Issue	**Antimicrobial Resistance (AMR) and Food Safety**
Background	The emergence and spread of drug-resistant pathogens that have acquired new resistance mechanisms leads to antimicrobial resistance (AMR). AMR compromises the ability of humans to treat infectious diseases, undermining other advances in health and medicine [1]. According to the World Bank, it is estimated that if AMR is not addressed by 2050, the global economy may lose nearly 4% of the annual gross domestic product (GDP). This situation could push up to 28 million people into poverty in developing countries because AMR affects economic productivity, livestock production, and health care costs [2]. Antimicrobials are vital for managing the animal's health and treating relevant diseases. However, its use as a preventive medication or growth promoter contributes to AMR in humans [3]. AMR occurs naturally. However, inappropriate use of medicines (e.g, use of antibiotics for viral infections such as cold or flu, or sharing antibiotics), low-quality medicines, and poor prevention and control of infection intensify the development and spread of drug resistance [4]. Consequently, the misuse of antimicrobials could result in the deposition of drug residues in the tissues and organs of animals that may enter the food chain once the animal is slaughtered and processed into food [3]. Recognizing AMR as a public health threat and following a whole-of-government approach, the Malacañang Palace issued Administrative Order No.42, creating an inter-agency committee for formulating and implementing a National Plan to combat AMR in the Philippines [5]. In response, the Department of Agriculture (DA) designated Regional AMR Coordinators through a Special Order to engage with all concerned stakeholders and implement programs and activities [6]. Furthermore, through its attached bureaus, the DA annually celebrates" World Antimicrobial Awareness Week" to raise awareness of the prudent use of antimicrobials by working with stakeholders across all sectors [7].
General Description	**Definition of Antimicrobials** *From the United Nations Environment Program (UNEP)* Antimicrobials are agents that kill or inhibit microorganisms' growth. They include antibiotics, fungicides, antiviral agents, and parasiticides. Disinfectants, antiseptics, other pharmaceuticals, and natural products may also have antimicrobial properties. Antimicrobial agents are essential for human and animal health and welfare [8]. *From Codex Alimentarius*

Antimicrobial agent is any substance of natural, semi-synthetic, or synthetic origin that, at in vivo concentrations, kills or inhibits the growth of microorganisms by interacting with a specific target [9].

From Food and Agriculture Organization (FAO)
Antimicrobial is a naturally occurring, semi-synthetic, or synthetic substance that kills or inhibits the replication of microorganisms.

Definition of AMR
From World Health Organization (WHO)
AMR is the ability of any microorganism (bacteria, viruses, and fungi) to withstand the effect of one or more antimicrobial agents at clinically attainable concentrations, usually resulting in treatment failure [1].

From FAO
AMR is an inherited or acquired characteristic of microorganisms that survive or proliferate in concentrations of an antimicrobial that would otherwise kill or inhibit them. It occurs naturally over a period of time through genetic changes and can spread from person to person or between people and animals, including from food of animal origin [10].

From Codex Alimentarius
AMR is the ability of a microorganism to multiply or persist in the presence of an increased level of an antimicrobial agent relative to the susceptible counterpart of the same species.

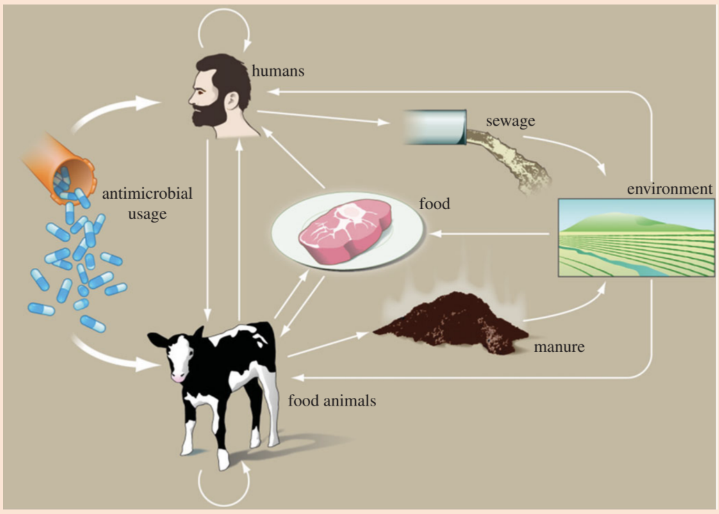

Figure 1. Diagram of transmission routes of AMR between farm animals, environment, and humans [10]

Based on the definitions provided above, AMR makes infections difficult to treat and increases the risk of disease spread, severe illness, and death [1]. Since most antimicrobials in clinical use are naturally produced by soil microorganisms, such microorganisms are the source of many resistance genes. Bacteria that can metabolize antimicrobials and use these as a source of nutrients have been found to express multi-drug resistance [10].

Types of Resistance [10]

There are two types of bacterial resistance. AMR can be either intrinsic or acquired.

1. *Intrinsic Resistance* is mediated by chromosomal genes. It is usually linked to the physiological or anatomical characteristics of the bacteria, a trait shared by all organisms within the same genus or species. An example of intrinsic resistance is the resistance to penicillin G by most Gram-negative bacteria due to the outer membrane in their cell wall. This outer membrane is absent in Gram-positive bacteria.
2. *Acquired Resistance* is brought about by an evolutionary process by which microorganisms adapt to antibiotics through several mechanisms [13]. These are
   - vertical transmission, described as the development of resistance in bacterial clones due to chromosomal mutations, and
   - horizontal transmission, which is the acquisition of DNA from different microbes or, in the case of bacteria, horizontal gene transfer (HGT) or mobile genetic elements (MGE). HGT occurs when genes from a cell are transferred into another through transformation, transduction, and conjugation.

Causes of Antibiotic Resistance [14]

The following are the major causes of antibiotic resistance that contribute to genetic selection pressure leading to the emergence of multidrug-resistant bacterial infections in the community:

- imprecise usage and inadequate regulations;
- lack of awareness leading to excessive or inept antibiotic use;
- poor sanitation/hygiene;
- release of non-metabolized antibiotics or their residues into the environment through manure/feces; and
- use of antibiotics as growth promoters in poultry and livestock rather than as infection control.

Mechanism of Bacterial Resistance

Expression of AMR genes can act as a defense mechanism against antimicrobial or toxin-producing competitors. In natural ecosystems, environmental changes and the intensification of agriculture and industry affects the emergence of resistance in bacterial populations [10].

As a result, several mechanisms render a bacterial cell resistant to one or several antimicrobials. These mechanisms can be organized into five broad categories such as

1. *Modification or protection of the drug target* [10]. A change in structure may decrease the drug's ability to bind or inhibit drug binding. A case in point is the alterations in the structure and/or the number of penicillin-binding proteins (PBPs). A change in the number (i.e., an increase in PBPs that have a decrease in drug binding ability or reduction of PBPs with normal drug binding) of PBPs impacts the amount of drug that can bind to that target [14].
2. *Inactivation of a drug, enzymatic modification, or degradation of the antimicrobial* [10]. Drug inactivation can be observed in the actual

degradation of the drug or by transferring a chemical group to the drug [14];

3. *Decreased accumulation of the antimicrobial within the cell by active drug efflux* [10]. The efflux pumps function primarily to eliminate bacterial cell toxic substances. Many of these pumps will transport a large variety of compounds, including the antibiotic ingredient [14].
4. *Overproduction of the target enzyme* [10]. Bacteria can also overproduce the target of the antibiotics, leading to an excess of the protein target of the antibiotics compared to the antibiotic itself. Thereby there is enough target protein for the bacteria to function despite the presence of antibiotics [15].
5. *Acquisition of alternative metabolic pathways to those inhibited by the microbial* [10]. Acquired resistance genes may enable a bacterium to produce an alternative metabolic pathway that bypasses the drug's action [16].

For better appreciation, Figure 2 provides an image of a bacterium showing antibiotic targets and how the resistance mechanism could be observed through these targets.

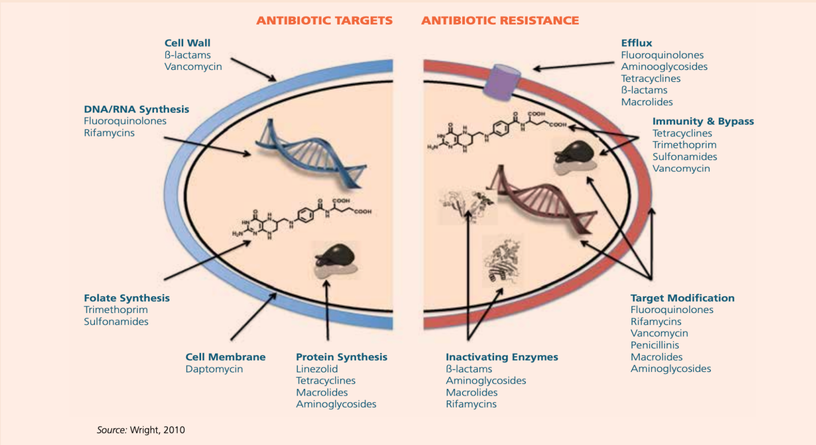

Figure 2. Antibiotic targets and mechanism of resistance [10]

Mode of Transmission

Antimicrobial-resistant bacteria originating in an animal can be transmitted to humans through the environment, food products, and/or by direct contact [11].

1. Risk pathways for the spread of AMR via environment
    - *Drug or pharmaceutical manufacturers*. Waste or sewages of pharmaceutical manufacturers contain incredibly high concentrations of antimicrobial residues [10].
    - *Water (includes treated for human consumption).* It is one of the essential vehicles in spreading AMR. It can spread AMR, resistant bacteria, and resistant genes far and wide through the flow of natural bodies and anthropogenic influences such as irrigation. Human consumes AMR genes (indirectly) through the crops irrigated by water (with AMR) [10]

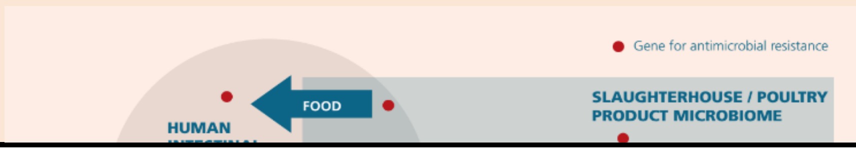

Figure 3. The conceptual framework for the spread of AMR genes in a poultry production system [10]

2. Risk pathways for the spread of AMR via food distribution
    - *Retail meats.* Trade in food products and human travel could significantly affect AMR's spread (locally and globally). During transportation, people and products (being transported) have the potential to disseminate AMR bacteria and resistance genes [10].
    - *Application of manure to crops.* A significant amount of AMR can be detected during the harvesting of vegetables while manure is still present in the soil [10].

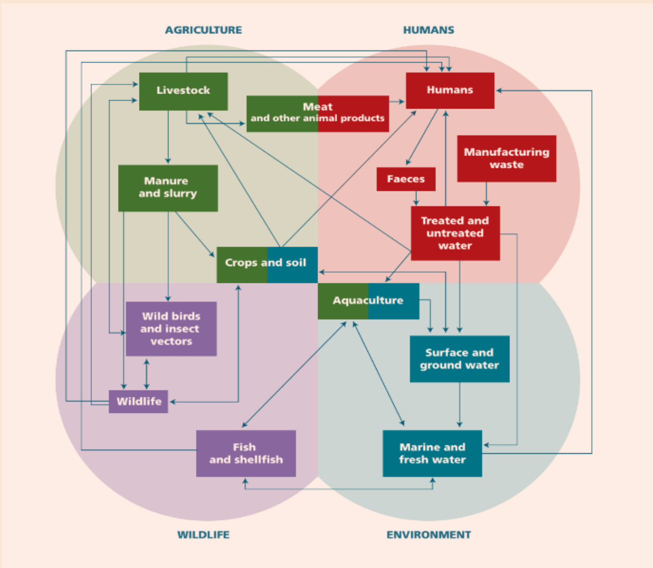

Figure 4. Potential transmission pathways of antimicrobial-resistant bacteria, resistance genes, and antimicrobial residues at the agriculture-human-environment-wildlife interface [10]**.**

3. Through Direct Contact
   Bacteria can spread between people through direct contact, aerosols (or through air), and exposure to bodily fluids (i.e. close contact) [14]

For Food Safety: Hazard Presence in Food

Hazards
The three recommended interrelated hazards to be assessed separately for AMR in food are [17]:

1. *Antibiotic.* Antibiotics are medicines used to prevent and treat bacterial infections in humans and animals [1]
2. *Antibiotic-Resistant Bacteria.* Bacteria exhibiting resistance to the effect of antibiotic

	3. *Antibiotic Resistance Gene (ARG).* ARGs are mobile genetic elements that can pass between microorganisms via horizontal gene transfer, even from the dead to living cells [17]. **Spread of Resistance from Farm Animals to Humans** Remnants of antimicrobial or antimicrobial drug residues can be found in meat, milk, fish, honey, or eggs due to poor practices when rearing food-producing animals. The residues may be the drug itself or its metabolites [18]. Misuse or overuse of antimicrobials in different sectors, AMR became a public health concern as this can affect humans through the spread and transfer of resistant organisms via ingestion of the products.
Adverse Health Effects on Human	Consumption of food containing excessive levels of veterinary drug residues may have adverse health effects on humans, such as allergies. This may also lead to the development of antimicrobial drug-resistant microorganisms in humans [18]. Some studies reported that food products containing veterinary drug residues in excess amounts may have several human health impacts. These include [19]: 1. drug-resistant microorganisms can enter humans through direct contact with animals or indirectly via animal products and by-products. 2. allergy of hypersensitivity reactions 3. carcinogenic effects 4. disruption of normal intestinal flora 5. mutagenic effect 6. teratogenic effect Exposure to antibiotic, antibiotic-resistant bacteria, and ARGs results in 1. the emergence of antibiotic-resistant pathogenic bacteria; 2. spread of antibiotic-resistant pathogenic bacteria (human exposure or infection results); and 3. transmission of ARGs to the other bacteria. Accumulative impact from exposure would lead to the loss of therapeutic selection of antimicrobials that may render disease persistence due to ineffectiveness of treatment [20].
Mitigating Measures	To minimize the negative impacts of AMR and following the whole-of-government approach, the following specific measures are implemented and recommended to be implemented by the relevant authorities: **Umbrella Framework: The iAMResponsible campaign in the Philippines** The Food and Agriculture Organization of the United Nations (UN-FAO), launched the “iAMResponsible” campaign call20ing for more responsible use of antimicrobials, including antibiotics.

The Philippines responded to the call for action against the threat of AMR by establishing the Inter-Agency Committee for the Formulation and Implementation of the National Action Plan to Combat Antimicrobial Resistance in the Philippines (ICAMR) in 2014. The ICAMR is composed of the Department of Health (DOH), the Department of Agriculture (DA), the Department of Science and Technology, the Department of Interior and Local Government, and the Department of Trade and Industry (DTI). Local government units and private sectors are also included in the initiative, where assistance would be requested as it may arise [21].

Competent Authority [22]

1. Implement marketing authorization, including efficient registration procedures to evaluate the safety and efficacy of antimicrobials
2. Implement quality control of antimicrobial agents
3. Conduct assessment of therapeutic efficacy
4. Conduct an assessment of the potential of antimicrobial agents to select for resistance.
5. Establish acceptable daily intake (ADI), maximum residue limit (MRL), and withdrawal periods in food-producing animals
6. Establish a summary of product characteristics for each VMP containing antimicrobial agents
7. Conduct post-market surveillance of antimicrobial

To assist in analyzing the risk of AMR to animal and human health, the competent authority may refer to the OIE Risk Analysis Model (Annex). Key steps in this model are briefly described below:

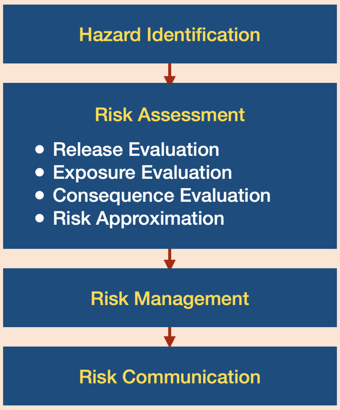

Figure 5. OIE Antimicrobial Resistance Risk Analysis Model [22]

Standards. The Bureau, as a contribution to the iAMResponsible campaign, developed and promoted the following Philippine National Standards (PNS):

1. PNS/BAFS 48: 2016 Philippine National Standard (PNS) Veterinary Drug Residues in Food: Maximum Residue Limits (MRLs)
   The PNS sets out the MRLs for certain veterinary drugs of specific species and provides risk management recommendations.
2. Code of Good Animal Husbandry Practices related standards
   - Code of Good Animal Husbandry Practices GAHP (PNS/BAFS 60-2008)

	○ Good Animal Husbandry Practices (GAHP) for Chickens: Broilers and Layers (PNS/BAFS 184:2016) ○ Code of Good Animal Husbandry Practices for Dairy Cattle and Water Buffalo (PNS/BAFS 199-2017) ○ Code of Good Animal Husbandry Practices for Beef Cattle and Buffalo ○ (PNS/BAFS 200-2017) ○ Code of Good Animal Husbandry Practices for Goats (PNS/BAFS 201-2017) ○ Code of Good Animal Husbandry Practices for Sheep (PNS/BAFS 202-2017) ○ Code of Good Animal Husbandry Practices (GAHP) for Swine (PNS/BAFS 267-2019) ○ Code of Good Animal Husbandry Practices (GAHP) for Ducks (PNS/BAFS 271-2019) **Veterinarians [22]** 1. Promote responsible use of antimicrobial agents 2. Choose appropriate antimicrobial agents 3. Guarantee the appropriate use of the antimicrobial agents chosen 4. Record relevant data 5. Check proper labeling of veterinary medicinal products 6. Attend training for continued professional development **Food Animal Producers [22]** 1. Implement animal health and animal welfare programs 2. Attend training
Researchers/ Editors	Researchers: Alpha M. Lanuza, DVM Katrina L. Maminta Aubrey Katreena L. Ramos Editors: Mary Grace R. Mandigma
Reference/s	[1] World Health Organization (WHO). (2021). Antimicrobial resistance. Retrieved from https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance [2] The World Bank- The International Bank for Reconstruction and Development. (2016). By 2050, drug-resistant infections could use global economic damage on par with 2008 financial crisis. Retrieved from https://www.worldbank.org/en/news/press-release/2016/09/18/by-2050-drug-resistant-infections-could-cause-global-economic-damage-on-par-with-2008-financial-crisis [3] Singapore Food Agency. (2022). Veterinary drug residues in food. Retrieved from https://www.sfa.gov.sg/food-information/risk-at-a-glance/veterinary-drug-residues-in-food

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Annex

Analyzing the risks to animal and human health from antimicrobial-resistant microorganisms of animal origin [22]

Key steps of OIE AMR Risk Analysis Model shown in Figure 5 are briefly described below:

a. Hazard identification
   Hazard is the resistant microorganism or resistance determinant that emerges from using a specific antimicrobial agent in animals.
b. Risk assessment
   Assessment of human and animal health risks from antimicrobial-resistant microorganisms.
   - Release evaluation
     Describes the probability of the release of each potential hazard under each specified set of conditions for amounts and timing

and how these might change as a result of various actions, events, or measures.

- Exposure evaluation
  Describes the biological pathways necessary for exposure of humans to the resistant microorganisms or resistance determinants released from a given antimicrobial use in animals and estimates the probability of the exposures occurring.
- Consequence evaluation
  Describes the relationship between specified exposures to resistant microorganisms or resistance determinants and the consequences of those exposures. It also describes the potential consequences of a given exposure and estimates its probability.
- Risk Approximation/Estimation
  A risk estimation integrates the results from the release assessment, exposure assessment, and consequence assessment to produce overall estimates of risks associated with the hazards. Thus, risk estimation considers the whole risk pathway, from hazard identification to unwanted consequences.

The general principles of risk assessment apply equally to qualitative and quantitative risk assessment. At least a qualitative risk assessment is recommended to be undertaken.

Recommended data needed for the conduct of AMR risk assessment:

1. Release evaluation
   - animal species (category such as food-producing, zoo, entertainment or companion animal, and, where appropriate, production type)
   - number of animals treated and their age, geographical distribution and, where appropriate, sex;
   - prevalence of infection or disease
   - data on trends in antimicrobial agent use
   - data on extra-label or off-label use;
   - methods and routes of administration of the antimicrobial agent;
   - dosage regimen
   - pharmacokinetics and relevant pharmacodynamics of the antimicrobial agent;
   - prevalence of pathogens that are likely to develop resistance in an animal
   - species;
   - prevalence of commensal bacteria which are able to transfer resistance to
   - human pathogens;
   - mechanisms and pathways of direct or indirect transfer of resistance;
   - potential linkage of virulence attributes and resistance;
   - cross-resistance or co-resistance with other antimicrobial agents;
   - data on trends and occurrence of resistant microorganisms obtained through
   - surveillance of animals, products of animal origin and animal waste products.

2. Exposure evaluation
    - human demographics;
    - prevalence of resistant microorganisms in food at the point of consumption;
    - microbial load in contaminated food
    - environmental contamination with resistant microorganisms;
    - occurrence in animal feed of resistant microorganisms
    - transfer of resistant microorganisms and their resistance determinants
    - measures are taken for microbial decontamination of food;
    - survival capacity and dissemination of resistant microorganisms during the food production process
    - disposal practices for waste products
    - capacity of resistant microorganisms to become established in humans;
    - human-to-human transmission of the microorganisms under consideration;
    - capacity of resistant microorganisms to transfer resistance to human commensal microorganisms and zoonotic agents;
    - amount and type of antimicrobial agents used to treat humans;
    - pharmacokinetics, such as metabolism, bioavailability, and distribution to the gastrointestinal flora.
3. Consequence evaluation
    - microbial dose and subsequent host response interactions;
    - variation in susceptibility of exposed populations or subgroups of the population;
    - variation and frequency of human health effects resulting from loss of efficacy of antimicrobial agents and associated costs;
    - potential linkage of virulence attributes and resistance;
    - changes in food consumption patterns due to loss of confidence in the safety of food products and any associated secondary risks;
    - interference with antimicrobial therapy in humans;
    - importance of the antimicrobial agent in human medicine;
    - prevalence of resistance in human bacterial pathogens under consideration.
4. Risk Approximation/Estimation
    - number of people falling ill and the proportion of that number infected with antimicrobial-resistant microorganisms;
    - adverse effects on vulnerable human sub-population (children, immunocompromised persons, elderly, pregnant, etc.);
    - increased severity or duration of infectious disease;
    - number of person/days of illness per year;
    - deaths (total per year; probability per year or reduced life expectancy for a random member of the population or a member of a specific sub-population) linked to antimicrobial resistant microorganisms when compared with deaths linked to sensitive microorganisms of the same species;

	• severity of the disease caused by the target resistant microorganisms; • availability and cost of alternative antimicrobial therapy; • potential impact of switching to an alternative antimicrobial agent (e.g. • alternatives with potential increased toxicity); • occurrence of antimicrobial resistance in target pathogens observed in • humans; • consequences of the overall risk impacts (e.g. illness and hospitalization).