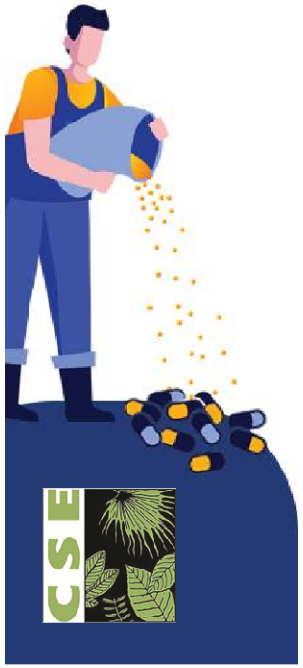
CSE webinar -
Aug 27, 2021

Conserving the Use of Critically Important Antimicrobials in Food-producing Animals

Gaps and Possibilities in Global Guidance and Indian Policy Framework

Amit Khurana, Director, Food Safety and Toxins Programme, CSE



Growing need to conserve the use of Critically Important Antimicrobials

GLASS 2021 report shows high resistance against critically important antimicrobials

Four infection sites for high priority pathogens

Blood stream infections:

- *E. coli* against third-generation cephalosporins, ampicillin, ciprofloxacin
- *K. pneumoniae* against ceftriaxone and ciprofloxacin
- *Acinetobacter* spp. to different carbapenems and aminoglycosides
- *Salmonella* spp. against ciprofloxacin
- Methicillin-resistant *Staphylococcus aureus*

Urinary tract infections:

- *E. coli* against ciprofloxacin, ceftriaxone, ampicillin
- *K. pneumoniae* against ciprofloxacin, ceftriaxone

Gastrointestinal infections: *Shigella* spp. against ciprofloxacin, ceftriaxone

Genital infections: *N. gonorrhoea* against ciprofloxacin

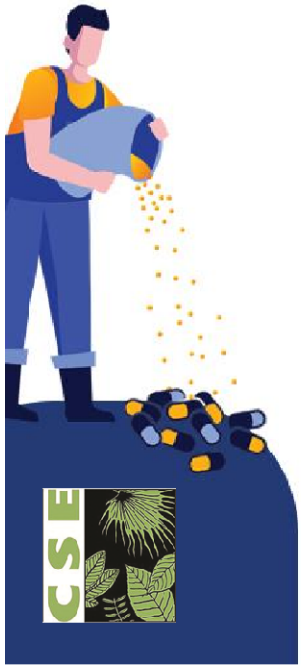
Data from 3,106,602 laboratory-confirmed infections;

24,803 surveillance sites;

70 countries

WHO's global tuberculosis report: >0.5 million developed rifampicin-resistant TB in 2019; of which 78% had MDR-TB.

WHO's list of Critically Important Antimicrobials for human medicine (2018)



Recognizing the importance of antimicrobials to human medicine, the WHO has ranked all medically important antimicrobials for **risk management of antimicrobial resistance (AMR) due to non-human use of antimicrobials**

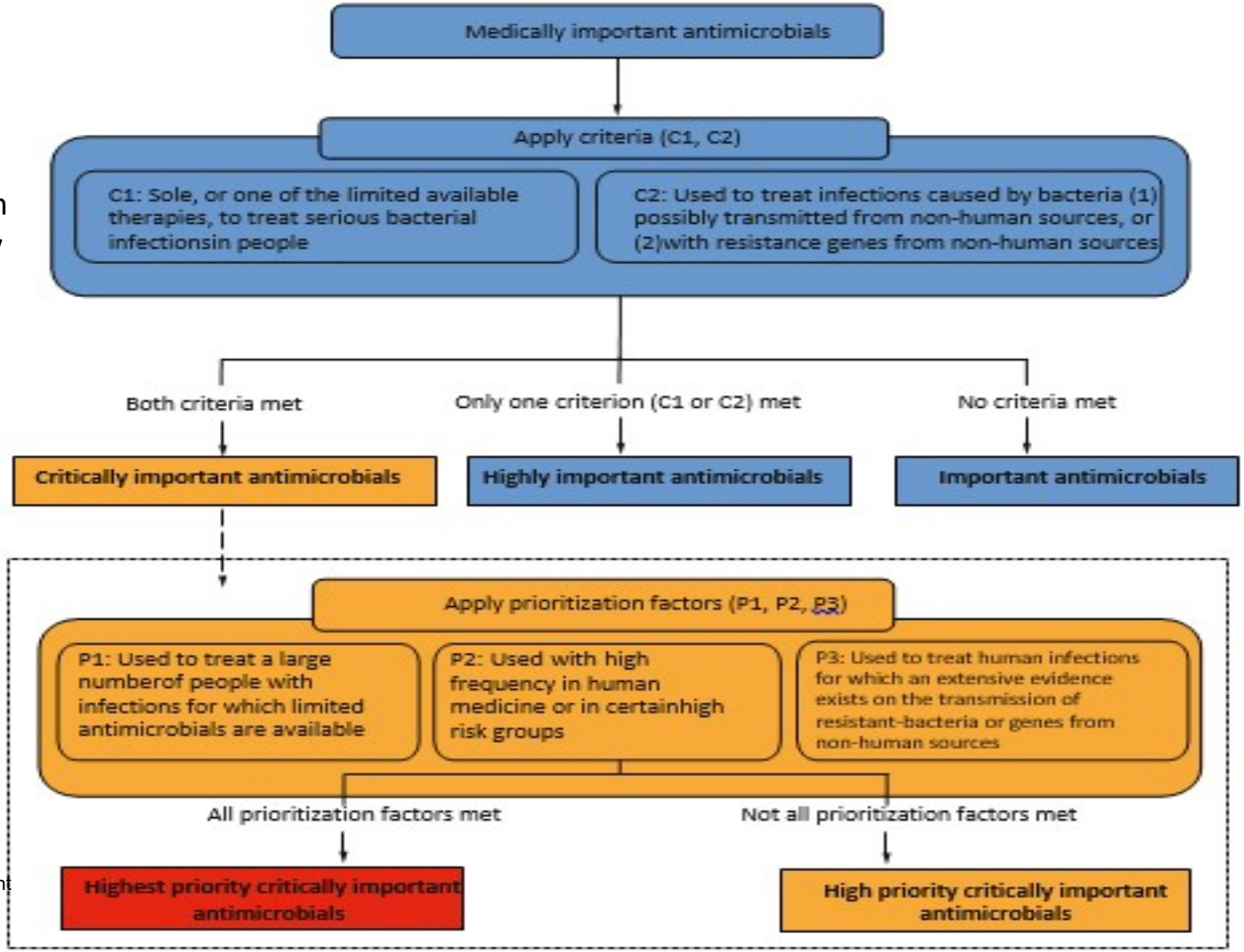
Based on a criteria, antimicrobials are categorized into **critically important antimicrobials**, highly important antimicrobials and important antimicrobials

Critically Important Antimicrobials are:

Sole or one of the limited available therapies to treat serious bacterial infections in humans and are used to treat bacterial infections transmitted from non-human sources or infections from bacteria that may acquire resistance genes from non-human sources

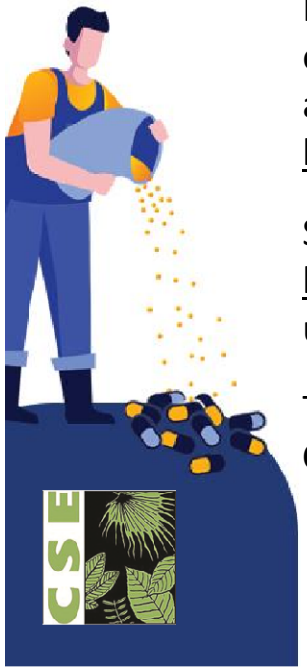
Further categorized into **highest priority critically important antimicrobials (HPCIAs)** and high priority critically important antimicrobials based on three additional prioritization factors. **HPCIAs meet all three.**

Categorisation of medically important antimicrobials into **Critically Important Antimicrobials (CIAs)** and their further prioritization into **Highest Priority Critically Important Antimicrobials (HPCIAs)**



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

Classes of Critically Important Antimicrobials (2018 WHO list)



Sixth version; first version in 2005 following WHO-FAO-OIE expert meetings in 2003

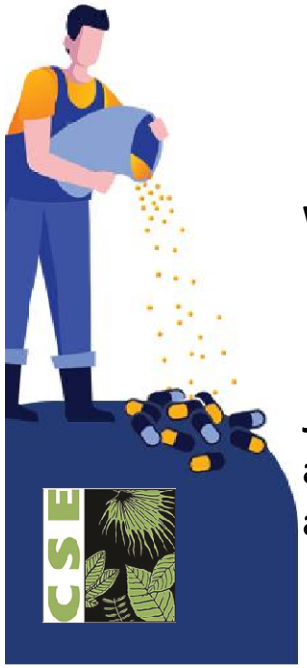
Intended to ensure that all antimicrobials, especially critically important antimicrobials, are used prudently both in human and veterinary medicine

Supports strategies to mitigate human-health risks associated with antimicrobial use in food-producing animals

Total of 178 antimicrobials; **17 classes of CIAs; five out of which are HPCIAs**

Highest priority critically important antimicrobials
Cephalosporins (third-, fourth- and fifth-generation)
Glycopeptides (Also includes lipoglycopeptides)
Macrolides and ketolides
Polymyxins
Quinolones (also includes fluoroquinolones)
Critically important antimicrobials (other than HPCIAs)
Aminoglycosides
Ansamycins
Carbapenems and other penems
Glycylcyclines
Lipopeptides
Monobactams
Oxazolidinones
Penicillins (antipseudomonal)
Penicillins (aminopenicillins)
Penicillins (aminopenicillins with beta-lactamaseinhibitors)
Phosphonic acid derivatives
Drugs used solely to treat tuberculosis/mycobacterial d iseases

Additional global efforts suggesting the need to conserve CIAs



Most critically important antimicrobials under WHO's "AWaRe" classification of 2019 EML are categorized as "Watch" or "Reserve"

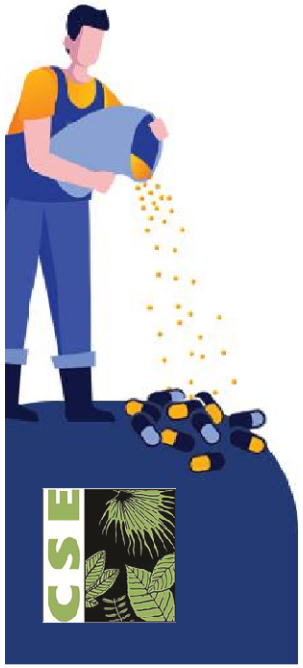
- 19 CIAs in AWaRe category. **Seven in Reserve, 11 in Watch,** five in Access
- Reserve: last-resort, highly selected patients
- Watch: first-or-second choice antibiotics; only for specific and limited infective syndromes

WHO global priority pathogens list, 2017

- Global push for research of new antibiotics against bacteria with high resistance to CIAs

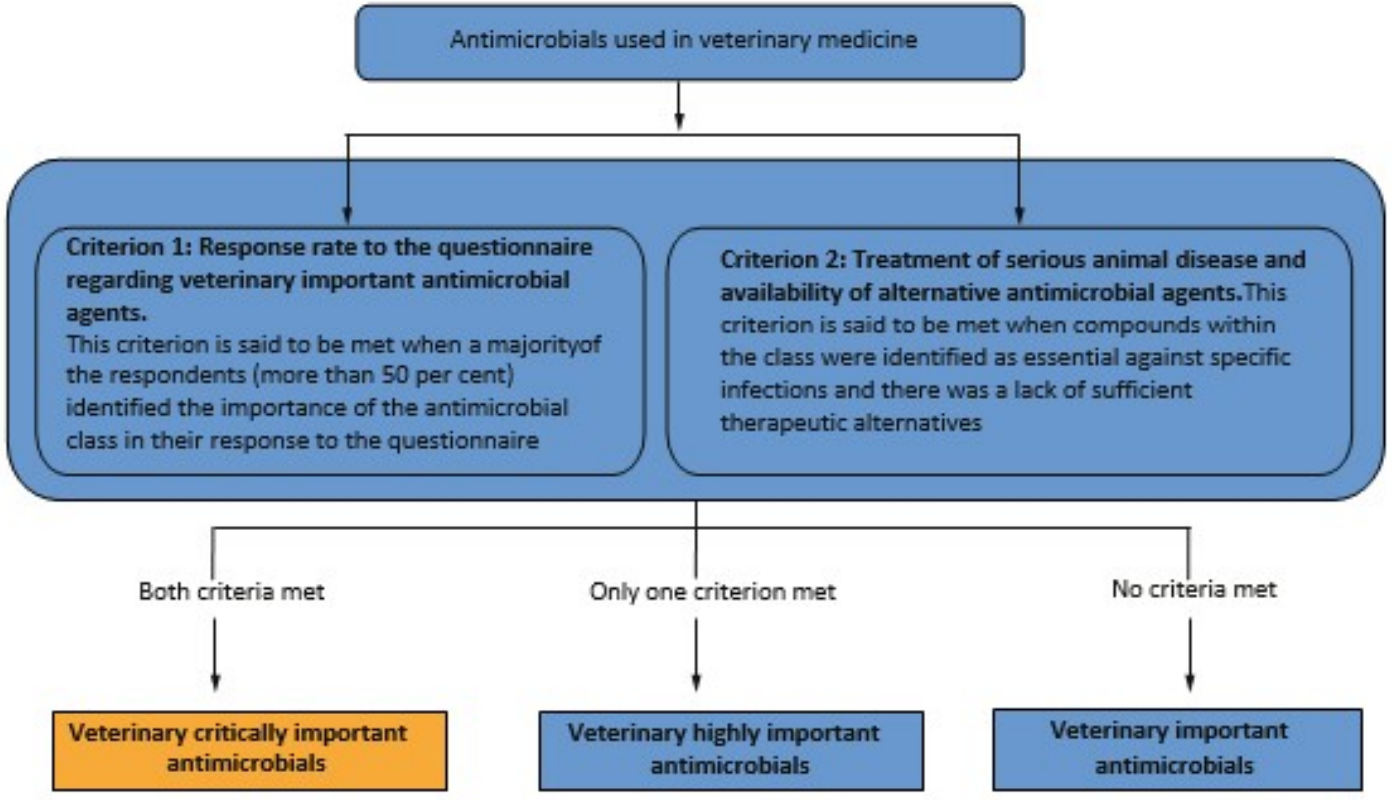
Joint inter-agency report from the European Union released in 2021 confirms association between antimicrobial use in food-producing animals and AMR in animals as well as in humans

- Focus on six antimicrobial classes. Out of these 5 are CIAs and 4 HPCIAs



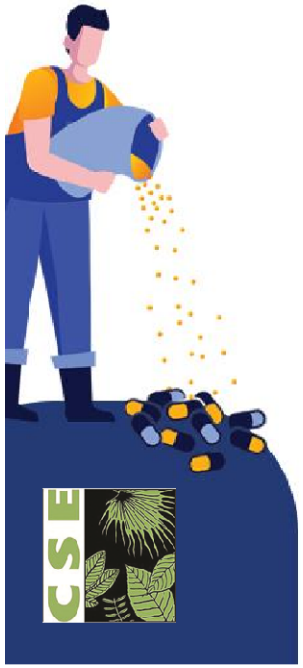
Gaps in global guidance on use of critically important antimicrobials in food-producing animals

Separate OIE list of antimicrobial agents of veterinary importance for food-producing animals (criteria)



Species: avian, equine, bee, rabbit, bovine, ovine, caprine, fish, camel, swine; First list in 2007; most recent list in 2019

Key Issue 1: Significant overlap in antimicrobials considered critical for humans and food-producing animals



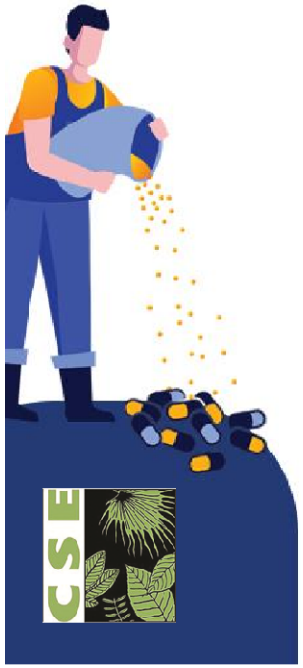
47 antimicrobials in OIE list overlap with WHO list

- 38 veterinary critically important antimicrobials (VCIAs) and nine veterinary highly important antimicrobials (VHIAs);
- **Overlap with nine WHO CIA classes; 28 antibiotics from four HPCIA classes** (third-, fourth- generation cephalosporins, macrolides and ketolides, quinolones and fluroquinolones, polymyxins)
- **39 antimicrobials for >1 species; 28 for >3 species of food-producing animals**

Tripartite organizations have for many years well recognized the public-health concern due to this overlap (*FAO/OIE/WHO expert meeting in Rome in 2007*)

"The overlap of these lists calls for careful consideration to appropriately balance the need for animal health and the public-health aspects."- *Manual on Prudent and efficient use of antimicrobials in pigs and poultry, FAO, 2019*

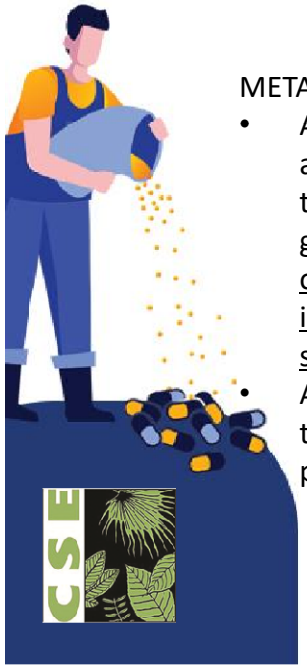
Example of how the report captures the overlap



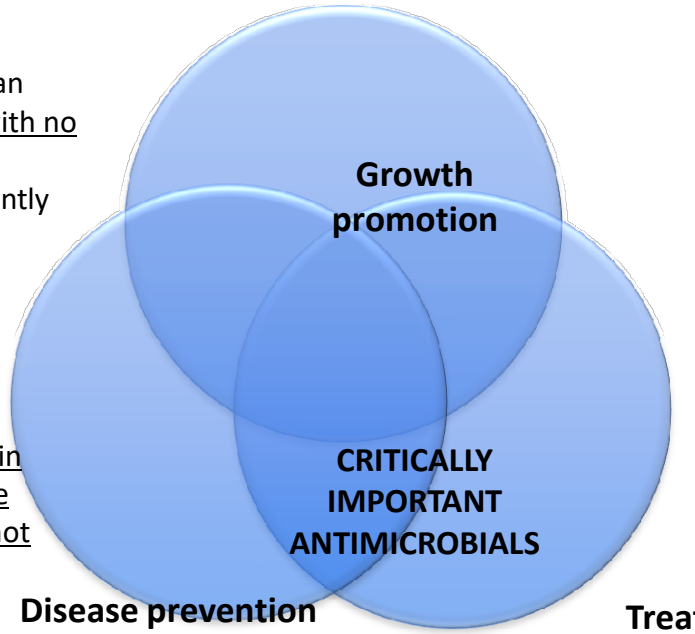
Antimicrobial (OIE list)	OIE categorization	Species (OIE list)	Antimicrobial class (WHO)
Highest priority critically important antimicrobials			
Cefoperazone	Veterinary critically important antimicrobials	BOV, CAP, OVI	Cephalosporins (third-, fourth- and fifth- generation)*
Cefquinome		BOV, CAP, EQU, 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	

Key Issue 2: Need for coherence in position on use of critically important antimicrobials in food-producing animals

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



- **Prophylaxis/ prevention**
- **Metaphylaxis/ control**

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

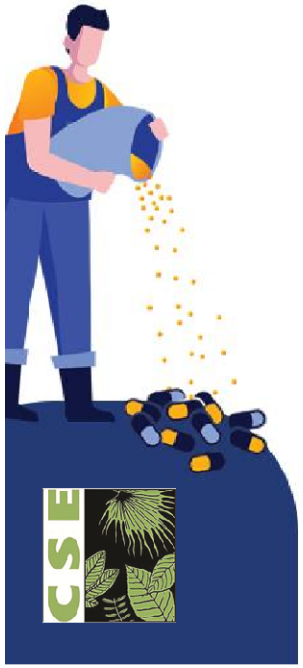
TREATMENT
Use of antimicrobials at therapeutic dose to treat an infectious disease having clinical signs and/or symptoms

Interpretation of global guidance on use of critically important antimicrobials in food-producing animals (1/2)

	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 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

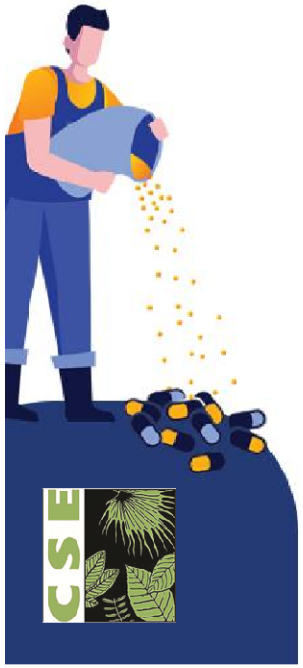
Interpretation of global guidance on use of critically important antimicrobials in food-producing animals (2/2)



- 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.
- More coherence was seen in the position of WHO and FAO.

WHO position on use of antimicrobials in food-producing animals

WHO Guidelines on Use of Medically Important Antimicrobials in Food-Producing Animals, 2017



Growth promotion and prevention: “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”

Control: “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”

Treatment: “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, 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

OIE position on use of antimicrobials in food-producing animals (1/3)

OIE list of antimicrobial agents of veterinary importance, 2019

Provides specific recommendations for **two classes of HPCIAs - fluoroquinolones, third- and fourth-generation cephalosporins, and colistin** (HPCIA: polymyxin class).

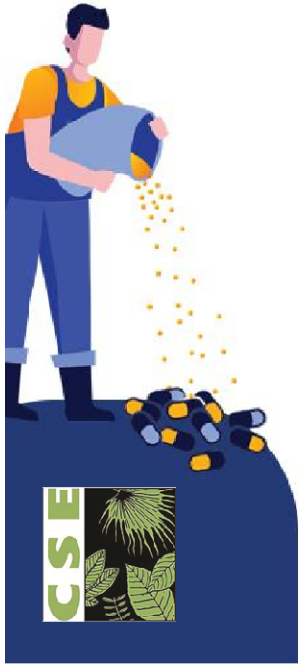
- "not to be used as preventive treatment applied by feed or water in the absence of clinical signs in the animal(s) to be treated".
- "not to be used as a first-line treatment unless justified, when used as a second-line treatment, it should ideally be based on the results of bacteriological tests".
- "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".
- "urgently prohibit their use as growth promoters".

This means that 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.

OIE position on use of antimicrobials in food-producing animals (2/3)

OIE list of antimicrobial agents of veterinary importance, 2019



Growth promotion: “classes in the WHO category of HPCIAs should be the highest priorities for countries in phasing out the use of antimicrobial agents as growth promoters”.

It also says that “responsible and prudent use of antimicrobial agents does not include the use of antimicrobial agents for growth promotion in the absence of **risk analysis**”.

A clarification 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 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.

Moreover 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; No such model list of antimicrobials with low or high risk as part of the global guidance for countries to leverage on.

OIE position on use of antimicrobials in food-producing animals (3/3)

OIE list of antimicrobial agents of veterinary importance, 2019

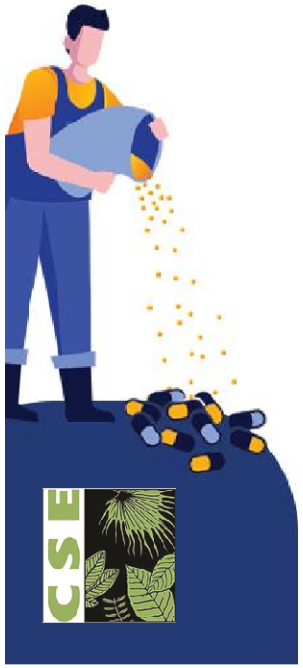
The OIE list does not include antimicrobial classes/subclasses used **only in human medicine**. However, it mentions that:

"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".

This means that antimicrobial classes/subclasses used only in human medicine can still be used.

FAO document on use of antimicrobials in food-producing animals (1/2)

Manual on Prudent and Efficient Use of Antimicrobials in Pigs and Poultry, 2019



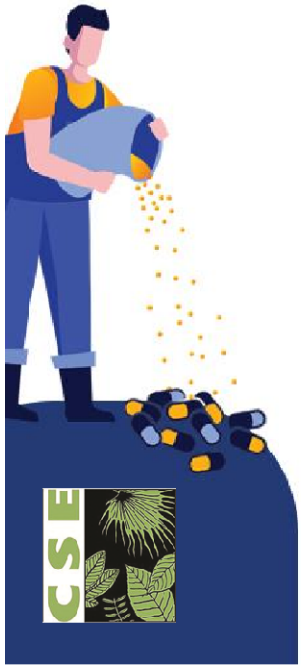
Suggests that prudent and medically effective use of antibiotics include:

- Phasing out use of antibiotics as growth promoters;
- Avoiding regular preventive use of antibiotics;
- Avoiding use of the HPCIAs 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".

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.

FAO document on use of antimicrobials in food-producing animals (2/2)

Recommendations for Prudent and Responsible Use of Veterinary Medicines in Aquaculture, 2019



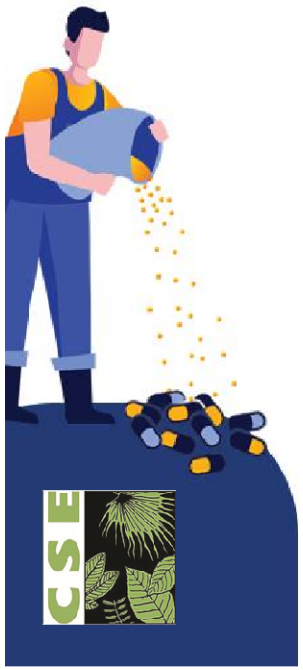
- Recommends to aquatic health professionals and specialists that antimicrobial agents of lesser importance in human medicine should be chosen and those for which emergence of resistance is expected to be in an advanced stage not be selected.

- Mentions that antimicrobial agents should not be used prophylactically.

This means that, 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.

Codex position on use of antimicrobials in food-producing animals

Code of practice to minimize and contain antimicrobial resistance, 2005



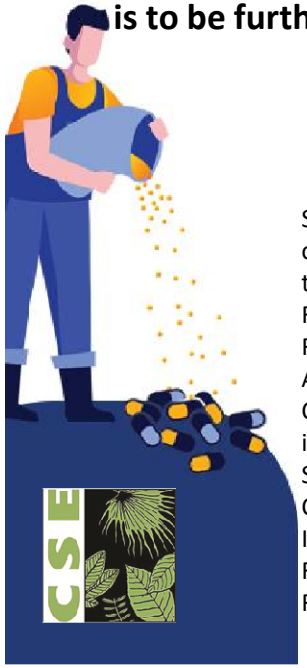
- Says, “responsible use of veterinary antimicrobial drugs in food-producing animals does not include the use for growth promotion of veterinary antimicrobial drugs that belong to or are able to cause cross resistance to classes of antimicrobial agents used (or submitted for approval) in humans in the absence of a risk analysis”.

- 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”.

- 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”.

This means that Codex’s currently applicable guidelines, though not specifically referring to use of CIAs, 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

- **The 2005 Code of Practice is being revised.**
- **The text related to principle 5 and 7 of the Codex draft was adopted at the 43rd session of the Codex Alimentarius Commission in 2020 at step 5.**
- **The text related to principle 6 is to be further considered.**



Source: Proposed Draft of the Code of Practice to Minimize and Contain Foodborne Antimicrobial Resistance at Step 5 of Adoption in the Codex Commission as provided in the Report of the Seventh Session of the Codex Ad-Hoc Intergovernmental Task Force on Antimicrobial Resistance, 2020

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

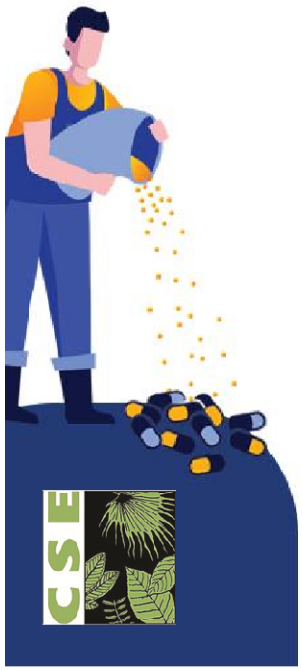
Principle 5: Responsible and prudent use of antimicrobial agents does not include the use for growth promotion of antimicrobial agents that are considered medically important. Antimicrobial agents that are not considered medically important should not be used for growth promotion unless potential risks 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

Issue 3: Need for clarity and strong action on use of antimicrobials for disease prevention in food-producing animals (1/2)



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 possible reason could be the difference in the way antimicrobial use is categorized:

- WHO categorizes such use as **therapeutic, growth promotion** and **disease prevention**.
- FAO recognizes such use as **therapeutic, metaphylactic** and **prophylactic,** and **growth promotion (sub-therapeutic)**
- OIE categorizes as "**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**). 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.

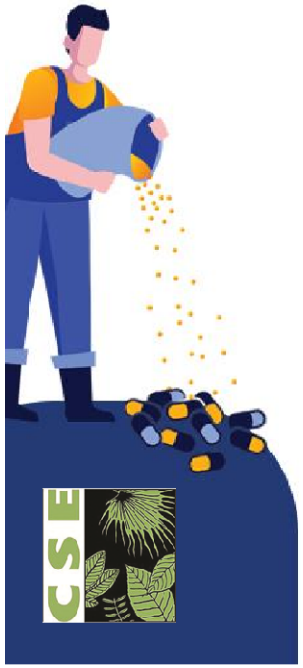
Issue 3: Need for clarity and strong action on use of antimicrobials for disease prevention in food-producing animals (2/2)

The second possible reason is the difference in the definition and the wording adopted:

- 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.**

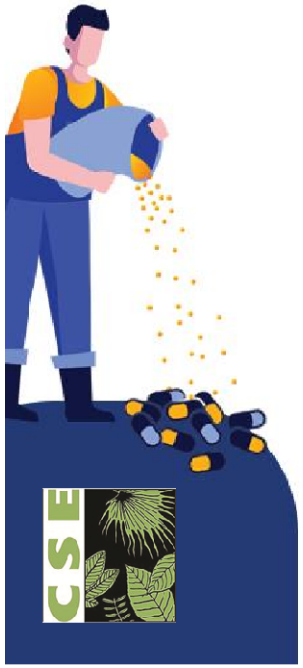
Difference in definition of disease prevention by Tripartite organizations

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."	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."	"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."



Recommendations for global guidance to conserve the use of critically important antimicrobials

The Tripartite should consider developing a uniform and strong guidance for countries on the use of critically important antimicrobials across all food-animal sectors (1/2)

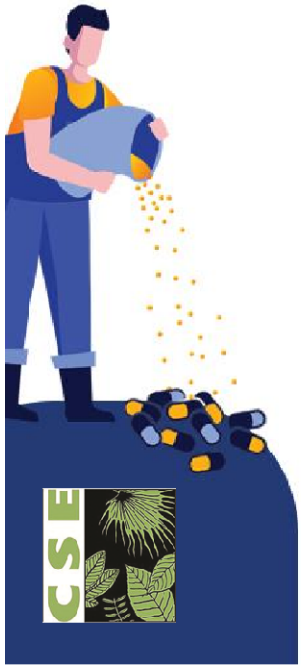


This should include a clear message for all categories of critically important antimicrobials w.r.t. their use as growth promoters and for disease prevention, control and treatment in sectors such as poultry, dairy and aquaculture.

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.

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.

The Tripartite should consider developing a uniform and strong guidance for countries on the use of critically important antimicrobials across all food-animal sectors (2/2)

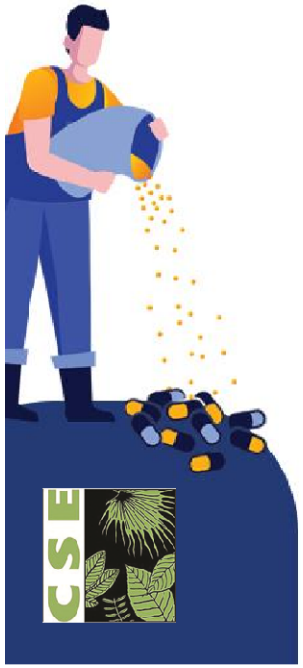


This guidance should consider stronger and specific action against critically important antimicrobial use for disease prevention and control. In particular, strong action is required against routine group preventive use of antibiotics, which often substitutes good rearing practices. The guidance should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

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.

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



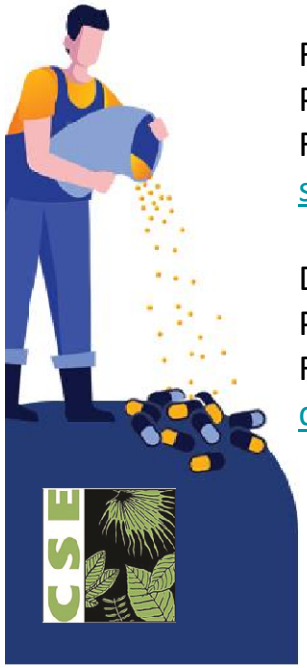
- There is some action at the global and national level, but there still however is a big gap with respect to overall global understanding and related to developing countries of the global South.
- This gap can be filled by information focusing on critically important antimicrobials w.r.t. food-animal 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.

For information, contact:

Amit Khurana
Director
Food Safety and Toxins programme
k_amit@cseindia.org

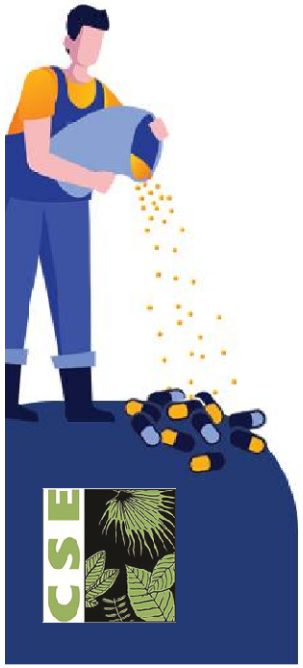
Rajeshwari Sinha
Programme Manager
Food Safety and Toxins programme
s_rajeshwari@cseindia.org

Deepak Bhati
Programme Officer
Food Safety and Toxins programme
deepak.bhati@cseindia.org



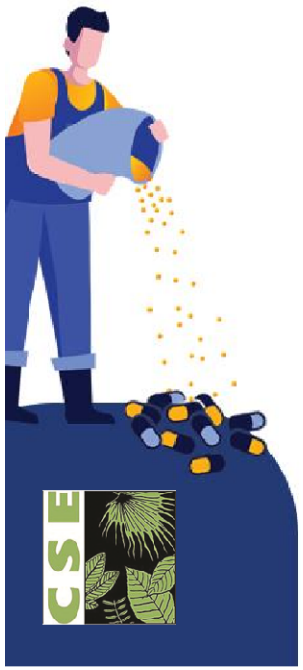
website: www.cseindia.org
Email: cse@cseindia.org

GLASS report, 2021 presents high resistance in infection-causing bacteria against several critically important antimicrobials in humans



	Median resistance rate (per cent)	Interquartilerange	No. of reporting countries	No. of patients with AST results
Blood stream 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	–	–

GLASS report, 2021 presents high resistance in infection-causing bacteria against several critically important antimicrobials in humans

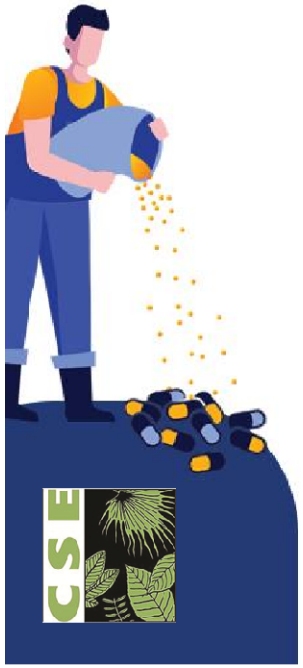


Urinary tract infections				
E. coli resistant to ciprofloxacin	43.1	22.5–58.6	28	1,961,032
E. coli resistant to ciprofloxacin (community)*	30-40	–	16	267,553
E. coli resistant to ciprofloxacin (hospital)*	40-50	–	28	102,829
E. coli resistant to ceftriaxone*	40-50	–	26	748,780
E. coli resistant to ampicillin*	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
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.

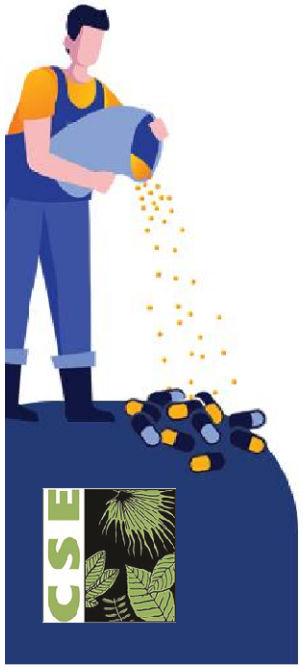
Data for 2019 ; * Resistance range is inferred from figures as actual values are not mentioned in text of the report. A broad range which is indicative is mentioned. These are few example with relatively higher resistance for different CIA classes. In such cases interquartile range is not provided in the table. ** AST: Antimicrobial Susceptibility Testing;

Joint inter-agency report confirms association between antimicrobial use in food-producing animals and AMR in animals and humans



- Associations between consumption of an antimicrobial class and bacterial resistance to the antimicrobials in this class in the same population
  - ESBL producing and AmpC beta-lactamase-producing *E. coli* —3rd and 4th-generation cephalosporins
  - Indicator *E. coli*—fluoroquinolones
  - *Salmonella* spp. —fluoroquinolones and other quinolones—poultry
  - *E. coli*—polymyxins—specifically in poultry and pigs
  - Indicator *E. coli* and *Salmonella* spp. —aminopenicillins—poultry
  - *C. jejuni*—macrolides— poultry

Joint inter-agency report confirms association between antimicrobial use in food-producing animals and AMR in animals and humans



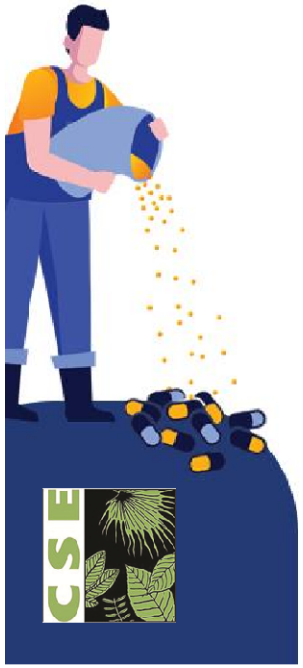
- Associations between **resistance in bacteria from humans** with **antimicrobial consumption in animals as well as resistance in bacteria from food-producing animals**
  - Invasive *E. coli* isolates—3rd and 4th generation cephalosporins consumption in food-producing animals and humans
  - Invasive *E. coli* isolates—fluoroquinolones consumption in food-producing animals
  - Invasive *E. coli* isolates—*f*luoroquinolone resistance in indicator *E. coli* isolates from different food-producing animal species
  - *C. jejuni*—fluoroquinolone consumption in food-producing animals and humans
  - *C. jejuni*—*f*luoroquinolone resistance in *C. jejuni* —turkeys and broilers
  - C. jejuni—*c*onsumption of fluoroquinolones and resistance in *C. jejuni*—poultry
  - Invasive E. coli—*a*mpicillin resistance in indicator *E. coli* from food-producing animals (turkeys, broilers, pigs and calves)
  - Invasive *E. coli* and in *Salmonella* spp.—aminopenicillin consumption in food-producing animals
  - *C. jejuni*—resistance to macrolides in *C. jejuni*—turkeys

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-lactamaseinhibitor)	Access
Piperacillin/tazobactam	Penicillins (antipseudomonal)	Watch
Meropenem	Carbapenems	Watch
Meropenem-vaborbactam		Reserve
Linezolid	Oxazolidinones	Reserve
Fosfomycin (Intra-Venous)	Phosphonic acid derivatives	Reserve

Global push for research of new antibiotics against bacteria with high resistance to CIAs

WHO priority pathogens list (PPL)" in 2017 focussed on identifying the most important resistant bacteria for which there is an urgent need for new treatments. The 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

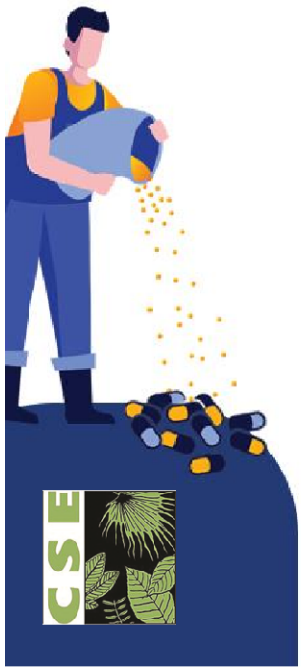
Priority 2: HIGH (contain other increasingly drug-resistant bacteria that cause more common diseases)

- *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

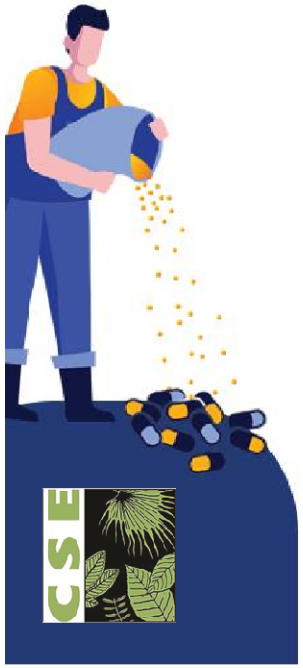
Priority 3: MEDIUM (contain other increasingly drug-resistant bacteria that cause more common diseases)

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

Overlap- OIE categorized VCIA and VHIA with WHO CIAs



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 WHOand 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

^ Critically important antimicrobials other than highest priority critically important antimicrobials

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