 WHO list*). There are 17 classes of critically important antimicrobials, five of which are highest priority critically important antimicrobials (see *Annexure 1: WHO list of critically important antimicrobials for human medicine*).

Figure 1: Categorization of medically important antimicrobials and prioritization of critically important antimicrobials



Source: Critically Important Antimicrobials for Human Medicine, WHO, 2018

Table 1: Critically important antimicrobials as per the 2018 WHO list

Antimicrobial class	Antimicrobials (examples)[#]
Highest priority critically important antimicrobials	
Cephalosporins (third-, fourth- and fifth-generation)	Cefixime, cefodizime, cefoperazone, cefotaxime, cefpodoxime, cefquinome, ceftazidime, ceftiofur, ceftizoxime, ceftriaxone
Glycopeptides*	Avoparcin, teicoplanin, vancomycin
Macrolides and ketolides	Azithromycin, clarithromycin, erythromycin, flurithromycin, roxithromycin, spiramycin, tulathromycin, tylosin, tylvalosin
Polymyxins	Colistin, polymyxin B
Quinolones**	Ciprofloxacin, danofloxacin, enrofloxacin, flumequine, gatifloxacin, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, oxolinic acid
Critically important antimicrobials^	
Aminoglycosides	Amikacin, apramycin, dihydrostreptomycin, gentamicin, kanamycin, neomycin, streptomycin, tobramycin
Ansamycins	Rifampicin, rifamycin
Carbapenems and other penems	Ertapenem, imipenem, meropenem
Glycylcyclines	Tigecycline
Lipopeptides	Daptomycin
Monobactams	Aztreonam
Oxazolidinones	Linezolid
Penicillins (antipseudomonal)	Piperacillin, ticarcillin
Penicillins (aminopenicillins)	Amoxicillin, ampicillin
Penicillins (aminopenicillins with beta-lactamase inhibitors)	Amoxicillin-clavulanic acid, ampicillin-sulbactam
Phosphonic acid derivatives	Fosfomycin
Drugs used solely to treat tuberculosis/ mycobacterial diseases	Bedaquiline, ethambutol, isoniazid, pyrazinamide

Note: Highly important antimicrobial classes are amphenicols, cephalosporins (first- and second-generation) and cephamycins, lincosamides, penicillins (amidinopenicillins), penicillins (anti-staphylococcal), penicillins (narrow spectrum), pseudomonic acids, riminofenazines, fusidic acid, streptogramins, sulfonamides, dihydrofolate reductase inhibitors and combinations, sulphones, tetracyclines; important antimicrobial classes are aminocyclitols, cyclic polypeptides, nitrofurans derivatives, nitroimidazoles, pleuromutilins.

[#] Complete list provided in Annexure 1

* Also includes lipoglycopeptides

** Also includes fluoroquinolones

^ Critically important antimicrobials other than highest priority critically important antimicrobials

Source: Critically Important Antimicrobials for Human Medicine, WHO, 2018

1.2 Growing global resistance against critically important antimicrobials

A. WHO reports show high resistance against critically important antimicrobials

The recently released fourth Global Antimicrobial Resistance Surveillance System (GLASS) report in 2021 reflects high resistance in infection-causing bacteria against several critically important antimicrobials in humans.[7] This report captures data from 3,106,602 laboratory-confirmed infections reported by 24,803 surveillance sites in 70 countries. GLASS gathers AMR data on four infection sites for high priority pathogens, including:

- Blood stream infections (BSIs) caused by *Acinetobacter* spp., *E. coli*, *K. pneumoniae*, *Salmonella* spp., *S. aureus* and *S. pneumoniae*
- Urinary tract infections (UTIs) caused by *E. coli* and *K. pneumoniae*
- Gastrointestinal infection caused by *Salmonella* spp. and *Shigella* spp.
- Genital infections caused by *N. gonorrhoeae*

As per the report, bloodstream infections (BSIs) are linked to a high rate of morbidity and an overall crude mortality rate of 15–30 per cent worldwide. *E. coli* resistant to third-generation cephalosporins had a median resistance rate of 36.6 per cent, while methicillin-resistant *Staphylococcus aureus (*MRSA) had a median resistance rate of 24.9 per cent. In 2020, these two were new AMR indicators included in the monitoring framework of the SDGs. The median rates of resistance in *E. coli* were shown to be greater (58.3 per cent) in low- and middle-income countries (LMICs) compared to higher-income countries (17.5 per cent) (HICs). This was also the case with MRSA, which had a 33.3 per cent median rate of resistance in LMICs and 15 per cent in HICs. High resistance was also seen in *E. coli* against ceftriaxone, ampicillin and ciprofloxacin as well as in *K. pneumoniae* against ceftriaxone and ciprofloxacin. Median resistance rates of *Acinetobacter* spp. to different carbapenems and aminoglycosides as well as in *Salmonella* spp. against ciprofloxacin were also fairly high.

The report showed resistance to UTIs as consistently high. Median resistance in *K. pneumoniae* against ciprofloxacin was 36.4 per cent and in *E. coli* against ciprofloxacin was 43.1 per cent. In both, bacteria resistance was higher in samples from hospitals than in community samples. High resistance was also seen in *E.coli* against ampicillin and ceftriaxone and in *K. pneumoniae* against ceftriaxone.

For gastrointestinal infections, the median resistance rate for *Shigella* spp. against ciprofloxacin was 19.4 per cent.

In the case of genital infections, the median resistance rate of *N. gonorrhoea* against ciprofloxacin was 76.8 per cent (see *Table 2: Global resistance against critically important antimicrobials as per WHO's GLASS 2021 report*).

Table 2: Global resistance against critically important antimicrobials as per WHO's GLASS 2021 report#

	Median resistance rate (per cent)	Interquartile range*	No. of reporting countries	No. of patients with AST** results
Bloodstream infections				
E. coli resistant to third-generation cephalosporins (LMICs)	58.3	39.8–70.2	32	22,371
E. coli resistant to third-generation cephalosporins (HICs)	17.5	11.3–25.2	31	218,031
E. coli resistant to ceftriaxone*	30-40	–	55	126,630
E. coli resistant to ampicillin*	70-80	–	57	194, 891
E. coli resistant to ciprofloxacin*	40-50	–	63	213,010
K. pneumoniae resistant to ceftriaxone*	50-60	–	56	45,414
K. pneumoniae resistant to ciprofloxacin*	40-50	–	62	75,627
Methicillin-resistant *S. aureus* (LMICs)	33.3	19.5–55.6	29	23,031
Methicillin-resistant *S. aureus* (HICs)	15.0	6.8–36.0	30	83,837
Acinetobacter spp. resistant to imipenem	64.3	10.5–79.1	55	17,793
Acinetobacter spp. resistant to meropenem	64.0	18.4–78.0	57	18,340
Acinetobacter spp. resistant to doripenem	54.7	43.4–73.2	4	312
Acinetobacter spp. resistant to amikacin*	30-40	–	53	15,705
Acinetobacter spp. resistant to gentamicin*	50-60	–	56	15,310
Salmonella spp. resistant to ciprofloxacin	23.3	4.9–32.8	32	11,483
Salmonella spp. resistant to levofloxacin	10.0	5.7–23.7	12	1,329
S. pneumoniae resistant to cefotaxime	0.2	0–3.0	25	11,678
S. pneumoniae resistant to ceftriaxone	0.5	0–1.6	31	10,006
S. pneumoniae resistant to fluoroquinolones	29.2	20.0–36.7	–	–
Urinary tract infections				
E. coli resistant to ciprofloxacin	43.1	22.5–58.6	28	1,961,032
E. coli resistant to ciprofloxacin (community)*	30-40	–	16	267,553
E. coli resistant to ciprofloxacin (hospital)*	40-50	–	28	102,829
E. coli resistant to ceftriaxone*	40-50	–	26	748,780
E. coli resistant to ampicillin*	70-80	–	24	1,568,996
K. pneumoniae resistant to ciprofloxacin	36.4	28.5–52.3	41	251,266
K. pneumoniae resistant to ciprofloxacin (community)*	30-40	–	16	46,820
K. pneumoniae resistant to ciprofloxacin (hospital)*	40-50	–	16	27,343
K. pneumoniae resistant to ceftriaxone*	50-60	–	34	140,509
K. pneumoniae resistant to meropenem*	10-20	–	38	231,790
Gastrointestinal infections				
Salmonella spp. resistant to ciprofloxacin	9.3	3.3–18.2	31	9,431

	Median resistance rate (per cent)	Interquartile range*	No. of reporting countries	No. of patients with AST** results
Salmonella spp. resistant to ceftriaxone	2.1	0.1–6.5	23	6,222
Shigella spp. resistant to ciprofloxacin	19.4	7.3–31.9	20	4,229
Shigella spp. resistant to ceftriaxone	18.5	6.5–34.4	12	1,183
Shigella spp. resistant to azithromycin*	10-20	–	4	1,537
Genital infections				
N. gonorrhoea resistant to ciprofloxacin	76.8	65.7–97.3	18	8,831

Note: The report provides resistance as median rates. It defines interquartile range (IQR) as a measure of variability, based on dividing a data set into quartiles. Quartiles divide a rank-ordered data set into four equal parts. The IQR is the difference between the first and third quartiles. The first quartile, denoted as Q1, is the value in the data set that holds 25 per cent of the values below the median. The third quartile, denoted as Q3, is the value in the data set that holds 25 per cent of the values above the median.

Data for 2019

* Resistance range is inferred from figures as actual values are not mentioned in text of the report. A broad range which is indicative is mentioned. These are few example with relatively higher resistance for different CIA classes. In such cases interquartile range is not provided in the table.

** AST: Antimicrobial Susceptibility Testing; Source: Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report, WHO, 2021

According to WHO's Global Tuberculosis Report 2020, in 2019 close to half a million people worldwide developed rifampicin-resistant tuberculosis (RR-TB), of which 78 per cent had multidrug-resistant TB (MDR-TB).[8] MDR/RR-TB was found in 3.3 per cent of new TB cases and 17.7 per cent of previously treated patients.

B. European Union report confirms association between antimicrobial use in food-producing animals and AMR in animals as well as in humans

The recently released "Third joint inter-agency report on integrated analysis of consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals in the European Union/European Economic Area" establishes a positive association between antimicrobial use in food-producing animals and AMR in animals and humans.[9] The 2021 report focuses on six antimicrobials classes (third- and fourth-generation cephalosporins, fluoroquinolones, polymyxins, aminopenicillins, macrolides and tetracyclines), five out of which are critically important antimicrobials, including four highest priority critically important antimicrobials. The report mainly covers data from 2016–18. In some cases, data has also been included from 2014 and 2015.

In both food-producing animals and humans, associations were observed between consumption of an antimicrobial class and bacterial resistance to the antimicrobials in this class in the same population. For example, in the case of food-producing animals, a statistically significant positive association was observed for one or more years between:

- Prevalence of extended-spectrum beta-lactamase (ESBL)-producing *E. coli* and AmpC beta-lactamase-producing *E. coli* and consumption of third- and fourth-generation cephalosporins;

- Consumption of fluoroquinolones and other quinolones and resistance to fluoroquinolones in indicator *E. coli* from food-producing animals; also observed in multivariate analysis;

- Consumption of fluoroquinolones and other quinolones in poultry and resistance to fluoroquinolones in *Salmonella* spp. from poultry. A direct effect was also found, in the multivariate analysis, from the consumption of fluoroquinolones and other quinolones on the occurrence of resistance in *Salmonella* spp. from food-producing animals;

- Consumption of polymyxins in animals overall, as well as specifically in poultry and pigs, and resistance to polymyxins in *E. coli* from food-producing animals;

- Consumption of aminopenicillins in food-producing animals and ampicillin resistance in indicator *E. coli* and in *Salmonella* spp. from poultry; and

- Consumption of macrolides in poultry and resistance to macrolides in *C. jejuni* from poultry.

In addition, resistance in bacteria from humans was associated with antimicrobial consumption in animals as well as resistance in bacteria from food-producing animals which, in turn, was related to antimicrobial consumption in animals. For example, a statistically significant positive association was observed for one or more years between:

- Resistance to third-generation cephalosporins through a univariate analysis in invasive *E. coli* isolates from humans and the consumption of third- and fourth-generation cephalosporins, both in humans and in food-producing animals for all the years;

- Fluoroquinolone resistance through a univariate analysis in invasive *E. coli* isolates from humans with both consumption of fluoroquinolones and other quinolones in food-producing animals and fluoroquinolone resistance in indicator *E. coli* isolates from the different food-producing animal species (broilers, turkeys, pigs and calves); this was not confirmed in multivariate analysis;

- Consumption of fluoroquinolones and other quinolones in both food-producing animals and in humans and fluoroquinolone resistance in *Campylobacter jejuni* from humans;

- Fluoroquinolone resistance in *C. jejuni* from turkeys and broilers was significantly associated with fluoroquinolone resistance in *C. jejuni* from humans;

- A multivariate analysis showed a direct effect of both consumption of fluoroquinolones and other quinolones in poultry and resistance in *C. jejuni* from poultry on the occurrence of fluoroquinolone resistance in *C. jejuni* from humans;

- Ampicillin resistance in indicator *E. coli* from food-producing animals (turkeys, broilers, pigs and calves) and ampicillin resistance in invasive *E. coli* from humans was observed, and between *Salmonella* spp. from turkeys and from humans;

- Consumption of aminopenicillins in food-producing animals and resistance to aminopenicillins in invasive *E. coli* and in *Salmonella* spp. (particularly *S. typhimurium*), respectively, from humans. In both, the multivariate analysis for *E. coli* and for *Salmonella* spp., aminopenicillin resistance in bacterial isolates from humans was significantly associated with resistance in bacterial isolates from food-producing animals, which, in turn, was significantly associated with consumption of aminopenicillins in food-producing animals; and

- Resistance to macrolides in *C. jejuni* from turkeys was associated with resistance to macrolides in *C. jejuni* from humans.

C. Most of the critically important antimicrobials under WHO's "AWaRe" classification are categorized as "Watch" or "Reserve"

WHO's "Model list of essential medicines" contains several critically important antimicrobials, demonstrating the importance of these antimicrobials used at a global level. This list overall comprises those essential medicines that satisfy the priority health care needs of the population.[10] In 2017, the Essential Medicines List (EML) further included the **Access, Watch, Reserve ("AWaRe") classification of antibiotics** to promote antibiotic stewardship and reduce AMR. The AwaRe classification was further reviewed and expanded in 2019.

There are 19 critically important antimicrobials that are part of the AWaRe classification. Collectively, these form 23 single dose or combinations through different routes of administration. Of these, seven are in the Reserve, 11 in the Watch, and five in the Access category. This includes several highest priority critically important antimicrobials (see *Table 3: Critically important antimicrobials from the twenty-first EML 2019 as per the AWaRe classification*).

Table 3: Critically important antimicrobials from the twenty-first EML 2019 as per the AWaRe classification

Antimicrobial	Antimicrobial class	AWaRe category
Highest priority critically important antimicrobials		
Cefixime	Third-, fourth- and fifth-generation cephalosporins	Watch
Cefotaxime		Watch
Ceftazidime		Watch
Ceftazidime-avibactam		Reserve
Ceftriaxone		Watch
Azithromycin	Macrolides and ketolides	Watch
Clarithromycin		Watch
Vancomycin (Intra-Venous)	Glycopeptides and lipoglycopeptides	Watch
Vancomycin (oral)		Watch
Colistin	Polymyxins	Reserve
Polymyxin B		Reserve
Ciprofloxacin	Quinolones and fluoroquinolones	Watch
Critically important antimicrobials^		
Amoxicillin	Penicillins	Access
Ampicillin		Access
Amikacin	Aminoglycosides	Access
Gentamicin		Access
Plazomicin		Reserve
Amoxicillin/clavulanic Acid	Penicillins (aminopenicillin with beta-lactamase inhibitor)	Access
Piperacillin/tazobactam	Penicillins (antipseudomonal)	Watch
Meropenem	Carbapenems	Watch
Meropenem-vaborbactam		Reserve
Linezolid	Oxazolidinones	Reserve
Fosfomycin (Intra-Venous)	Phosphonic acid derivatives	Reserve

Note: Drugs used for the treatment of tuberculosis were not analysed as they are not part of AWaRe classification.

^ Critically important antimicrobials other than highest priority critically important antimicrobials.

AWaRe categories

ACCESS GROUP
- First- or second-choice antibiotics
- Offer the best therapeutic value, while minimizing the potential for resistance

WATCH GROUP
- First- or second-choice antibiotics
- Only indicated for specific, limited number of infective syndromes
- More prone to be a target of antibiotic resistance and thus prioritized as targets of stewardship programs and monitoring

RESERVE GROUP
- "Last resort"
- Highly selected patients (life-threatening infections due to multi-drug resistant bacteria)
- Closely monitored and prioritized as targets of stewardship programs to ensure their continued effectiveness

D. Global push for research of new antibiotics against bacteria with high resistance to critically important antimicrobials

Recognizing that common infection-causing bacteria are becoming resistant to several critically important antimicrobials classes, WHO also focussed on identifying at the global level the most important resistant bacteria for which there is an urgent need for new treatments and developed in 2017 a "WHO priority pathogens list (PPL)" of antibiotic-resistant bacteria. The list is divided into three categories according to the urgency of need for new antibiotics: critical, high and medium priority.

According to the WHO list, infection-causing resistant bacteria of concern are as follows:

Priority 1: CRITICAL (includes multidrug-resistant bacteria that pose a particular threat in hospitals, nursing homes and among patients whose care requires devices such as ventilators and blood catheters)

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

Priority 2: HIGH (contain other increasingly drug-resistant bacteria that cause more common diseases)

- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter* spp., fluoroquinolone-resistant
- *Salmonellae*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM (contain other increasingly drug-resistant bacteria that cause more common diseases)

- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella* spp., fluoroquinolone-resistant

2. Gaps in global guidance on use of critically important antimicrobials in food-producing animals

A review and analysis of guidance by the individual Tripartite organizations pointed towards the following gaps with regard to their position and/or recommendations on the use of antimicrobials—particularly critically important antimicrobials—in food-producing animals:

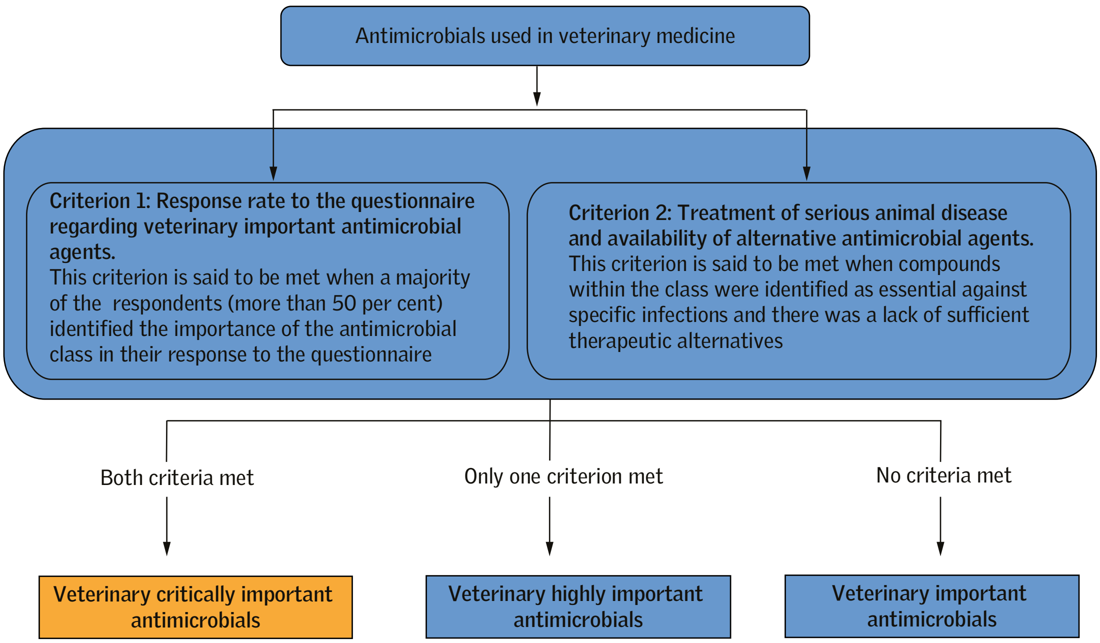
- Significant overlap in antimicrobials considered critical for humans and food-producing animals;
- Need for coherence in position on use of critically important antimicrobials in food-producing animals; and
- Need for clarity and strong action on use of antimicrobials for disease prevention in food-producing animals.

2.1 Significant overlap in antimicrobials considered critical for humans and food-producing animals

In addition to the WHO list of critically important antimicrobials, OIE also has a separate list of antimicrobial agents of veterinary importance for food-producing animals. This list divides antimicrobials used in veterinary medicine into three categories: veterinary critically important antimicrobials (VCIA), veterinary highly important antimicrobials (VHIA) and veterinary important antimicrobials (VIA). It also mentions species such as avian, equine, bee, rabbit, bovine, ovine, caprine, fish, camel and swine for which these antimicrobials can be used.[11]

The first list of antimicrobial agents of veterinary importance was adopted in 2007 by OIE on the basis of responses from 66 OIE member countries to a questionnaire and has undergone several updates. The most recent list was released in 2019 (see *Figure 2: Categorization of antimicrobials used in veterinary medicine* and *Annexure 2: OIE list of antimicrobial agents of veterinary importance*).

Figure 2: Categorization of antimicrobials used in veterinary medicine



It was found that 47 antimicrobials (antibiotics) in the OIE list were also part of the latest WHO list of critically important antimicrobials. These 47 antimicrobials, which belong to nine WHO critically important antimicrobial classes, are categorized into 38 veterinary critically important antimicrobials and nine veterinary highly important antimicrobials. Twenty-eight of these 47 are from four highest priority critically important antimicrobial classes. Except for eight of these 47 overlapping antimicrobials, all are recommended and can be used in multiple species of food-producing animals. For example, there are 39 antimicrobials recommended for more than one and 28 for more than three species of food-producing animals (see *Table 4: Overlap—OIE categorized veterinary critically important antimicrobials/veterinary highly important antimicrobials with WHO critically important antimicrobials).*

It is noteworthy that the Tripartite organizations have for many years well recognized the public-health concern due to this overlap. The WHO list of "Critically important antimicrobials for human medicine" mentions, "FAO/OIE/WHO expert meeting met in Rome in 2007 to consider the WHO and OIE lists of critically important antimicrobials and begin to address the overlap of the two lists, for example, the potential hazards to public health resulting from this overlap and the combinations of pathogen, antimicrobial and animal species of most concern. The meeting concluded that the lists of critically important antimicrobials should be revised on a regular basis in a collaborative and coordinated approach by FAO, OIE and WHO." Similarly, an FAO 2019 manual, *Prudent* *and efficient use of antimicrobials in pigs and poultry*, recognizes that "the overlap of these lists calls for careful consideration to appropriately balance the need for animal health and the public-health aspects."[12]

Table 4: Overlap—OIE categorized veterinary critically important antimicrobials/ veterinary highly important antimicrobials with WHO critically important antimicrobials

Antimicrobial (OIE list)	OIE categorization	Species (OIE list)	Antimicrobial class (WHO)
Highest priority critically important antimicrobials			
Cefoperazone	Veterinary critically important antimicrobials	BOV, CAP, OVI	Cephalosporins (third-, fourth- and fifth-generation)*
Cefquinome		BOV, CAP, EQU, LEP, OVI, SUI	
Ceftiofur		AVI, BOV, CAP, EQU, LEP, OVI, SUI	
Ceftriaxone		AVI, BOV, OVI, SUI	
Erythromycin		API, AVI, BOV,CAP, EQU, LEP, OVI, PIS, SUI	Macrolides and ketolides
Gamithromycin		BOV	
Josamycin		AVI, PIS, SUI	
Kitasamycin		AVI, SUI, PIS	
Oleandomycin		BOV	
Spiramycin		AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI	
Tildipirosin		BOV, SUI	
Tilmicosin		AVI, BOV, CAP, LEP, OVI, SUI	
Tulathromycin		BOV, SUI	
Tylosin		API, AVI, BOV, CAP, LEP, OVI, SUI	
Tylvalosin		AVI, SUI	
Ciprofloxacin		AVI, BOV, SUI	Quinolones and fluoroquinolones
Danofloxacin		AVI, BOV, CAP, LEP, OVI, SUI	
Difloxacin		AVI, BOV, LEP, SUI	
Enrofloxacin		AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI	
Flumequine	Veterinary highly important antimicrobials	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI	
Marbofloxacin	Veterinary critically important antimicrobials	AVI, BOV, EQU, LEP, SUI	
Nalidixic acid	Veterinary highly important antimicrobials	BOV	
Norfloxacin	Veterinary critically important antimicrobials	AVI, BOV, CAP, LEP, OVI, SUI	
Ofloxacin		AVI, SUI	
Orbifloxacin		BOV, SUI	
Oxolinic acid	Veterinary highly important antimicrobials	AVI, BOV, LEP, PIS, SUI, OVI	
Polymyxin E (colistin)		AVI, BOV, CAP, EQU, LEP, OVI, SUI	Polymyxins
Polymyxin B		BOV, CAP, EQU, LEP, OVI, AVI	

Antimicrobial (OIE list)	OIE categorization	Species (OIE list)	Antimicrobial class (WHO)
Critically important antimicrobials^			
Amikacin	Veterinary critically important antimicrobials	EQU	Aminoglycosides
Apramycin		AVI, BOV, LEP, OVI, SUI	
Dihydrostreptomycin		AVI, BOV, CAP, EQU, LEP, OVI, SUI	
Framycetin		BOV, CAP, OVI	
Gentamicin		AVI, BOV, CAM, CAP, EQU, LEP,OVI, SUI	
Kanamycin		AVI, BOV, EQU, PIS, SUI	
Neomycin		API, AVI, BOV, CAP, EQU, LEP, OVI, SUI	
Paromomycin		AVI, BOV, CAP, OVI, LEP, SUI	
Streptomycin		API, AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI	
Tobramycin		EQU	
Amoxicillin		AVI, BOV, CAP, EQU, OVI, PIS, SUI	Penicillins (aminopenicillins)
Ampicillin		AVI, BOV, CAP, EQU, OVI, PIS, SUI	
Hetacillin		BOV	
Ticarcillin		EQU	Penicillins (antipseudomonal)
Amoxicillin + clavulanic acid		AVI, BOV, CAP, EQU, OVI, SUI	Aminopenicillins with beta-lactamase inhibitors
Ampicillin + sulbactam		AVI, BOV, SUI	
Rifampicin	Veterinary highly important antimicrobials	EQU	Ansamycins
Rifaximin		BOV, CAP, EQU, LEP, OVI, SUI	
Fosfomycin		AVI, BOV, PIS, SUI	Phosphonic acid derivatives

Note: There are VCIAs such as carbomycin, mirosamycin, terdecamycin, sarafloxacin, as well as VHIAs like miloxacin not listed here as they are not mentioned in WHO CIA list; Apramycin is mentioned in the OIE list as to be used only used in animals, but is also covered by the WHO list. However, fortimycin, another antimicrobial of the same class (aminoglycoside) is also stated to be used only in animals by OIE, but is not mentioned in the WHO CIA list; Other antimicrobial classes like amphenicols, tetracyclines, streptogramins, aminocyclitols, cephalosporin first- and second-generation, fusidane, lincosamides, penicillins (anti-staphylococcal) are VCIAs/VHIAs/VIAs as per the OIE and are medically important (but not CIAs) as per WHO and therefore not included in this table.

Abbreviations—AVI: avian, API: bee, BOV: bovine, CAP: caprine, CAM: camel, EQU: equine, LEP: rabbit, OVI: ovine, PIS: fish, SUI: swine

* The OIE-listed cephalosporins belong to the third and fourth generation

^ Critically important antimicrobials other than highest priority critically important antimicrobials

Source: OIE List of Antimicrobial Agents of Veterinary Importance, 2019

2.2 Need for coherence in position on use of critically important antimicrobials in food-producing animals

Critically important antimicrobials are used in all kinds of food-producing animals such as poultry, aquaculture, dairy and pigs for different purposes, including use for growth promotion, disease prevention and treatment. Disease prevention is further categorized into prevention (also known as prophylaxis) and control (also known as metaphylaxis) (see *Figure 3: Use of critically important antimicrobials in food-producing animals for different purposes*).

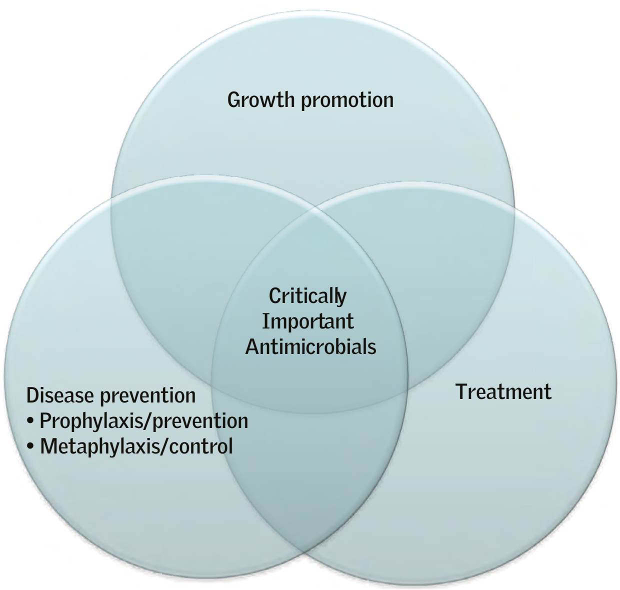
The Tripartite, Codex and IACG have made public their position on these different uses and on use of critically important antimicrobials in the form of standards, guidelines, recommendations.

An assessment of the positions of the Tripartite clearly suggests that there is need for more clarity and coherence in these guidance on certain aspects. In the present scenario, they can create scope for misinterpretation among various country-level stakeholders from animal and human sectors. The lack of clarity also does not help develop consensus and can result in limited action, ultimately leading to overuse and misuse of critically important antimicrobials in the food-producing animal sector.

Figure 3: Use of critically important antimicrobials in food-producing animals for different purposes

PROPHYLAXIS/PREVENTION
- Antimicrobials administered to an individual or group of animals with no clinical sign of a disease
- Often done routinely/ intermittently

METAPHYLAXIS/CONTROL
- Antimicrobials administered in therapeutic doses to a group of animals wherein one or more animals are infected but others do not show clinical signs.
- Acts as a treatment for those who are ill but preventive for others



GROWTH PROMOTION
- Use of antimicrobials to increase the rate of weight gain or efficiency of feed utilization
- Routinely used at a mass scale through feed at sub-therapeutic doses

TREATMENT
- Use of antimicrobials at therapeutic dose to treat an infectious disease having clinical signs and/or symptoms

The *WHO Guidelines on Use of Medically Important Antimicrobials in Food-Producing Animals*, published in 2017, recommends "complete restriction of use of all classes of medically important antimicrobials in food-producing animals for growth promotion and for prevention of infectious diseases that have not yet been clinically diagnosed".[13]

For control, it suggests, "antimicrobials classified as critically important for human medicine should not be used for control of the dissemination of a clinically diagnosed infectious disease identified within a group of food-producing animals".

For treatment, it suggests that "antimicrobials classified as highest priority critically important for human medicine should not be used for treatment of food-producing animals with a clinically diagnosed infectious disease".

This means that as recommended by WHO, critically important antimicrobials should not be used for growth promotion and prevention (including control) while highest priority critically important antimicrobials should not be used for the treatment of food-producing animals.

On the other hand, the OIE list of antimicrobial agents of veterinary importance provides specific recommendations only for two classes of highest priority critically important antimicrobials—fluoroquinolones, third- and fourth-generation cephalosporins, and colistin (a highest priority critically important antimicrobial belonging to class polymyxin). It mentions that these are "not to be used as preventive treatment applied by feed or water in the absence of clinical signs in the animal(s) to be treated". Further, it says that these are "not to be used as a first-line treatment unless justified, when used as a second-line treatment, it should ideally be based on the results of bacteriological tests". It also says that their "extra-label/off label use should be limited and reserved for instances where no alternatives are available. Such use should be in agreement with the national legislation in force". It also recommends to "urgently prohibit their use as growth promoters".[14]

In addition, with regard to growth promoter use, OIE mentions that the "classes in the WHO category of Highest Priority Critically Important Antimicrobials should be the highest priorities for countries in phasing out the use of antimicrobial agents as growth promoters". It also says, "responsible and prudent use of antimicrobial agents does not include the use of antimicrobial agents for growth promotion in the absence of risk analysis".[15]

This means, that as per OIE recommendations, fluoroquinolones, third- and fourth-generation cephalosporins, and colistin should be prohibited as growth promoters and not used as preventive treatment. However, they can be used for control and treatment.

This also means that all other critically important antimicrobials can be used for prevention and treatment. A clarification received from OIE detailed that it should be available on prescription by a veterinarian, with adequate doses to control an expected pathogen and for a limited time.

Regarding growth promotion, highest priority critically important antimicrobials should be the highest priority to phase out in countries. A clarification received from OIE suggests that all other molecules, including other critically important antimicrobials, should be phased out in the absence of a formal risk analysis. This also means that for classes for which there are no specific restrictions, and/or the risk is low, they can be still be used as growth promoters.

However, risk analysis is expected to be done at the country level, which would be a difficult task for most countries as it is complex and resource-intensive and includes hazard identification, risk assessment, risk management and risk communication. Moreover, there is no such model list of antimicrobials with low or high risk as part of the global guidance for countries to leverage on.

The OIE list does not include antimicrobial classes/subclasses used only in human medicine. However, it mentions that "recognising the need to preserve the effectiveness of the antimicrobial agents in human medicine, careful consideration should be given regarding their potential use (including extra-label/off-label use)/authorisation in animals".[16] **This means that antimicrobial classes/subclasses used only in human medicine can still be used.**

The *FAO Action Plan on Antimicrobial Resistance 2016-2020* promotes good practices in food and agriculture systems and the prudent use of antimicrobials as one of its focus areas. It also mentions providing assistance to countries in the development of policies to phase out the use of antimicrobials as growth promoters.

FAO's *Manual on Prudent and Efficient Use of Antimicrobials in Pigs and Poultry*, published in 2019, suggests that the prudent and medically effective use of antibiotics includes:

- Phasing out use of antibiotics as growth promoters;
- Avoiding regular preventive use of antibiotics;
- Avoiding use of the highest priority critically important antimicrobials for human medicine in animals and adhering to the OIE List of Antimicrobials of Veterinary Importance; and

- Striving for individual treatment of animals with the correct dose and duration and avoiding using antibiotics for group treatments except for poultry flocks, especially via feed.

With respect to control, it mentions that preventive use of antibiotics should be applied only in "exceptional situations, such as when a few animals in a group have been diagnosed with an infection that has probably already been infecting—or will soon be infecting—the rest of the group and the economic consequences are likely to be severe".

As part of FAO technical guidelines for responsible fisheries in 2019, the *Recommendations for Prudent and Responsible Use of Veterinary Medicines in Aquaculture* recommends to aquatic health professionals and specialists that antimicrobial agents of lesser importance in human medicine should be chosen and those for which emergence of resistance is expected to be in an advanced stage not be selected.[17] It also mentions that antimicrobial agents should not be used prophylactically. FAO's *Code of Conduct for Responsible Fisheries*, published in 1995, encourages that member states ensure safe, effective and minimal use of therapeutants, hormones and drugs, antibiotics and other disease control chemicals.[18]

This means that as per the FAO guidance with respect to poultry and pigs, highest priority critically important antimicrobials should be avoided. All antibiotics should be avoided for preventive use but can be used for control purposes. Antibiotic use for growth promotion should be phased out.

For aquaculture too, it suggests that antimicrobials important for human health and those with high resistance should not be used. Antimicrobials should also not be used for prevention purposes.

The IACG, in its 2019 report *No Time to Wait: Securing the Future from Drug-Resistant Infections* to the United Nations Secretary General recommended to "phase out the use of antimicrobials for growth promotion, consistent with guidance from the Tripartite agencies and Codex Alimentarius, starting with an immediate end to the use of HPCIAs".[19]

This means that antimicrobial use as growth promoters should be phased out and highest priority critically important antimicrobials should be the priority. The IACG did not make any recommendations on the use of critically important antimicrobials for other purposes.

Codex's existing *Code of Practice to Minimize and Contain AMR*, adopted in 2005, says, "responsible use of veterinary antimicrobial drugs in food-producing animals does not include the use for growth promotion of veterinary antimicrobial drugs that belong to or are able to cause cross resistance to classes of antimicrobial agents used (or submitted for approval) in humans in the absence of a risk analysis". It further mentions that it "should be terminated or phased out in the absence of risk-analysis" and the "risk analysis should be undertaken by the appropriate national regulatory authority". It also mentions to "use veterinary antimicrobial drugs only when necessary and not as a replacement for good management and farm hygiene, or other disease prevention methods such as vaccination".[20]

This means that Codex's currently applicable guidelines, though not specifically referring to use of critically important antimicrobials, gives due importance to the issue of resistance in humans due to animal use of antimicrobials. It also implies that in general antimicrobial use (for example prevention, control and treatment) substitutes good animal-rearing practices. This Code is being revised. The report of the *Seventh Session of the Codex Ad-Hoc Intergovernmental Task Force on Antimicrobial Resistance*, published in July 2020, provides the Proposed Draft of the Code of Practice to Minimize and Contain Foodborne Antimicrobial Resistance at Step 5 of Adoption in the Codex Commission.[21] The text related to principle 5 and 7 of the Codex draft was adopted at the 43rd session of the Codex Alimentarius Commission (CAC) in 2020 at step 5.[22] The text related to principle 6 is to be further considered (see *Box: Text related to Principle 5, 6 and 7 in the proposed Codex draft*).

Text related to Principle 5, 6 and 7 in the proposed Codex draft

Principle 5: Responsible and prudent use of antimicrobial agents does not include the use for growth promotion of antimicrobial agents that are considered medically important. Antimicrobial agents that are not considered medically important should not be used for growth promotion unless potential risks to human health have been evaluated through procedures consistent with the Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance.

[**Principle 6:** Medically important antimicrobial agents should only be used for therapeutic purposes (treatment, control/metaphylaxis or prevention/prophylaxis of disease)].

Principle 7: Medically important antimicrobials should only be administered or applied for prevention/prophylaxis where professional oversight has identified well-defined and exceptional circumstances, appropriate dose and duration, based on clinical and epidemiological knowledge, consistent with the label, and in line with national legislation. Countries could use additional risk management measures for medically important antimicrobials considered highest priority critically important as described in the WHO List of Critically Important Antimicrobials for Human Medicine, the OIE List of Antimicrobial Agents of Veterinary Importance, or national lists, where available, including restrictions proportionate to risk and supported by scientific evidence.

Principle 7bis: When used for the control of disease/metaphylaxis, medically important antimicrobial agents should only be used on the basis of epidemiological and clinical knowledge and a diagnosis of a specific disease and follow appropriate professional oversight, dose, and duration.

It is clear that the position of the Tripartite organizations varies on certain aspects. Overall, there is a greater degree of uniformity with regard to use of antimicrobials as growth promoters and phase-out of highest priority critically important antimicrobials for the same purpose. However, at the other extreme, positions vary on the use of antimicrobials for disease prevention and control as well as the use of highest priority critically important antimicrobials for treatment. Overall, more coherence was seen in the position of WHO and FAO. Clearly, there is need for more clarity, coherence and, most importantly, a uniform message from the Tripartite organizations. In the absence of this, chances of consensus among national-level animal- and human-health stakeholders are low and the possibility for misinterpretation remains high. This can result in limited action, leading to misuse and overuse of critically important antimicrobials in the food-producing animal sector (see *Table 5: Interpretation of global guidance on use of critically important antimicrobials in food-producing animals*).

Table 5: Interpretation of global guidance on use of critically important antimicrobials in food-producing animals

	WHO	OIE	FAO
Highest priority critically important antimicrobials (Quinolones and fluoroquinolones, third- and fourth-generation cephalosporins and colistin)			
Growth promotion	Should not be used	Should not be used	Should not be used
Prevention	Should not be used	Should not be used	Should not be used
Control	Should not be used	Could be used	Should not be used
Treatment	Should not be used	Could be used	Should not be used
Highest priority critically important antimicrobials (Macrolides and ketolides, polymyxins other than colistin, glycopeptides and lipoglycopeptides, fifth-generation cephalosporins)			
Growth promotion	Should not be used	Should not be used	Should not be used
Prevention	Should not be used	Could be used	Should not be used
Control	Should not be used	Could be used	Should not be used
Treatment	Should not be used	Could be used	Should not be used
Critically important antimicrobials^			
Growth promotion	Should not be used	Should not be used*	Should not be used
Prevention	Should not be used	Could be used	Should not be used
Control	Should not be used	Could be used	Could be used**
Treatment	Could be used	Could be used	Could be used

Note: For easy reference words used to reflect position are "should not be used" and "could be used". The exact wording is mentioned in text. The red text highlights incoherence.
* Could be used if there are no specific restrictions are mentioned in the OIE list, or if risk is low upon formal risk analysis
** Under exceptional circumstances
^ Critically important antimicrobials other than highest priority critically important antimicrobials

2.3 Need for clarity and strong action on use of antimicrobials for disease prevention in food-producing animals

Use of antimicrobials for disease prevention in intensive food-animal production settings is common across different food-animal sectors and geographies. Such intensive farm settings are characterized by large-scale production, high stocking densities in confined conditions and huge dependence on chemicals like antimicrobials. Breeds raised are often genetically selected for productivity and therefore lack resilience to diseases. These settings also act as breeding grounds for the emergence and spread of infectious diseases, wherein antimicrobials are often used regularly for mass application to substitute good animal rearing practices, farm hygiene and sanitation.

As reflected in the aforementioned, there is greater consensus among the Tripartite organizations in the definition and position around antimicrobial use for growth promotion and treatment. This is not the case with disease prevention.

One of the possible reasons could be the difference in the way antimicrobial use is categorized. All Tripartite organizations recognize that antimicrobial use can be therapeutic as well as non-therapeutic in food-producing animals but the specifics vary. For example, the 2017 WHO *Guidelines on Use of Medically Important Antimicrobials in Food-Producing Animals* categorizes such use as therapeutic, growth promotion and disease prevention. Similarly, the 2016 FAO report *Drivers, Dynamics and Epidemiology of Antimicrobial Resistance in Animal Production* recognizes such use as therapeutic, metaphylactic and prophylactic, and growth promotion (sub-therapeutic). In both the cases, it could be inferred that all antimicrobial use other than for treatment that is mentioned as therapeutic is non-therapeutic use.

This becomes different in the case of OIE, which in *OIE Standards, Guidelines and Resolutions on Antimicrobial Resistance and the Use of Antimicrobial Agents,* published in 2020, categorizes as “veterinary medical use” and “veterinary non-medical use”. “Veterinary medical use” includes treating, controlling or preventing infectious disease and “veterinary non-medical use” indicates use other than “veterinary medical use” and includes growth promotion. Clearly, this adds to the confusion. First, it is a quite a different way of classification from that adopted by WHO and FAO. Second, it implies that prevention, control and treatment are similar and therefore under one category, i.e. “veterinary medical use”. Third, it also implies that use in prevention and control happens under veterinary supervision, which is not necessarily the case.

The second possible reason is the difference in the definition and the wording adopted by the Tripartite organizations and the way it is further categorized. For example, WHO includes both prevention and control as part of disease prevention whereas OIE and FAO define each separately. Both WHO and FAO use the word "prophylaxis", FAO uses "metaphylaxis" and OIE uses "prevention and control" while explaining. But, most importantly, the wording used to define and the emphasis put on certain words varies (see *Table 6: Difference in definition of disease prevention by Tripartite organizations*).

There is a need for review and consensus among the Tripartite organizations, which would in turn enable action against indiscriminate and unsafe use of antimicrobials for disease prevention at the global and national level.

Further, there is a need for a strong position on the issue of disease prevention as the ongoing scenario can continue to impact the reduction goals of overall antimicrobial use because disease prevention is likely a big proportion among all antimicrobial use in food-producing animals. This can severally impact the reduction of critically important antimicrobials as a substantial number of them are used for this purpose possibly in higher quantities. A purpose which is otherwise least regulated or supervised.

It is noteworthy here that the European Union plans to ban starting 2022 all preventative group treatments in animals (see *Box: European Union plans to ban all preventative group treatments in animals*).[23]

Table 6: Difference in definition of disease prevention by Tripartite organizations

WHO	FAO	OIE
"Disease prevention use (or prophylactic use) refers to use of antimicrobials in healthy animals considered to be at risk of infection or prior to the onset of clinical infectious disease. This includes use for control of the dissemination of a clinically diagnosed infectious disease identified within a group of animals, and prevention of an infectious disease that has not yet been diagnosed clinically."[24]	Prophylaxis: "The administration of an antimicrobial to susceptible but healthy animals to prevent the occurrence of infectious disease." Metaphylaxis: "The administration of an antimicrobial at therapeutic doses to all animals within a group in which some individuals have exhibited infection. Metaphylaxis acts both as a treatment for those animals currently infected and a preventive measure against infection in those animals who are healthy but risk becoming infected."[25]	"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 drug is not administered." "To control: means to administer an antimicrobial agent to a group of animals containing sick animals and healthy animals (presumed to be infected), to minimize or resolve clinical signs and to prevent further spread of the disease."[26]

European Union plans to ban all preventative group treatments in animals

The Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products, which is applicable on 28 January 2022 states that "Antimicrobial medicinal products shall not be applied routinely nor used to compensate for poor hygiene, inadequate animal husbandry or lack of care or to compensate for poor farm management." Regarding prophylaxis, it says, "Antimicrobial medicinal products should not be used for prophylaxis other than in well-defined cases for the administration to an individual animal or restricted number of animals when the risk for infection is very high or its consequences are likely to be severe. Antibiotic medicinal products should not be used for prophylaxis other than in exceptional cases only for the administration to an individual animal." Regarding metaphylaxis, it says, "Antimicrobial medicinal products should be used for metaphylaxis only when the risk of spread of an infection or of an infectious disease in a group of animals is high and where no appropriate alternatives are available." It further mentions that "such restrictions should allow the decrease of prophylactic and metaphylactic use in animals towards representing a smaller proportion of the total use of antimicrobials in animals."

3. Recommendations for global guidance to conserve use of critically important antimicrobials

It is clear that critically important antimicrobials are a valuable resource for global public health and must be used judiciously. The world cannot afford to lose this critical public good as the chances of development of new antibiotics are bleak. Use of critically important antimicrobials therefore should be markedly reduced and optimized as their overuse is making them ineffective in saving lives, suffering and resources. There is no alternative. This can be done with interventions targeted at critically important antimicrobials in both human and non-human sectors. Doing so will not only help human health but also animal health and productivity of food systems.

In the case of food-producing animals, the most sustainable approach is to produce food in settings that are less dependent on chemicals and antimicrobials, unlike intensive food systems. Such settings are suited to prevent the occurrence of the disease so that less antimicrobials are needed. If large-scale production is aimed through such systems, it will take time. Meanwhile, in the short and medium terms, there is a significant level of action that can be taken to conserve the use of critically important antimicrobials.

Broadly, there is a huge need for a uniform and stronger guidance on different aspects of antimicrobial use that can help reduce use of critically important antimicrobials. The ongoing guidance from individual Tripartite organizations is creating confusion at the national level. This is particularly important for low- and middle-income countries of the global South, which are typically quite dependent on the global guidance for their national action. In addition, critically important antimicrobial-specific interventions at the global level across stewardship, surveillance of use and resistance in all food-animal sectors is the need of the hour. The much-needed action includes:

- **The WHO-FAO-OIE Tripartite should consider developing a uniform and strong guidance for countries on the use of critically important antimicrobials across all food-animal sectors**. This should include a clear message for all categories of critically important antimicrobials w.r.t. their use as growth promoters and for disease prevention, control and treatment in sectors such as poultry, dairy and aquaculture. It should be specific about antibiotics that could be used in a particular sector along with explanations related to disease and conditions wherein antimicrobials can be used. It should specify which antibiotics must be immediately prohibited and those that need to be phased out over a limited period of time.

- o While such guidance should be a collectively agreed-upon message from human and non-human global stakeholder agencies, it should be strong and ambitious enough to conserve the use of critically important antimicrobials instead of the lowest possible consensus-based decision. For example, it should aim at immediate prohibition of all critically important antimicrobials instead of highest priority critically important antimicrobials for growth promotion.

- o This guidance should consider stronger and specific action against critically important antimicrobial use for disease prevention and control. In particular, strong action is required against routine group preventive use of antibiotics, which often substitutes good rearing practices. The guidance should come up with an agreed-upon definition of disease prevention and control and consider recognizing such use as non-therapeutic.

- o This uniform message which can be adopted and/or adapted by countries should help reduce chances of misinterpretation as well as generate greater consensus among national stakeholders. In addition, this should help civil society organizations to effectively push for necessary action.

- o This clear information should also be able to help countries develop their sector-specific road maps to conserve the use of critically important antimicrobials, based on local realities of use and resistance across different sectors (human and non-human) and help develop sector-specific targets for critically important antimicrobial use and reductions.

- **Concerted intervention is required to develop a good understanding of global and country-level use of critically important antimicrobials and resistance trends in food-animal sectors.** There is some action at the global and national level, such as the OIE annual reports, antimicrobial agents intended for use in animals; national surveillance efforts by certain countries of the European Union capturing different sectors and antimicrobials; and recent EU report on association between antimicrobial use in humans and animals and AMR in both. There still however is a big gap with respect to overall global understanding and related to developing countries of the global South. This gap can be filled by information focussing on critically important antimicrobials w.r.t. food-animal sectors and type of use (growth promotion, disease prevention, control and treatment). It is also important to develop greater understanding on the linkages between antimicrobial use in food-producing animals and resistance in animals and humans for an informed future action.

SECTION 2

CRITICALLY IMPORTANT ANTIMICROBIAL USE IN FOOD-PRODUCING ANIMALS IN INDIA

4. Critically important antimicrobials: Practices, resistance trends and gaps in policies

Developing countries such as India look up more than countries of the developed world to the guidance of the individual Tripartite organizations. This also gets reflected through the fact that several European nations have taken concerted action against critically important antimicrobials for many years in contrast to limited and recent action by developing nations.

This case study on critically important antimicrobial use in the Indian food-animal sector captures current practices, resistance trends and policies gaps. It reflects the collective impact of the global guidance and national policy-related action.

4.1 Use of critically important antimicrobials in dairy, poultry and aquaculture sector

Overall, in dairy, poultry and aquaculture sectors, 27 critically important antimicrobials from seven classes are used. Eighteen are from three highest priority critically important antimicrobial classes, i.e. macrolides and ketolides; third-, fourth- and fifth-generation cephalosporins; and quinolones and fluoroquinolones. Nineteen are part of the OIE list of antimicrobials of veterinary importance and eight are not.

In the dairy sector, 21 critically important antimicrobials from six classes are used. Thirteen are from two highest priority critically important antimicrobial classes, i.e. third-, fourth- and fifth-generation cephalosporins and quinolones and fluoroquinolones. Fourteen are part of the OIE list of antimicrobials of veterinary importance. Antimicrobials are also used to some extent for—apart from treatment—prevention and control of diseases as, for instance, in dry cow therapy as a preventive measure for mastitis. Apart from bacterial infections, they are also administered for viral diseases such as to address secondary infections (see *Table 8: Critically important antimicrobials used in the Indian dairy sector to prevent, control or treat diseases*). There are also examples on use of alternative to antibiotics (see *Box: Ethnoveterinary medicines: Alternative to antibiotics in the Indian dairy sector*).

Table 8: Critically important antimicrobials used in the Indian dairy sector to prevent, control or treat diseases

Antimicrobial	Antimicrobial class	Disease
Highest priority critically important antimicrobials considered veterinary critically important antimicrobials		
Cefoperazone	Third-, fourth- and fifth-generation cephalosporins	Mastitis
Ceftiofur*		Mastitis, haemorrhagic septicaemia, anthrax
Ceftriaxone		Mastitis, haemorrhagic septicaemia; viral disease: foot and mouth disease
Cefquinome		Mastitis
Ciprofloxacin	Quinolones and fluoroquinolones	Anthrax, diarrhoea; viral disease: foot and mouth disease
Enrofloxacin*		Mastitis, haemorrhagic septicaemia, diarrhoea; viral disease: foot and mouth disease, infectious bovine rhinotracheitis
Norfloxacin		Diarrhoea
Ofloxacin		Diarrhoea
Critically important antimicrobials considered veterinary critically important antimicrobials		
Amoxicillin	Penicillins	Mastitis; viral disease: foot and mouth disease
Ampicillin		Mastitis, black quarter, brucellosis; viral disease: foot and mouth disease, infectious bovine rhinotracheitis
Amikacin	Aminoglycosides	Mastitis, brucellosis
Gentamicin		Mastitis, diarrhoea; viral disease: foot and mouth disease
Streptomycin		Mastitis, black quarter, brucellosis, tuberculosis; viral disease: foot and mouth disease
Critically important antimicrobials considered veterinary highly important antimicrobials		
Rifampicin	Ansamycins	Brucellosis, tuberculosis
Highest priority critically important antimicrobials not mentioned in OIE list		
Cefotaxime	Third-, fourth- and fifth-generation cephalosporins	Mastitis, haemorrhagic septicaemia
Ceftazidime		Mastitis
Ceftizoxime		Mastitis
Levofloxacin	Quinolones and fluoroquinolones	Mastitis
Moxifloxacin		Mastitis
Critically important antimicrobials not mentioned in OIE list		
Ethambutol	Drugs used solely to treat tuberculosis or other mycobacterial disease	Tuberculosis
Isoniazid		Tuberculosis

Note: In addition to the above, antimicrobials which are not critically important and used in Indian dairy sector include tetracycline, oxytetracycline, doxycycline, trimethoprim, sulfamethoxazole, sulfadimidine, cloxacillin, benzylpenicillin, nitrofural, cefalexin, ornidazole and metronidazole.

* Ceftiofur, enrofloxacin are known to be used in animals, but they can lead to development of cross-resistance in bacteria to other antibiotics belonging to the same class, which are critically important for use in humans

Source: Information based on CSE research and interaction with experts from the Indian dairy sector

Ethnoveterinary medicines: Alternative to antibiotics in the Indian dairy sector

Ethnoveterinary medicines are emerging as an alternative to antibiotics to treat cases of mastitis in dairy cows. These herbal formulations—comprising aloe vera, turmeric, lime (calcium hydroxide) and mustard oil—are promoted by the National Dairy Development Board (NDDB), India. NDDB is working with more than 1,500 district cooperative societies in 24 milk unions across nine states under its Mastitis Control Popularisation Project. Since 2016–17, it has trained more than 6,000 animal husbandry personnel in ethnoveterinary medicines. NDDB has so far treated over 1.17 lakh mastitis cases with ethnoveterinary medicines, with a cure rate of 79 per cent. For other common ailments like fever, diarrhoea, and foot and mouth disease, a cure rate of 82 per cent has been seen from 2.44 lakh cases.

In the poultry sector, 14 critically important antimicrobials from four classes are used. Eight are from two highest priority critically important antimicrobial classes i.e. macrolides and ketolides and quinolones and fluoroquinolones. Twelve are part of the OIE list of antimicrobials of veterinary importance. Antimicrobials are used for growth promotion, prevention, control and treatment. It is believed that often their use as growth promoter can have a preventive effect and vice versa. Apart from bacterial infections, they are also administered for fungal infections and viral diseases such as to address secondary bacterial infections (see *Table 9: Critically important antimicrobials used in the Indian poultry sector to prevent, control or treat diseases*).

Critically important antimicrobials are also found in feed and feed premixes sold in the Indian market. These include erythromycin, neomycin, streptomycin, penicillin, tylosin and tylvalosin and were found to be recommended for growth promotion and/or prevention or control of specific diseases by feed and feed premix manufacturers.

In the aquaculture sector, only three critically important antimicrobials are used from quinolones and fluoroquinolones, which is a highest priority critically important antimicrobial class. All are part of the OIE list of antimicrobials of veterinary importance. These are mostly used for prevention, control or treatment of infections caused by bacteria, including *Vibrio* spp., *Aeromonas* spp. and others such as *Pseudomonas* sp., *Flavobacterium* sp., *Edwardsiella* spp. Other commonly used antimicrobials in aquaculture include tetracycline, oxytetracycline, doxycycline, trimethoprim, sulfamethoxazole, cefalexin, furazolidone, chloramphenicol and nitrofurans. These are not considered critically important for human use but are medically important (see *Table 10: Critically important antimicrobials used in the Indian aquaculture sector to prevent, control or treat diseases*).

Table 9: Critically important antimicrobials used in the Indian poultry sector to prevent, control or treat diseases

Antimicrobial	Antimicrobial class	Disease
Highest priority critically important antimicrobials considered veterinary critically important antimicrobials		
Ciprofloxacin	Quinolones and fluoroquinolones	Pullorum disease, fowl typhoid, colibacillosis, salmonellosis
Enrofloxacin*		Fowl cholera, infectious coryza, pullorum disease, fowl typhoid, colibacillosis, necrotic enteritis, salmonellosis, chronic respiratory disease; viral diseases: Ranikhet disease, infectious bronchitis, avian influenza, Marek's disease, infectious bursal disease
Norfloxacin		Colibacillosis
Erythromycin	Macrolides and ketolides	Infectious coryza
Tylosin*		Chronic respiratory disease; fungal disease: mycotoxicosis
Tylvalosin*		Chronic respiratory disease
Critically important antimicrobials considered veterinary critically important antimicrobials		
Amoxicillin	Penicillin	Necrotic enteritis; viral disease: Ranikhet disease
Ampicillin		Necrotic enteritis
Amikacin	Aminoglycosides	Infectious coryza, pullorum disease, fowl typhoid, colibacillosis, salmonellosis
Gentamicin		Pullorum disease, fowl typhoid, salmonellosis
Neomycin		Pullorum disease, colibacillosis, necrotic enteritis; fungal disease: aspergillosis, mycotoxicosis
Streptomycin		Fowl cholera
Highest priority critically important antimicrobials not mentioned in OIE list		
Azithromycin	Macrolides and ketolides	Fowl cholera
Levofloxacin	Quinolones and fluoroquinolones	Fowl cholera, Infectious coryza, pullorum disease, fowl typhoid, colibacillosis, necrotic enteritis, salmonellosis; viral disease: Ranikhet disease

Note: In addition to the above, antimicrobials that are not critically important and are used in the Indian poultry sector include tetracycline, oxytetracycline, doxycycline, trimethoprim, sulfamethoxazole, tiamulin, cefalexin, furazolidone and chloramphenicol.

*Enrofloxacin, tylosin and tylvalosin are known to be used in animals, but they can lead to development of cross-resistance in bacteria to other antibiotics belonging to the same class, which are critically important for use in humans

Source: Information based on CSE research and interaction with experts from Indian poultry sector

Table 10: Critically important antimicrobials used in the Indian aquaculture sector to prevent, control or treat diseases

Antimicrobial	Antimicrobial class	Disease
Highest priority critically important antimicrobials considered veterinary critically important antimicrobials		
Ciprofloxacin	Quinolones and fluoroquinolones	For one or more of the following: Infections caused by *Aeromonas* spp.: e.g. motile aeromonad septicaemia, hemorrhagic septicemia, red sore, tail rot and fin rot, furunculosis Infections caused by *Vibrio* spp.: e.g. vibriosis, intestinal necrosis, anaemia Infections caused by *Pseudomonas* sp.: e.g. pseudomonas septicaemia, fin rot Infections caused by *Flavobacterium* sp.: e.g. columnaris disease, bacterial gill disease Infections caused by *Edwardsiella* sp.: e.g. edwardsiellosis
Enrofloxacin*		
Oxolinic acid		

*Enrofloxacin is known to be used in animals and aquaculture, but it can lead to development of cross-resistance in bacteria to other antibiotics belonging to the same class, which is critically important for use in humans

Source: Information based on CSE research and interaction with experts from Indian aquaculture sector

It is clear what kind of antimicrobials are used. However, it is not clear how much antimicrobials or critically important antimicrobials are used in Indian dairy, poultry and aquaculture settings. There is no national surveillance. OIE publishes the data on antimicrobial agents intended for use in animals annually, but since no country-specific data is available, it is difficult to know about the status in India. A recent study, however, published in 2020 in the journal *Antibiotics* indicated that in 2017 India was among the top 10 countries in terms of veterinary antimicrobial consumption, accounting for 2.2 per cent of the total 75 per cent of antimicrobial consumption accounted for by the 10 countries.[27] Although the percentage is low, the study estimates that consumption in the case of India is likely to rise by 7 per cent by 2030. This could be due to the growing demand for cheap protein and rising intensification in farms.

4.2 Recommended use of critically important antimicrobials in humans and resistance trends

Analysis of India's *National Treatment Guidelines for Antimicrobial Use in Infectious Diseases* reveals that critically important antimicrobials used in food-animals in India are recommended for the treatment of several infections in human health as empirical, definitive, first- or second-line medications.[28] They are recommended for common and for serious infections such as urinary tract infections (UTIs), bloodstream infections, cardiovascular infections, biliary tract infections, neonatal and paediatric infections, pneumonia and other respiratory tract infections, gastrointestinal and intra-abdominal infections, skin and soft tissue infections, obstetric and gynaecological infections, and meningitis (see *Box: Specific examples wherein critically important antimicrobials are recommended for human health in India*).

Specific examples wherein critically important antimicrobials are recommended for human health in India

- **Cefoperazone** for treatment of obstetric sepsis during pregnancy, microbiologically infected burn wounds, infection of vascular catheters, ventilator-associated or hospital-acquired pneumonia, catheter-associated urinary tract infection in adults.
- **Ceftriaxone** for use in adults but is also in children for septicaemia, neonatal meningitis, severe pneumonia, complicated or severe UTI, antimicrobial coverage for paediatric surgical procedures.
- **Azithromycin** for use in acute pharyngitis, enteric fever, bacterial dysentery, community-acquired pneumonia, acute rheumatic fever, chemoprophylaxis in children.
- **Ciprofloxacin** for treatment of cornea infections, multi-drug resistant bacterial infections, acute inflammatory infective diarrhoeas, serious infected diabetic ulcers, infected burn wounds, severe acute pelvic inflammatory disease, acute prostatitis.
- **Amikacin** for pyelonephritis, pneumonia and in children for urinary tract infection, septicaemia or pneumonia in infants with severe sepsis.
- **Gentamicin** for endocarditis, obstetric sepsis during pregnancy, corneal infections, osteomyelitis, septic arthritis and in children for the treatment of neonatal meningitis, septicaemia, pneumonia.
- **Ampicillin** for infective endocarditis, group B streptococcal disease, septic abortion, peritonitis, vancomycin resistant enterococcus and neonatal meningitis, severe pneumonia, neonatal septicaemia.
- **Amoxicillin** is advised for the treatment of cellulitis, acute pharyngitis, rhinosinusitis, acute bacterial exacerbation of chronic obstructive pulmonary disease, asymptomatic bacteriuria (an obstetrics and gynaecology infection), obstetric sepsis during pregnancy, acute otitis media, acute rheumatic fever and other acute ear infection.

The resistance data for human samples against critically important antimicrobials use in food-producing animals in India were also reviewed. As per the resistance trends from the National Centre for Disease Control, resistance is high in almost all bacteria tested against critically important antimicrobials for which data is available. These include cefotaxime, ceftazidime, ciprofloxacin, levofloxacin, erythromycin, gentamicin, amikacin and ampicillin and many of these are highest priority critically important antimicrobials. As per the susceptibility trends (as measured) from the Indian Council of Medical Research, susceptibility is on the lower side except in a few cases.

While both data sources do not report on exactly the same bacteria, other than in the case of *Pseudomonas* sp. it could be inferred that the results indicate the same scenario, i.e. when there is high degree of resistance, susceptibility is also low (see *Table 11: Resistance and susceptibility trends in bacteria against critically important antimicrobials*).

Table 11: Resistance and susceptibility trends in bacteria against critically important antimicrobials

Antibiotic (class)	*S. aureus*	*Enterococcus* sp.	*E. coli*	*Klebsiella* sp.	*Pseudomonas* sp.	*Acinetobacter* sp.	*S. aureus*	*E. faecalis*	*E. faecium*	*E. coli*	*K. pneumoniae*	*P. aeruginosa*	*A. baumannii*
	Per cent resistance (NCDC, 2019)						Per cent susceptibility (ICMR, 2019)						
Cefotaxime (third-, fourth- and fifth-generation cephalosporins)*	–	–	78.0	79.0	–	–	–	–	–	14.5	21.3	–	–
Ceftazidime (third-, fourth- and fifth-generation cephalosporins)*	–	–	–	–	53.0	78.0	–	–	–	20.0	25.3	63.1	12.2
Ciprofloxacin (quinolones and fluoroquinolones)*	66.0	77.0	79.0	71.0	54.0	65.0	17.8	16.4	8.0	20.8	36.0	57.7	–
Levofloxacin (quinolones and fluoroquinolones)*	–	–	–	–	–	–	–	–	–	19.0	35.0	56.5	19.1
Erythromycin (macrolides and ketolides)*	60.0	80.0	–	–	–	–	40.2	–	–	–	–	–	–
Gentamicin (aminoglycosides)	23.0	48.0	–	–	49.0	55.0	–	57.5	35.0	–	–	62.2	–
Amikacin (aminoglycosides)	–	–	–	47.0	45.0	60.0	–	–	–	79.2	50.1	67.9	20.4
Ampicillin (penicillins)	–	61.0	87.0	–	–	–	–	80.8	18.1	–	–	–	–

Note: "–" indicates data is not available; Resistance and Susceptibility refer to results of antimicrobial susceptibility testing where bacteria cannot be treated with the antimicrobial (resistance) or can be treated with the antimicrobial (susceptible).
* Highest Priority Critically Important Antimicrobials
Sources: (a) National Antimicrobial Resistance Surveillance Network (NARS-Net India) AMR Annual report 2020, Reporting period: January–December 2019
(b) Antimicrobial Resistance Surveillance and Research Network, Annual Report, Indian Council of Medical Research, January–December 2019

Early in 2021, the Department of Biotechnology, India, in collaboration with WHO India, developed the Indian Priority Pathogen List (IPPL) to guide research, discovery and development of new and effective antibiotics from the Indian perspective.[29] The list includes the most important resistant bacteria at the national level in India for which there is an urgent need to develop novel drugs and treatments. In alignment with the Global Priority Pathogen List, the identified bacterial pathogens have been stratified into critical, high and medium priority tiers (see *Box: Indian Priority Pathogens List).*

While data from Indian Network for Fisheries and Animals Antimicrobial Resistance (INFAAR) is not available in the public domain, studies in the food-animal sector report high resistance against critically important antimicrobials. For example, in the dairy sector, pathogens such as *E. coli and S. aureus* isolated from dairy cows and farm environments have been found resistant to antimicrobials like penicillin, oxacillin, kanamycin, amoxicillin, or methicillin.[30, 31] Similarly, in the poultry sector, resistance has been found in Extended-Spectrum Beta-Lactamase (ESBL)-producing *E. coli* and *Salmonella* isolates from different samples (e.g. eggs, feed, water, faeces and cloaca) such

Indian Priority Pathogens List

Critical priority

Enterobacteriaceae (*Klebsiella pneumoniae* and *Escherichia coli*): Carbapenem, tigecycline and colistin-R

Non-fermenting bacteria (*Acinetobacter baumannii* and *Pseudomonas aeruginosa*): Carbapenem and colistin-R

High priority

Staphylococcus aureus: methicillin-resistant *S. aureus*, heterogenous vancomycin-intermediate *S. aureus*, daptomycin-NS, linezolid-R

Enterococcus species: Vancomycin and linezolid-R, daptomycin-NS

Salmonella species (typhoidal and non-typhoidal): Azithromycin, third-generation cephalosporins and carbapenem-NS

Medium priority

Streptococcus pneumoniae: Cephalosporin, fluoroquinolones and linezolid-R

Staphylococcus, coagulase-negative: Vancomycin and linezolid-R

Shigella species: Third-generation cephalosporins and azithromycin-R

Haemophilus influenza: Third-generation cephalosporin and carbapenem-NS

Neisseria meningitides: Fluoroquinolones and third-generation cephalosporins-NS

Note: R: resistant; NS: non-susceptible; Mycobacteria, including *Mycobacterium tuberculosis*, were not included in this prioritization exercise as it is a well-established global and national priority for which innovative new treatments are urgently needed and being developed.

as against cefotaxime, ceftazidime, cefpodoxime and clindamycin, oxacillin, penicillin or vancomycin.[32, 33] In the case of aquaculture, resistance has been observed in bacteria such as *E. coli*, *Salmonella* spp., *S. aureus, Pseudomonas entomophila, Edwardsiella tarda, Comamonas* sp., *Delftia tsuruhatensis, Aeromonas* sp. isolated from fish. This has been reported against streptomycin, trimethoprim, meropenem, doripenem, imipenem, cefoperazone, cefixime, cefotaxime, or ceftriaxone.[34, 35]

4.3. Policies for and gaps in critically important antimicrobials in food-producing animals

Most Indian policies and guidelines for the food-animal sector in India do not target critically important antimicrobials except one against colistin by the Ministry of Health and Family Welfare in 2019. As there is no explicit mention against other critically important antimicrobials in the advisories or guidance, it suggests that these can in fact be used (see *Table 12: Gaps in policies, and guidelines on critically important antimicrobial use in India*).

Table 12: Gaps in policies, and guidelines on critically important antimicrobial use in India

Policy/guideline (stakeholder)	Key features and gaps
Gazette Notification dated July 19, 2019 (Ministry of Health and Family Welfare)[36]	Prohibited the sale, manufacture and distribution of colistin and its formulations in food-producing animals, poultry, aqua-farming and animal feed supplements. Gaps: No action on other critically important antimicrobials. They are still used in practice.
Guidelines for Regulating Coastal Aquaculture, under the Coastal Aquaculture Authority Rules, 2005 (Coastal Aquaculture Authority)[37]	Prohibits a set of antibiotics from use in aquaculture which includes critically important antimicrobial classes like fluoroquinolones, glycopeptides, and critically important antimicrobials like neomycin, nalidixic acid. Gaps: Banned antibiotics limited to only few critically important antimicrobials; these are applicable only to shrimp aquaculture. There is no such policy for freshwater aquaculture by concerned stakeholder in fisheries ministry/department.
Farmer Manual (dairy sector) (Department of Animal Husbandry and Dairying)[38]	Recommends the use of four antibiotics (penicillin, gentamicin, streptomycin, and enrofloxacin) for treatment of various diseases. Gaps: All recommended antibiotics for use are critically important antimicrobials.
Poultry Farm Manual (Department of Animal Husbandry and Dairying)[39]	Advises the use of only enrofloxacin, gentamicin, sulpha drugs and tylosin for common poultry diseases. Gaps: Many of the recommended antibiotics are critically important antimicrobials.

Policy/guideline (stakeholder)	Key features and gaps
Poultry Feed Specification (fifth revision 1374:2007) (Bureau of Indian Standards)[40]	Recommends not using antibiotics with systemic action as growth promoters in feed. These include chloramphenicol, doxycycline, tetracycline, nitrofuran, furazolidone. Also mentions phasing out of gut acting antibiotics in five years. *Gaps: Antibiotic growth promoters still allowed in feed. Even critically important antimicrobials are used as feed additives or supplements for feed. Besides, this is a voluntary standard, therefore non-binding. Revision of the standard is under process for many years.
Drugs and Cosmetics Act, 1940 (Central Drugs Standards Control Organisation)[41]	The definition of drug mentioned is "all medicines for internal or external use of human beings or animals and all substances intended to be used for or in the diagnosis, treatment, mitigation or prevention of any disease or disorder in human beings or animals, including preparations applied on human body for the purpose of repelling insects like mosquitoes". Gaps: The word "prevention" is found to used to justify antimicrobial use for disease prevention. Another gap is that it does not refer to antimicrobials in feed, therefore antimicrobial for growth promoter use in feed gets out of its purview and has remained unregulated so far. In addition, it also does not mention crops, which makes it difficult to regulate antibiotics used in crops.

* The poultry feed specification is currently being modified in this regard and there are discussions underway to prohibit all medically important antimicrobials in feed. The draft standard is yet to be agreed by stakeholders and issued.

Globally, there are examples of restricting the use of critically important antimicrobials in some developed and developing countries (see *Box: Global best practices on restricting critically important antimicrobial use in food-producing animals).*

Global best practices on restricting critically important antimicrobial use in food-producing animals

The Antimicrobial Advice Ad Hoc Expert Group (AMEG) of the European Medicines has recently classified antibiotics for veterinary use. This is based on the potential consequences to public health of increased AMR when used in animals and the need for their use in veterinary medicine.[42, 43] The classification comprises of four categories A to D (A—Avoid, B—Restrict, C—Caution and D—Prudence). Most classes of critically important antimicrobials are positioned under categories A, B and C. The details are as follows:

- Avoid: Carbapenems, glycopeptides, ketolodes, lipopeptides, glycylcyclines, monobactams, oxazolodinones, phosponic acid derivatives
- Restrict: Quinolones (fluoroquinolones and other quinolones), third- and fourth-generation cephalosporins (with the exception of combinations with β-lactamase inhibitors), polymyxins
- Caution: Aminoglycosides (except spectinomycin), aminopenicillins (in combination with β-lactamase inhibitors), macrolides

The European Union is also planning to ban all preventative group treatments in animals starting 2022.[44] In addition, the Guidelines for Prudent Use of Antimicrobials in Veterinary Medicine of the European Union recognize the need for careful considerations before using critically important antimicrobials in animals.[45]

Apart from recent measures planned/adopted by the Europe as a whole, some European countries have taken action at their own level recently or many years ago to conserve critically important antimicrobials such as cephalosporins, fluoroquinolones and macrolides to some extent.

For example, in 2016, France prohibited medicines containing one or more critically important antibiotic substances in veterinary medicine for preventive use. For other uses (curative or metaphylaxis), they can be prescribed under certain conditions, or prohibited. The conditions for their prescription are performing a clinical examination and obtaining laboratory results indicating that the bacterial strain identified is sensitive only to this critically important antibiotic substance.[46]

Denmark restricted the use of fluoroquinolones in animal husbandry through regulatory action in 2002.[47] Similarly, the use of cephalosporins in the pig industry and dairy cattle industry was voluntarily stopped in 2010 and 2014 respectively. The Swedish Veterinary Association guides that use of fluoroquinolones, cephalosporins and macrolides in veterinary medicine should be limited and used only when no other alternatives are present.[48]

In the Netherlands, the Guideline Classification of Veterinary Antimicrobials classifies antimicrobials used in veterinary medicine as first, second and third choice.[49, 50] Third-choice antimicrobials, it says, are those critical for human health and should be used only in individual animals if bacteriological studies have shown there are no other alternatives. It identifies highest priority critically important antimicrobials such as third- and fourth-generation cephalosporins, fluoroquinolones as third-choice antimicrobials. In addition, there is also another category of antimicrobials that is forbidden from use in food-producing animals. These include critically important antimicrobials such as carbapenems, glycopeptides, oxazolidones and daptomycin, mupirocin, tigecycline which are used as "last resort" resources reserved for human use and should never be used with animals not even via the cascade control.

In USA, fluoroquinolones and cephalosporins are prohibited by the US Food and Drug Administration from extra-label or unapproved uses in food-producing animals.[51]

In addition to initiatives in high-income countries, there have been recent initiatives in few countries in the developing part of the world. For example, Malaysia has banned use of colistin in 2019 and six other antibiotics from being used in food-producing animals in 2021 for their use as growth promoter and in prophylaxis. Five out of these six are critically important antimicrobials. These include erythromycin, enrofloxacin, tetracycline, ceftiofur, tylosin and fosfomycin. It also plans to phase out by 2025 use of critically important antimicrobials and veterinary critically important antimicrobials in the animal sector. In Indonesia and Argentina,[52] colistin has been banned for use in animals/food-animals just as in India.

With global momentum developing towards phasing out the use of highest priority critically important antimicrobials as growth promoters in food-producing animals, many developing countries such as Bangladesh, Malaysia, Thailand, Indonesia, Vietnam, Sri Lanka, Singapore, South Korea, Cambodia and Brazil have prohibited antimicrobials—including critically important antimicrobials—as growth promoters or in feed as additives. China had banned the use of four antimicrobials—lomefloxacine, pefloxacine, ofloxacin and norfloxacin—in animal feed in 2015, and colistin as a feed additive for animals in 2017. All kinds of growth-promoting drug feed additives (except for Chinese traditional medicine) were planned to be withdrawn in China after January 1, 2020.

5. Recommendations for Indian policy framework to conserve use of critically important antimicrobials

India needs to focus on conserving the use of critically important antimicrobials, which are commonly used across several food-animal sectors. Such use of important public-health good needs to be better regulated and markedly reduced in different food-animal sectors. Already, critically important antimicrobials are becoming ineffective in treating several common as well as serious infections as high resistance can be seen against them. With rising demand of food and protein from animals, the Indian food-producing animal sector is growing and will depend more on chemicals. India therefore needs a concerted effort to ensure that critically important antimicrobials are not misused or overused and are used more carefully and responsibly. This will not only help human health but also animal health and productivity of food systems.

India should consider developing a road map and necessary policy framework to conserve the use of critically important antimicrobials. This may include both human and non-human sector initiatives. For different food-producing animals, this may include sector-specific road maps and change required in policies, regulations, standards and guidelines in addition to creating awareness, building capacity and better enforcement. Specifically, such a road map/policy framework should include:

- New/revised guidelines that recommend antimicrobials for all food-animal sectors such as dairy and poultry. The guidelines should aim to phase out use of critically important antimicrobials for all non-therapeutic purposes with immediate priority given to highest priority critically important antimicrobials. Use of critically important antimicrobials for therapeutic purposes should not be resorted to when alternative effective antibiotics are available. All the necessary details on conditions of use should be mentioned. Their use for treatment should always be under professional supervision based on appropriate diagnosis and sensitivity testing.

- Use of highest priority critically important antimicrobials for treatment should also be considered for phase-out. They should only be allowed in exceptional situations as a last resort and through necessary policy instruments. Fluoroquinolones and third-, fourth- and fifth-generation cephalosporins are examples of restricted-use highest priority critically important antimicrobials in other parts of the world. A careful consideration should be made on the basis of Indian data. India has taken similar action against colistin, which needs to be expanded to include other highest priority critically important antimicrobials.

- Prohibition of antibiotic growth promoters in food-producing animals such as in the case of the poultry sector. The poultry feed standards are being modified but are voluntary. It is important that they are made mandatory and medically important antimicrobials—including critically important antimicrobials—are not allowed in feed.

- Antimicrobial use for disease prevention (including control) should be recognized as non-therapeutic and all measures should be adopted and/or promoted to discourage such use in farms. In particular, group preventive use should receive immediate attention. Necessary focus should also be placed on promoting and incentivizing use of non-antimicrobial alternatives, biosecurity, hygiene and sanitation, and good animal-rearing practices. These are often lacking in Indian farms and are substituted by mass use of antimicrobials to prevent and control diseases, which does more harm than good.

- The definition of "drug" in the Drugs and Cosmetics Act, 1940 includes the word "prevention". It is important to revise and/or clarify the definition to ensure that it is not used to justify the use of antimicrobials in disease prevention in food-producing animals. The definition also needs to ensure that antimicrobials in feed are regulated. As of now these are left unregulated but should ideally fall under the purview of this Act. In addition to food-producing animals, the definition also needs to include antimicrobial use in crops. Most of these are Schedule H drugs and are different from pesticides, which necessitates their regulation under the Drugs and Cosmetics Act in addition to the Central Insecticide Board and Registration Committee of the Ministry of Agriculture and Farmers' Welfare.

- A long-term research agenda should be developed and implemented for non-antimicrobial alternatives and their effectiveness understood in managing diseases in animal farms. Programmatic interventions should be made for their greater promotion and adoption.

- Setting up systems and mechanisms to gather data and enhance understanding on critically important antimicrobial use and resistance in food-producing animals. This data on sector-wise use should be analysed with resistance in animals and humans and the reports should be made public annually.

- Investment in creating awareness among farmers and building capacity for good animal-rearing practices to prevent occurrence and spread of disease at farms.
- Programmatic interventions to ensure that veterinarians prescribe antimicrobials responsibly only and when necessary.
- Routine monitoring by the central food regulator (FSSAI) and state food regulators on antimicrobial use and residues to ensure that withdrawal periods are followed and residue standards are met. FSSAI should also modify its standards as soon as use of a specific critically important antimicrobial is restricted or banned as in the case of colistin.

Annexures

Annexure 1: WHO list of critically important antimicrobials for human medicine

Antimicrobial class	Antimicrobial
Critically important antimicrobials	
Aminoglycosides	Amikacin, apramycin, arbekacin, astromicin, bekanamycin, dibekacin, dihydrostreptomycin, framycetin, gentamicin, isepamicin, kanamycin, neomycin, netilmicin, paromomycin, plazomicin, ribostamycin, streptomycin, tobramycin
Ansamycins	Rifabutin, rifampicin, rifamycin, rifapentine, rifaximin
Carbapenems and other penems	Biapenem, doripenem, ertapenem, faropenem, imipenem, meropenem, meropenem/vaborbactam, panipenem
Cephalosporins (third-, fourth- and fifth-generation)	Cefcapene, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefodizime, cefoperazone, cefoperazone-sulbactam, cefoselis, cefotaxime, cefovecin, cefozopran, cefpiramide, cefpirome, cefpodoxime, cefquinome, cefsulodin, ceftaroline fosamil, ceftazidime, ceftazidime-avibactam, ceftibuten, ceftiofur, ceftizoxime, ceftobiprole, ceftolozane, ceftriaxone, ceftriaxone-sulbactam, latamoxef, tazobactam
Glycopeptides and lipoglycopeptides	Avoparcin, dalbavancin, oritavancin, ramoplanin, teicoplanin, telavancin, vancomycin
Glycylcyclines	Tigecycline
Lipopeptides	Daptomycin
Macrolides and ketolides	Azithromycin, cethromycin, clarithromycin, dirithromycin, erythromycin, fidaxomicin, flurithromycin, gamithromycin, josamycin, kitasamycin, midecamycin, miocamycin, oleandomycin, rokitamycin, roxithromycin, spiramycin, telithromycin, tildipirosin, tilmicosin, troleandomycin, solithromycin, tulathromycin, tylosin, tylvalosin
Monobactams	Aztreonam, carumonam
Oxazolidinones	Cadazolid, linezolid, radezolid, tedizolid
Penicillins (antipseudomonal)	Azlocillin, carbenicillin, carindacillin, mezlocillin, piperacillin, piperacillin-tazobactam, sulbenicillin, ticarcillin, ticarcillin-clavulanic acid
Penicillins (aminopenicillins)	Amoxicillin, ampicillin, azidocillin, bacampicillin, epicillin, hetacillin, metampicillin, pivampicillin, sultamicillin, talampicillin, temocillin
Penicillins (aminopenicillins with beta-lactamase inhibitors)	Amoxicillin-clavulanic acid, ampicillin-sulbactam
Phosphonic acid derivatives	Fosfomycin
Polymyxins	Colistin, polymyxin B

Antimicrobial class	Antimicrobial
Quinolones and fluoroquinolones	Besifloxacin, cinoxacin, ciprofloxacin, danofloxacin, delafloxacin, difloxacin, enoxacin, enrofloxacin, fleroxacin, flumequine, garenoxacin, gatifloxacin, gemifloxacin, grepafloxacin, ibafloxacin, levofloxacin, lomefloxacin, marbofloxacin, moxifloxacin, nadifloxacin, nalidixic acid, norfloxacin, ofloxacin, orbifloxacin, ozenoxacin, oxolinic acid, pazufloxacin, pefloxacin, pipemidic acid, piromidic acid, pradofloxacin, prulifloxacin, rosoxacin, rufloxacin, sitafloxacin, sparfloxacin, temafloxacin
Drugs used solely to treat tuberculosis or other mycobacterial diseases	Bedaquiline, calcium aminosalicylate, capreomycin, cycloserine, delamanid, ethambutol, ethionamide, isoniazid, morinamide, para-aminosalicylic-acid, protionamide, pyrazinamide, sodium aminosalicylate, terizidone, tiocarlide
Highly important antimicrobials	
Amphenicols	Chloramphenicol, florfenicol, thiamphenicol
Cephalosporins (first- and second-generation) and cephamycins	Cefacetrile, cefaclor, cefadroxil, cefalexin, cefalonium, cefaloridine, cefalotin, cefalotin, cefamandole, cefapirin, cefatrizine, cefazedone, cefazolin, cefbuperazone, cefmetazole, cefminox, cefonicid, ceforanide, cefotetan, cefotiam, cefoxitin, cefprozil, cefradine, cefroxadine, ceftezole, cefuroxime, flomoxef, loracarbef
Lincosamides	Clindamycin, lincomycin, pirlimycin
Penicillins (amidinopenicillins)	Mecillinam, pivmecillinam
Penicillins (anti-staphylococcal)	Cloxacillin, dicloxacillin, flucloxacillin, meticillin (=methicillin), oxacillin, nafcillin
Penicillins (narrow spectrum)	Benzathine-benzylpenicillin, Benethamine-benzylpenicillin, benzylpenicillin (=penicillin G), clometocillin, penamecillin, penethamate hydriodide, pheneticillin, phenoxymethylpenicillin (=penicillin V), procaine benzylpenicillin, propicillin
Pseudomonic acids	Mupirocin
Riminofenazines	Clofazimine
Fusidane	Fusidic acid
Streptogramins	Pristinamycin, quinupristin-dalfopristin, virginiamycin
Sulfonamides, dihydrofolate reductase inhibitors and combinations	Brodimoprim, formosulfathiazole, iclaprim, phthalylsulfathiazole, pyrimethamine, sulfadiazine, sulfadimethoxine, sulfadimidine, sulfafurazole (=sulfisoxazole), sulfaisodimidine, sulfalene, sulfamazone, sulfamerazine, sulfamethizole, sulfamethoxazole, sulfamethoxypyridazine, sulfametomidine, sulfametoxydiazine, sulfametrole, sulfamoxole, sulphanilamide, sulfaperin, sulfaphenazole, sulfapyridine, sulfathiazole, sulfathiourea, tetroxoprim, trimethoprim
Sulfones	Aldesulfone sodium, dapsone
Tetracyclines	Chlortetracycline, clomocycline, demeclocycline, doxycycline, eravacycline, lymecycline, metacycline, minocycline, omadacycline, oxytetracycline, penimepicycline, rolitetracycline, tetracycline
Important antimicrobials	
Aminocyclitols	Spectinomycin
Polypeptides	Bacitracin
Nitrofurans derivatives	Furaltadone, furazolidone, furazidin, nifurtoinol, nitrofural, nitrofurantoin
Nitroimidazoles	Metronidazole, ornidazole, secnidazole, tinidazole
Pleuromutilins	Retapamulin, tiamulin, valnemulin

Annexure 2: OIE list of antimicrobial agents of veterinary importance

Antimicrobial agents (class/subclass)	Antimicrobial	Species of animal
Veterinary critically important antimicrobial agents (VCIA)		
Aminocyclitol	Spectinomycin	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI
Aminoglycosides	Dihydrostreptomycin	AVI, BOV, CAP, EQU, LEP, OVI, SUI
	Streptomycin	API, AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI
Aminoglycosides + 2 deoxystreptamine	Amikacin	EQU
	Apramycin	AVI, BOV, LEP, OVI, SUI
	Fortimycin	AVI, BOV, LEP, OVI, SUI
	Framycetin	BOV, CAP, OVI
	Gentamicin	AVI, BOV, CAM, CAP, EQU, LEP,OVI, SUI
	Kanamycin	AVI, BOV, EQU, PIS, SUI
	Neomycin	API, AVI, BOV, CAP, EQU, LEP, OVI, SUI
	Paromomycin	AVI, BOV, CAP, OVI, LEP, SUI
	Tobramycin	EQU
Cephalosporins third-generation	Cefoperazone	BOV, CAP, OVI
	Ceftiofur	AVI, BOV, CAP, EQU, LEP, OVI, SUI
	Ceftriaxone	AVI, BOV, OVI, SUI
Cephalosporins fourth-generation	Cefquinome	BOV, CAP, EQU, LEP, OVI, SUI
Macrolides C14-membered ring	Erythromycin	API, AVI, BOV,CAP, EQU, LEP, OVI, PIS, SUI
	Oleandomycin	BOV
Macrolides C15-membered ring	Gamithromycin	BOV
	Tulathromycin	BOV, SUI
Macrolides C16-membered ring	Carbomycin	AVI
	Josamycin	AVI, PIS, SUI
	Kitasamycin	AVI, PIS, SUI
	Mirosamycin	AVI, PIS, SUI, API
	Spiramycin	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI
	Terdecamycin	AVI, SUI
	Tildipirosin	BOV, SUI
	Tilmicosin	AVI, BOV, CAP, LEP, OVI, SUI
	Tylosin	API, AVI, BOV, CAP, LEP, OVI, SUI
	Tylvalosin	AVI, SUI
Macrolides C17-membered ring	Sedecamycin	SUI
Amdinopenicillins	Mecillinam	BOV, SUI
Aminopenicillin + beta-lactamase inhibitor	Amoxicillin + clavulanic acid	AVI, BOV, CAP, EQU, OVI, SUI
	Ampicillin + sulbactam	AVI, BOV, SUI
Aminopenicillins	Amoxicillin	AVI, BOV, CAP, EQU, OVI, PIS, SUI
	Ampicillin	AVI, BOV, CAP, EQU, OVI, PIS, SUI
	Hetacillin	BOV
Antistaphylococcal penicillins	Cloxacillin	BOV, CAP, EQU, OVI, SUI
	Dicloxacillin	BOV, CAP, OVI, AVI, SUI
	Nafcillin	BOV, CAP, OVI
	Oxacillin	BOV, CAP, EQU, OVI, AVI, SUI

Antimicrobial agents (class/subclass)	Antimicrobial	Species of animal
Carboxypenicillins	Ticarcillin	EQU
	Tobicillin	PIS
Natural penicillins	Benethamine penicillin	BOV
	Benzylpenicillin	AVI, BOV, CAM, CAP, EQU, LEP, OVI, SUI
	Benzylpenicillin procaine/ Benzathine penicillin	BOV, CAM, CAP, EQU, OVI, SUI
	Penethamate (hydroiodide)	BOV
Phenoxypenicillins	Phenethicillin	EQU
	Phenoxymethylpenicillin	AVI, SUI
Ureidopenicillin	Aspoxicillin	BOV, SUI
Quinolones second-generation (fluoroquinolones)	Ciprofloxacin	AVI, BOV, SUI
	Danofloxacin	AVI, BOV, CAP, LEP, OVI, SUI
	Difloxacin	AVI, BOV, LEP, SUI
	Enrofloxacin	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI
	Marbofloxacin	AVI, BOV, EQU, LEP, SUI
	Norfloxacin	AVI, BOV, CAP, LEP, OVI, SUI
	Ofloxacin	AVI, SUI
	Orbifloxacin	BOV, SUI
	Sarafloxacin	PIS
Sulfonamides	Sulfadoxine	BOV, EQU, OVI, SUI
	Sulfafurazole	BOV, PIS
	Sulfaguanidine	AVI, CAP, OVI
	Sulfamerazine	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI
	Sulfamethoxine	AVI, PIS, SUI
	Sulfamonomethoxine	AVI, PIS, SUI
	Sulfanilamide	AVI, BOV, CAP, OVI
	Sulfapyridine	BOV, SUI
	Sulfaquinoxaline	AVI, BOV, CAP, LEP, OVI
	Phthalylsulfathiazole	SUI
	Sulfacetamide	AVI, BOV, OVI
	Sulfachlorpyridazine	AVI, BOV, SUI
	Sulfadiazine	AVI, BOV, CAP, OVI, SUI
	Sulfadimethoxazole	AVI, BOV, SUI
	Sulfadimethoxine	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI
	Sulfadimidine (sulfamethazine, sulfadimerazin)	AVI, BOV, CAP, EQU, LEP, OVI, SUI
Sulfonamides + diaminopyrimidines	Ormetoprim + Sulfadimethoxine	PIS
	Sulfamethoxypyridazine	AVI, BOV, EQU, SUI
	Trimethoprim + Sulfonamide	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI
Tetracyclines	Chlortetracycline	AVI, BOV, CAP, EQU, LEP, OVI, SUI
	Doxycycline	AVI, BOV, CAM, CAP, EQU, LEP, OVI, PIS, SUI
	Oxytetracycline	API, AVI, BOV, CAM, CAP, EQU, LEP, OVI, PIS, SUI
	Tetracycline	API, AVI, BOV, CAM, CAP, EQU, LEP, OVI, PIS, SUI
Amphenicols	Florphenicol	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI
	Thiamphenicol	AVI, BOV, CAP, OVI, PIS, SUI

Antimicrobial agents (class/subclass)	Antimicrobial	Species of animal
Diaminopyrimidines	Baquiloprim	BOV, SUI
	Trimethoprim	AVI
	Ormetoprim	AVI, BOV, CAP, EQU, LEP, OVI, SUI
Veterinary highly important antimicrobial agents (VHIA)		
Cephalosporins first-generation	Cefacetrile	BOV
	Cefalexin	BOV, CAP, EQU, OVI, SUI
	Cefalonium	BOV, CAP, OVI
	Cefalotin	EQU
	Cefapyrin	BOV
	Cefazolin	BOV, CAP, OVI
Cephalosporins second-generation	Cefuroxime	BOV
Ansamycin-rifamycins	Rifampicin	EQU
	Rifaximin	BOV, CAP, EQU, LEP, OVI, SUI
Lincosamides	Lincomycin	API, AVI, BOV, CAP, OVI, PIS, SUI
	Pirlimycin	BOV, SUI, AVI
Phosphonic acid derivatives	Fosfomycin	AVI, BOV, PIS, SUI
Pleuromutilins	Tiamulin	AVI, CAP, LEP, OVI, SUI
	Valnemulin	AVI, SUI
Polypeptides	Bacitracin	AVI, BOV, LEP, SUI, OVI
	Enramycin	AVI, SUI
	Gramicidin	EQU
Polymyxins	Polymyxin B	BOV, CAP, EQU, LEP, OVI, AVI
	Polymyxin E (colistin)	AVI, BOV, CAP, EQU, LEP, OVI, SUI
Quinolones first-generation	Flumequin	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI
	Miloxacin	PIS
	Nalidixic acid	BOV
	Oxolinic acid	AVI, BOV, LEP, PIS, SUI, OVI
Veterinary important antimicrobial agents (VIA)		
Aminocoumarin	Novobiocin	BOV, CAP, OVI, PIS
Bicyclomycin	Bicozamycin	AVI, BOV, PIS, SUI
Fusidane	Fusidic acid	BOV, EQU
Orthosomycins	Avilamycin	AVI, LEP, SUI
Streptogramins	Virginiamycin	AVI, BOV, OVI, SUI
Thiostrepton	Nosiheptide	AVI, SUI

Note: Antimicrobials belonging to classes of ionophores (VHIA), arsenicals (VIA) and quinoxalines (VIA) have been excluded.

Abbreviations used in table-AVI: avian, API: bee, BOV: bovine, CAP: caprine, CAM: camel, EQU: equine, LEP: rabbit, OVI: ovine, PIS: fish, SUI: swine

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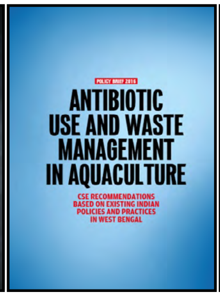
CSE's work on AMR in food systems and environment: India

Antibiotics in honey, 2010

Antibiotic use in poultry, 2014



Antibiotic use in aquaculture, 2016

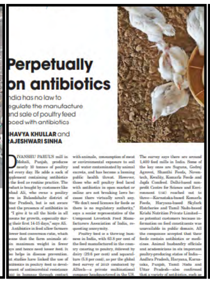
AMR in poultry environment, 2017

Antibiotic use in fast food supply chain, 2017

Disposal of pharma manufacturing waste, 2017

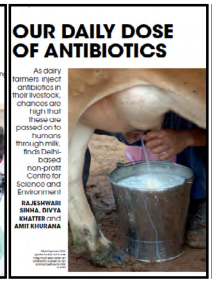
Antibiotic use in crops, 2019

Disposal of unwanted drugs, 2019



Antibiotic use in feed, 2020

Antibiotic use in fast food supply chain, 2020



Antibiotic use in dairy, 2020

Body Burden, 2020

Use of ethnoveterinary medicines in dairy sector, 2021

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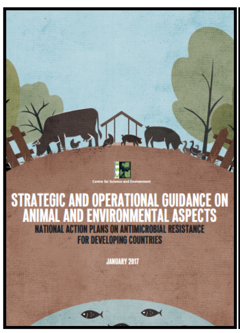
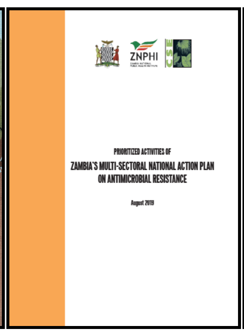
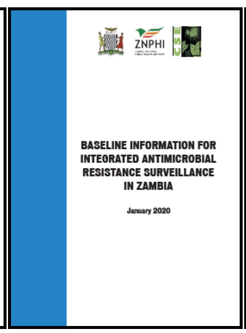


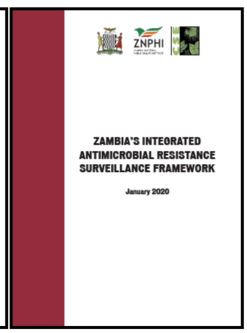
Strategic guidance for NAP for developing countries, 2016



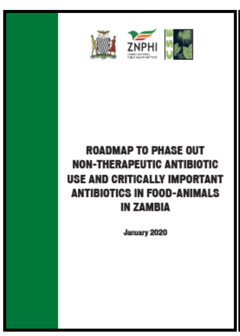
Prioritized NAP-AMR (Zambia, 2019)



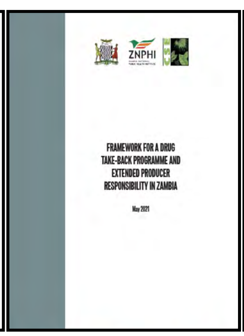
Baseline information for Integrated AMR surveillance (Zambia, 2020)



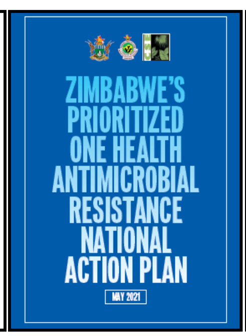
Framework for Integrated AMR surveillance (Zambia, 2020)



Roadmap to phase out antibiotic misuse in food-animals (Zambia, 2020)



Framework for drug take-back and EPR (Zambia, 2021)



Prioritized NAP-AMR (Zimbabwe, 2021)

Containing the silent pandemic of AMR 2021

This report highlights gaps and possibilities in the guidance of the Tripartite organizations on antimicrobial use in food-producing animals. It presents current practices in India with regard to their use in multiple food-animal sectors and identifies gaps and possibilities in policies and guidelines. It recommends conserving the use of critically important antimicrobials through a strong and more coherent global guidance as well as developing a road map and policy framework for India to conserve their use.

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