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Tittle: Antimicrobial Resistance in Poultry Farming

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Abstract:
Antimicrobial resistance (AMRemergence,)'s dissemination, and persistence are still a major worldwide health concern. Animal husbandry, especially poultry, accounts for a significant amount of global antibiotic use. Despite a growing amount of research examining AMR in industrial farming systems, there is a vacuum in understanding the establishment of bacterial resistance in resource-limited contexts originating from poultry. As countries progress from low-income to middle-income status, there will be a greater demand for high-quality animal protein sources.Increased promotion of intensive poultry farming could help with food security, but it might also put poultry, other domestic animals, wildlife, and human populations at danger of AMR infection. Because intensively produced poultry can operate as AMR animal reservoirs, monitoring is required to assess the effects on humans, other animals, and the environment. In order to inform future small-scale poultry farming growth, we present a comprehensive assessment of chicken production in low-resource settings.In order to fully comprehend the epidemiology and ecology of AMR in poultry in low-resource settings, more research is required.

Keywords: antimicrobial resistance, intensive poultry production, economic development, food security

1. INTRODUCTION

1.1 History of Antibiotic:

Penicillin, the first commercially available antibiotic, was discovered by Alexander Fleming in 1928.The emergence of different resistance mechanisms has hindered the practical application of the first successful antimicrobials, the sulfonamides, which were launched in 1937. Resistance to sulfonamides was initially identified in the late 1930s, and 70 years later, the same mechanisms are still at work. Resistance was originally developed by Streptococci and Gonococcibacteria.Antibiotic resistance first became a significant problem in the treatment of tuberculosis (TB). Antibiotic resistance is now a significant public health concern and a contributor to antimicrobial resistance around the world (Davies et al.,2010).Antimicrobials attack the cell membrane, cell wall, protein synthesis, nucleic acid synthesis, and the synthesis of biological metabolic products.(Tortora GJ et al.,2015).

As penicillin became more widely used, resistant bacteria capable of inactivating it became more frequent, leading synthetic research to modify the antibiotic's molecular structure to avoid cleavage by penicillinases (β-lactamases). Following the discovery that a large number of antibiotic genes are found in wild microbial species, the discovery of a bacterial penicillinase prior to the usage of the antibiotic is now of interest(D'Costa VM et al.,2006).

Antibiotics kill bacteria by either becoming cytotoxic or cytostatic, enabling the body's natural defenses, such as the immune system, to destroy them. They usually work by inhibiting bacterial cell synthesis, protein synthesis, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), membrane disorganisation, or other particular behaviour (Levy SB et al., 2004). Antibiotics can also penetrate bacteria's cell walls by binding to them and transporting them via energy-dependent transport pathways in ribosomal sites, resulting in protein synthesis inhibition (Maranan MC et al., 1997).

1.2 Antibiotic Resistance:

Antibiotic resistance occurs when an antibiotic loses its ability to effectively prevent bacterial development. In the presence of therapeutic levels of antibiotics, bacteria become "resistant" and begin to multiply (Overview of Bacteria 2017). Bacteria that reproduce even when antibiotics are present are known as resistant bacteria.Antibiotic resistance does not imply that the body has developed resistance to antibiotics; rather, bacteria have developed resistance to the antibiotics intended to destroy them.

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Antibiotics are usually effective against them, but when the microbes become less sensitive or resistant, it requires a higher than the normal concentration of the same drug to have an effect. The emergence of antimicrobial resistance was observed shortly after the introduction of new antimicrobial compounds (Levy SB et al., 2007). Antibiotic resistance can occur as a natural selection process where nature empowers all bacteria with some degree of low-level resistance (Levy SB,1992).

Antibiotic resistance can affect people at any age, as well as the healthcare, veterinary, and agriculture industries, making it one of the world's most pressing public health issues. At least 2.8 million people in the United States became infected with antibiotic-resistant bacteria or fungi per year, with more than 35,000 people dying as a result. No one can fully eliminate the possibility of being infected with a resistant strain of bacteria, but some people are at a higher risk than others (for example, people with chronic illnesses). We will lose the ability to cure diseases and control public health risks if antibiotics lose their efficacy.

The food chain is the most common route for antibiotic-resistant bacteria to spread between animal and human populations (Witte W, 1998). Antibiotics are provided to animals in certain developing countries in their food, water, or injectable, which may be the source of microbe resistance to that particular antibiotic (McEwen SA et al.,2002). Antibiotics used as growth promoters in cattle feed, for example, contribute to antibiotic resistance (Levy SB, 1993). In the rural villages of Barcelona, where one-fourth of children were found to be faecal carriers of these species, recent evidence indicates that poultry or pork could be a potential source of quinolone resistant Escherichia coli. Quinolones, on the other hand, were not given to all these kids (Garau J et al.,1999). Almost all antibiotics are available over the counter in developed countries and can be purchased without a prescription, which is one of the leading causes of resistance. If antibiotic resistance is to be reduced, the only way to do so is to educate patients and the general public (Zaman S et al.,2017).

1.3 Antimicrobial resistance in bacteria from poultry:

Poultry is one of the most widely eaten meats on the planet. Poultry flocks are often raised under harsh conditions, with large quantities of antimicrobials used to prevent and treat disease as well as promote growth. Antimicrobial-resistant poultry pathogens can cause treatment failure, resulting in financial losses, but they can also be a source of resistant bacteria/genes (including zoonotic bacteria) that can be harmful to humans.

The first use of antibiotic drugs in poultry reports from 1946 (Moore et al., 1946), and the first resistance in food animals was identified by (Starr and Reynolds, 1951), with concerns about the growth of resistance dating from 1969. (Dibner and Richards, 2005). Following the first cases of antibiotic-resistant bacterial infections in humans, it was suggested that the use of antibiotics as growth promoters be prohibited if the drugs are not prescribed for human use (e.g., penicillins, tetracyclines, and sulfonamides; Swann et al., 1969).

Antibiotic-resistant bacteria can be found in the intestinal flora of animals, which can then infect or colonise humans through the food chain. Food animals, including poultry, are often infected with such strains. Several food-borne pathogens, including Campylobacter and Salmonella, can be found in chickens (Kazwala R.R. et al.,1990).Bacterial contamination of chicken carcasses occurs most often during slaughter and processing, and these species may survive on the finished product. Salmonella, Aeromonas, Shigella, Campylobacter, and Yersinia were isolated in a study conducted by Bok et al on the incidence of food-borne pathogens on retail broilers in South Africa. Several chicken carcasses were also found to be contaminated with several pathogens (Bok H.E. et al.,1986).

In certain countries, the quinolone enrofloxacin is widely used in poultry processing, and there is a hypothesis (and mounting evidence) that the emergence of quinolone-resistant Campylobacter spp. is linked to this use. BothCampylobcter and Salmonella DT 104 (which is also found in poultry) have a tendency for developing quinolone resistance, but in the case of Salmonella species, it has only been defined as a slight loss in susceptibility rather than resistance (Moritz van Vuuren, 2001).

1.4 Categories of Antibiotics:

Antibiotics are classified according to their activity spectrum, which includes whether they are narrow, wide, or extended-spectrum agents. Narrow-spectrum antibiotics (such as Penicillin G) are only effective against gram-positive bacteria. Tetracyclines and chloramphenicol are broad-spectrum antibiotics that affect both gram-positive and gram-negative

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bacteria. An extended-spectrum antibiotic affects additional types of bacteria, normally gram-negative bacteria, as a result of chemical alteration. (The terms gram-positive and gram-negative are used to differentiate between bacteria with a thick meshwork of peptidoglycan [a peptide-sugar polymer] and bacteria with only a thin peptidoglycan layer in their cell walls, respectively) (Encyclopedia Britannica,2021).

1.5 Types of Antibiotics:

An antibiotic class is a set of drugs with chemical and pharmacologic properties that are similar. There are different types of antibiotics but the most commonly used antibiotics are given below:

a) Penicillins
b) Tetracyclines
c) Cephalosporins
d) Quinolones
e) Macrolides
f) Sulfonamides
g) Glycopeptides
h) Aminoglycosides

1.Penicillins:

The beta-lactam antibiotics are another name for this class, which refers to the structural formula of the antibiotics. Aminopenicillins, Antipseudomonal penicillins, beta-lactamase inhibitors, normal penicillins, and penicillinase resistant penicillins are the five classes of antibiotics that make up the penicillin class.

Common antibiotics in the penicillin class include: Amoxicillin and clavulanate, Ampicillin, Dicloxacillin, Oxacillin, Penicillin.

Certain beta-lactamase enzymes are naturally immune to certain penicillinase-activated penicillins (such as oxacillin or dicloxacillin). Others, such as amoxicillin or ampicillin, work better against bacteria when combined with a beta-lactamase inhibitor like clavulanate, sulbactam, or tazobactam (Penicillin, 2011).

2. Tetracyclines:

Tetracyclines treat acne, urinary tract infections (UTIs), intestinal tract infections, eye infections, sexually transmitted diseases, periodontitis (gum disease), and other bacterial infections by acting as a broad-spectrum antibiotic against a wide range of bacteria (Chopra I, Roberts M 2001). The tetracycline class contains drugs such as: Demeclocycline, Doxycycline, Eravacycline, Minocycline, Omadacycline, Tetracycline.

3. Cephalosporins:

Cephalosporins come in five generations, each with increased coverage across the class that included gram-negative infections. Newer generations of improved architectures are being built in order to cover a broader range of bacteria. Cephalosporins are similar to penicillins in that they are bactericidal (kill bacteria). Strep throat, ear infections, urinary tract infections, skin infections, lung infections, and meningitis are all treated with cephalosporins (Australian Medicines Handbook., 2011).

Medications in this category include: Azithromycin, Clarithromycin, and Erythromycin are antibiotics.Ceftaroline (Teflaro), a fifth-generation (or next-generation) cephalosporin, is effective against methicillin-resistant Staphylococcus aureus (MRSA). Avycaz includes avibactam, a beta-lactamase inhibitor.

4. Quinolones:

Quinolones, also known as fluoroquinolones, are a class of synthetic antibacterials with a wide spectrum of action. Quinolones may be used to treat difficult-to-treat urinary tract infections, hospital-acquired pneumonia, bacterial prostatitis, and even anthrax or plague when other treatments aren't working (Sweetman S, editor., 2011). Ciprofloxacin, Levofloxacin, and Moxifloxacin are examples of common fluoroquinolone medications.

5. Aminoglycosides:

Aminoglycosides bind to the 30S ribosome and serve as bactericidal antibiotics quickly, inhibiting bacterial synthesis (killing the bacteria). Intravenously (through a needle through a vein) is how these medications are normally administered (Cold Spring HarbPerspect Med., 2016).Gentamicin, Tobramycin, and Amikacin are some examples of this class.

6. Sulfonamides:

Some gram-positive and many gram-negative bacteria are susceptible to sulfonamides, but resistance is widespread. Sulfonamides are used to treat or prevent urinary tract infections (UTIs), pneumocystis pneumonia, and ear infections (otitis media) (Quinolone antibiotics Medchemcomm., 2019). Sulfamethoxazole and trimethoprim, Sulfasalazine, and Sulfisoxazole are also common names.

7. Macrolides:

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The macrolides can be used to treat infections such as community-acquired pneumonia, pertussis (whooping cough), and uncomplicated skin infections, among others. Ketolides are a newer generation of antibiotics that were designed to combat bacterial resistance to macrolide antibiotics. Dawn Merton Boothe (Dawn Merton Boothe., 2015). Azithromycin, Clarithromycin, and Erythromycin are the most commonly prescribed macrolides.

1.6 Beta Lactam antibiotics:

The Beta-Lactam ring imitates the D-alanyl D-alanine component of the peptide chain, which is usually bound by penicillin binding proteins during the peptidoglycan layer's assembly. This prevents the glycan strands from cross-linking, resulting in bacterial lysis (Clinical and Research Information on Drug-Induced Liver Injury., 2017).

1.6.1 Spectrum of activity of Penicillins:

Gram-positive: non-beta-lactamase producing gram-positive cocci (including viridans, group A streptococci, Streptococcus pneumoniae, anaerobic Streptococcus), Enterococcus spp., non-penicillinase producing strains of Staphylococcus aureus, coagulase negative Staphylococcus aureus, Clostridium spp. (excluding C. difficile), Actinomyces spp.

Gram-negative bacteria include Neisseria meningitides, Neisseria gonorrheae, and Pasteurella multocida.

Mechanism of Action:

By binding one or more of the penicillin binding proteins, it exerts bactericidal activity by inhibiting bacterial cell wall synthesis (PBPs). Inhibits certain PBPs involved in the activation of a bacterial autolytic mechanism, resulting in a bacterial autolytic effect.

1.6.2 Spectrum of activity of Tetracycline

Tetracyclines are broad-spectrum antibiotics that can destroy gram-positive and gram-negative bacteria, as well as atypical species like chlamydiae, mycoplasmas, and rickettsiae, as well as protozoan parasites. Semi-synthetically prepared or derived from Streptomyces strains.

1.6.3 Spectrum of activity of Cephalosporins

Cephalosporins, like penicillins, are broad-spectrum antibiotics. They have a beta-lactam ring that binds to penicillin-binding proteins and prevents bacterial cell wall synthesis, resulting in cell lysis and death. Cephalosporins are classified according to their antibacterial properties and the date of their introduction.

- First generation cephalosporins: These include cephalexin and cefazolin. They have good activity against a wide spectrum of Gram-positive bacteria including penicillinase-producing staphylococci. However, they are not active against methicillin-resistant staphylococci (MRSA). Enterococci are resistant.
- Second generation cephalosporins: Include cefaclor, cefuroxime and cefoxitin. They are more stable to hydrolysis by beta-lactamases produced by Gram-negative bacteria and therefore have enhanced activity against many of the Enterobacteriaceae, e.g. Escherichia coli, Salmonella.
- Third generation cephalosporin: Include Ceftriaxone they have the widest spectrum of activity compared to other generations of cephalosporins and are active against Gram-negative organisms, including many of the significant Enterobacteriaceae. They are also very active against streptococci.

1.6.4 Spectrum of activity of Aminoglycosides:

Aminoglycosides are an essential part of today's antibacterial arsenal. They are a clinically beneficial class of drugs for a variety of infections, including some protozoal infections, due to their wide spectrum of activity, rapid bactericidal action, and favourable chemical and pharmacokinetic properties.

1.6.5 Spectrum of activity of Quinolones:

Quinolones are broad-spectrum antibiotics that are active against both Gram-positive and Gram-negative bacteria, including mycobacteria, and anaerobes.

1.6.6 Spectrum of activity of Sulfonaamides:

All sulfonamides have a similar spectral profile. Gram-positive and gram-negative bacteria, Nocardia, Actinomyces spp., and some protozoa such as coccidia and Toxoplasma spp. are all inhibited by sulfonamides. In the spectral range of more active sulfonamides, many species of Streptococcus, Staphylococcus, Salmonella, Pasteurella, and even Escherichia coli can be

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found. Pseudomonas, Klebsiella, Proteus, Clostridium, and Leptospira spp., as well as rickettsiae, mycoplasmas, and most Chlamydia spp., are also highly resistant.

1.6.7 Spectrum of activity of Macrolides:

The macrolides are bacteriostatic antibiotics that work against a wide range of Gram-positive bacteria. The macrolides that are currently available are well tolerated, orally available, and commonly used to treat mild to moderate infections. The liver has been linked to a number of macrolide antibiotics.

1.7 Mode of action of Antibiotics:

Antibiotics act by disrupting various molecular targets within bacteria and cell surface, preventing growth or initiating killing.
There are 3 broad mechanisms:
1. Inhibitors of DNA synthesis
2. Inhibitors of bacterial protein synthesis
3. Inhibitors of bacterial cell wall synthesis

1.7.1 Injury to cell membrane

The selective permeability of a microorganism's plasma membrane leads to active transfer of energy in the form of ATP. Active transportation through integral transporter proteins regulates cytoplasmic content and gradient, such as micro and macromolecules and ions. As antimicrobials impair selective membrane permeability, ions are lost and the cellular ion gradient is skewed, resulting in cellular damage and death (Brooks GF, Carroll KC et al., 2013). The metabolic steps of fatty acid synthesis and membrane phospholipids are antimicrobial targets. Polymyxin B, a bactericidal antibiotic, is one of the few medicines that have been used to treat Gram-negative bacteria like Pseudomonas aeruginosa (Tortora GJ et al., 2015). By depolarizing membrane potential, Staphylococcus aureus releases potassium ions from the cytoplasm into the extracellular matrix (Brooks GF, Carroll KC et al., 2013). Inhibitors of cell membrane function include daptomycin, amphotericin B, colistin, imidazoles, and triazoles (Tortora GJ et al., 2015, Brooks GF, Carroll KC et al., 2013).

1.7.2 Effect of antibiotics against Cell wall synthesis

Peptidoglycan is used to construct the cell walls of microorganisms. Crosslinks between glycan polysaccharide strands bind polypeptides bound to N-acetyl muromic acid (NAM) of each polysaccharide strand. Transglycosylation and transpeptidation reactions are catalysed by penicillin-binding proteins (PBPs) attached to cell membrane as DD-peptidases to build peptidoglycan after bactoprenol, a membrane-bound acceptor, transfers UDP-NAM-pentapeptide and UDP-NAG from cytoplasm to outer site of cell membrane (Krmusaolu S. MRSA and MSSA., 2016).

1.7.2.1Degradation of structure and function of cell wall

Certain antibiotics, such as β -lactam antibiotics, bind to PBPs as a substrate and react with PBPs that have a high affinity for β-lactams. These drugs are structural analogues of acyl-D-alanyl-D-alanine, a substrate of PBP that binds to its active site during the transpeptidation reaction. Antibiotics that inactivate the transpeptidase domain of PBPs block the transpeptidation reaction. These cell wall inhibitors, which prevent peptidoglycan biosynthesis, destroy bacteria (Krmusaolu S. MRSA and MSSA 2016).

1.7.2.2 β-lactamases and the mechanisms of β-lactam resistance

β-lactamase, an enzyme produced by many Gram-positive and Gram-negative bacteria, inactivatesβ-lactam antibiotics by degrading the amide bond of the β-lactam ring. Extended-spectrum β-lactamases (ESBLs) are a type of β-lactamase that can hydrolyze the β-lactam rings of cefotaxime, ceftazidime, and aztreonam. They can be found in Gram-negative bacteria like Klebsiella pneumoniae and Escherichia coli (Brooks GF, Carroll KC et al., 2013). The blaZ gene produces β-lactamase, which is regulated by the plasmid or transposon genes blaI and blaRI. β-lactamase enzyme is synthesised as a result of upregulation of the blaZ gene, and the microorganism develops resistance to the β-lactam used (Krmusaolu S. MRSA and MSSA., 2016).

1.7.2.3 Inhibition of nucleic acid synthesis

Antibiotics can inhibit replication, transcription, and folate synthesis of microorganisms.

1.7.2.3.1 Inhibition of replication

Quinolones, such as nalidixic acid and ciprofloxacin, which are used to treat Pseudomonas spp. infections, avoid replication fork formation by inhibiting DNA gyrase by binding to the gyrA subunit. By binding to the gyrB subunit, novobiocin and coumermycin prevent the

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formation of replication forks by inhibiting DNA gyrase. When bacteria's gyrA and gyrB genes are mutated, bacteria become immune to antibiotics (Snyder L, Champness et al., 2007). Trimethoprim, hydroxyurea, 5-fluorodeoxyuridine, and 5-fluorouracil block the synthesis of deoxynucleotide precursors used in DNA replication. Mitomycin C works by binding guanine bases in both template strands of DNA to prevent replication (Snyder L, Champness et al., 2007).

1.7.2.3.2 Inhibition of transcription

Rifampin, an antibiotic from the rifamycine family, inhibits transcription initiation by binding to an RNA polymerase subunit. Rifampin is used to treat infections caused by Mycobacterium tuberculosis, Mycobacterium leprae, and bacteria for which treatment is difficult. Since it does not inhibit eukaryotic RNA polymerase, it is not harmful to humans (Snyder L, Champness et al., 2007).

1.7.2.3.3 Inhibition of protein synthesis

Puromycin, which mimics aminoacyl tRNA, enters the ribosome and is added to the polypeptide, but it is not translocated from the A site to the P site. The ribosome releases a polypeptide with puromycin at the carboxyl terminus, and translation is stopped. Puromycin is toxic to humans and animals because it prevents eukaryotic translation (Snyder L, Champnesset al., 2007). By binding to 23S rRNA, erythromycin, which belongs to the macrolide class of antibiotics, inhibits translation. Premature polypeptide is released in the translocation stage as a result of erythromycin blocking the E site, which is the exit site for peptidyl-tRNA.

Chloramphenicol, a bacteriostatic agent and 23S rRNA inhibitor, inhibits transcription by blocking the peptidyl transferase reaction, which prevents aminoacyl tRNA from binding to the A site of the ribosome.

1.8 Mechanism of Antibiotic Resistance

Antimicrobial resistance mechanisms are divided into four categories: (1) drug absorption limitation; (2) drug target modification; (3) drug inactivation; and (4) active drug efflux. Limiting absorption, drug inactivation, and drug efflux are examples of intrinsic resistance mechanisms; drug target change, drug inactivation, and drug efflux are examples of acquired resistance mechanisms (Chancey ST 2012, Mahon CR 2014).

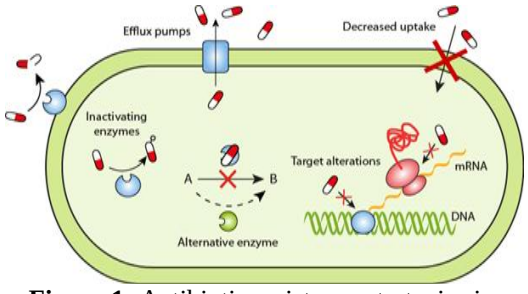

Figure 1: Antibiotic resistance strategies in bacteria. Courtesy of E. Wistrand-Yuen.

1.8.1 Limiting uptake of a drug:

There is a natural variation in bacteria's ability to limit antimicrobial agent uptake. In gram-negative bacteria, the LPS layer's structure and functions serve as a barrier to certain molecules. This confers inherent resistance to a subset of large antimicrobial agents on certain bacteria (Blair JM 2014). Since mycobacteria have a lipid-rich outer membrane, hydrophobic drugs like rifampicin and fluoroquinolones have better access to the cell, whereas hydrophilic drugs have less access (Kumar A 2005, Lambert PA 2002).

1.8.2 Modification of drug targets

Resistance to β-lactam drugs, which are almost exclusively used by gramme positive bacteria, is mediated by changes in the structure and/or number of PBPs (penicillin-binding proteins). PBPs are transpeptidases that help cells create peptidoglycan in their walls. The amount of drug that can bind to that target is affected by changes in the number of PBPs (increase in PBPs with decreased drug binding capacity, or decrease in PBPs with normal drug binding ability). A change in structure can reduce the drug's ability to bind or completely prevent it from binding (Reygaert W 2009, Beceiro A, 2013). Glycopeptides (such as vancomycin) inhibit cell wall synthesis, while lipopeptides (such as daptomycin) depolarize the cell membrane. Gram negative bacteria (those with a thick LPS layer) have built-in resistance to these antibiotics (Randall CP 2013). Resistance to drugs that target ribosomal subunits may arise from ribosomal mutation (aminoglycosides, oxazolidinones), ribosomal subunit methylation (aminoglycosides, macrolides—gram positive bacteria, oxazolidinones, streptogramins), most commonly involving erm genes, or ribosomal defence (aminoglycosides, macrolides (tetracyclines). The amount of drug interaction varies a lot between these mechanisms (Kumar S 2013, Roberts

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MC,2004). Resistance to drugs that target nucleic acid synthesis (fluoroquinolones) is mediated by changes in DNA gyrase (gramme negative bacteria—for example, gyrA) or topoisomerase IV (gramme positive bacteria—for example, grlA) (Hawkey PM. 2003, Redgrave LS, 2014). The active site of these enzymes is often mutated, and the resulting structural changes in the enzyme interfere with drug binding while allowing the natural substrate to bind (Huovinen P 1995, Vedantam G, 1998).

1.8.3 Drug inactivation

Transfer of acetyl, phosphoryl, and adenyl groups to the medication is the most popular method of drug inactivation by chemical group transfer. There have been a significant number of transferases discovered. Acetylation is the most widely used mechanism, with aminoglycosides, chloramphenicol, streptogramins, and fluoroquinolones all being known to use it. The aminoglycosides are known to be targeted by phosphorylation and adenylation (Blair JM 2015, Schwarz S, 2004).

1.8.4 β-lactamases

β-lactamases (also known as penicillinases and cephalosporinases) inactivate β-lactam drugs by hydrolyzing a particular site in the β-lactam ring structure, which causes the ring to open. The most common resistance mechanism used by gram negative bacteria against β-lactam drugs, as well as the most effective resistance mechanism against penicillin and cephalosporin drugs, is the synthesis of β-lactamases (Kumar S 2013, Bush K, 2010). ESBL producers may be immune to a variety of drugs, but they are usually vulnerable to β-lactamase inhibitors. The β-lactamase inhibitors are structurally similar to β-lactamases, and although they have limited antimicrobial activity on their own, they function synergistically with a β-lactam drug. Amoxicillin/clavulanic acid, ampicillin/sulbactam, and piperacillin/tazobactam are some of the most commonly used β-lactamase inhibitor/drug combinations (Pfeifer Y 2010, Schultsz C 2012, Bush K 2013, Jacoby GA 2009, Bevan ER 2017).

1.8.5 Efflux Pumps

Antimicrobial resistance may arise from the development of complex bacterial machinery capable of extruding a toxic compound from the cell (McMurry L 1980). The efflux pumps are mainly responsible for removing toxic substances from the bacterial cell, but many of them can transport a wide range of substances (multi-drug [MDR] efflux pumps). Many of these pumps' resistance capabilities are affected by the carbon source available (Blair JM 2014, Villagra NA 2012).The main facilitator superfamily (MFS), the small multidrug resistance family (SMR), the resistance-nodulation-cell-division family (RND), the ATP-binding cassette family (ABC), and the multidrug and toxic compound extrusion family are the five major families of efflux pumps (MATE). The structural conformation, energy source, range of substrates they can extrude, and type of bacterial organisms in which they are found vary between these families (Piddock LJ 2006).

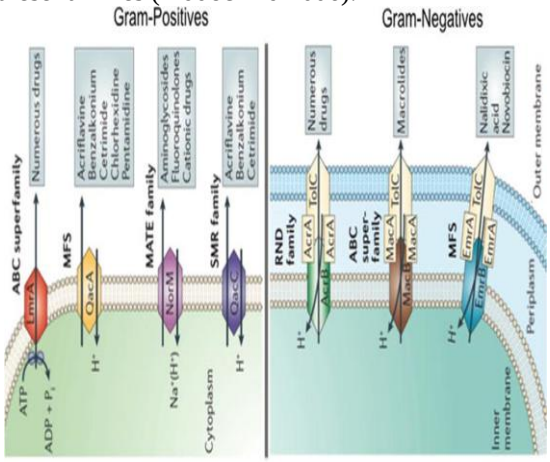

Figure:2

Representation of different types of efflux pumps in gram-positive and gram-negative bacteria

The ATP-binding cassette (ABC) superfamily, the main facilitator superfamily (MFS), the multidrug and toxic-compound extrusion (MATE) family, the small multidrug resistance (SMR) family, and the resistance nodulation division (RND) family are the five major families of efflux pumps shown. A diagrammatic comparison of all the families is shown, along with examples of drugs and compounds that can be used as a substrate.

1.9 Metallo-β-lactamase

Antibiotics known as β-lactams are the most widely used antibacterial agents, and resistance to these drugs is a growing concern. Antibacterial activity of β-lactam antibiotics spans a wide range of pathogens, including Gram-positive and Gram-negative pathogens. β-lactam antibiotics are the most widely used antibiotics in the world due to their beneficial properties

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(Livermore DM 2006, 2012). These antibiotics work by inhibiting a group of transpeptidase enzymes (also known as penicillin binding proteins or PBPs) that are needed for bacterial cell wall peptidoglycan synthesis (Sauvage E 2008).Bacterial resistance has been growing as a result of widespread use of β-lactam antibiotics, and it now poses a significant challenge to the continued use of antibiotic therapy (Babic M 2006). Antibiotics with a four-membered β-lactam ring that acts as a substrate for transpeptidase target enzymes are known as β-lactam antibiotics. Transpeptidase enzymes form an acyl-enzyme intermediate by reacting with the D-Ala-D-Ala terminus of a pentapeptide bound to N-acetylmuramic acid of the peptidoglycan polymer through an active site serine residue (Lee W, McDonough MA et al 2001).β-lactam antibiotics have a four-membered ring that resembles the D-Ala-D-Ala structure and can bind to the active site of transpeptidase enzymes, forming an acyl-enzyme with the active site serine (Buynak JD 2007, Shi Q, Meroueh SO 2011).Efflux, decreased permeability, altered transpeptidases, and inactivation by β-lactamases are all mechanisms by which bacteria develop resistance to β-lactam antibiotics. In Streptococcus pneumoniae, changing the sequence of target transpeptidases by mutation or recombination to produce enzymes that bind poorly to β-lactams is a major source of resistance (Hakenbeck R et al.,2012).

The hydrolysis of the amide bond in the β-lactam ring is catalysed by β-lactamases, which results in ineffective products. They are a common source of resistance in Gram-negative bacteria and some Gram-positive bacteria. On the bacterial chromosome or on plasmids, genes encoding β-lactamases may be found. β-lactamases have been classified into four classes based on their primary sequence homology (Ambler RP et al.,1991). Classes A, C, and D are active-site serine enzymes that catalyse the hydrolysis of the β-lactam through a serine-bound acyl intermediate (Ghuysen JM 1991).With the exception of monobactams, Class B metalloβ-lactamases (MBLs) have a wide substrate range and can catalyse the hydrolysis of virtually all β-lactam antibiotics. Mechanism-based inhibitors including clavulanate, sulbactam, and tazobactam, which are effective against serine-based class A β-lactamases, do not inhibit them (Drawz SM 2010, Pérez-Llarena FJ 2009).

1.9.1 New Delhi Metallo-Beta-Lactamase:

In 2008, NDM-1, the first New Delhi metallo-beta-lactamase (MBL), was discovered in an extensively drug-resistant (XDR) Klebsiella pneumoniae clinical isolate recovered from a patient's urine (Yong, D., Toleman et al.,2009).Epidemiology showed that the gene has already spread to a variety of bacteria species across six continents, including K. pneumoniae, E. coli, Enterobacter spp., Morganella morganii, and Acinetobacter baumannii(Johnson and Woodford, 2013), meaning that the plasmid encoding NDM has a huge potential to spread. Depending on the substitutions, the NDM subtypes differ from the NDM-1 prototype by one to five amino-acid substitutions and have varying levels of hydrolyzing activity against carbapenems and other beta-lactam substrates. NDM-7 with two substitutions of Asp130Asn and Met154Leu has the highest carbapenem-hydrolyzing activity among the first seven subtypes, followed by NDM-5 with Val88Leu and Met154Leu, NDM-6 with Ala233Val, and NDM-1 with Ala233Val (Rahman et al., 2014). Metal chelators, such as EDTA, inactivate MBLs (Drawz, Bonomo 2010).MBLs were discovered over forty years ago, but since they were chromosomally encoded and present in non-pathogenic species, they were not initially considered a serious problem for antibiotic therapy (Lim HM, Pene JJ et al., 1988). Urinary tract infections, septicaemia, respiratory infections, diarrhoea, peritonitis, device-associated infections, and soft tissue infections are all caused by NDM-1 generating E. coli entering the host's urinary tract, skin, lungs, and wounds (Kaase M et al.,2011).Cross-contamination during food processing or by body fluids may be the mode of transmission of the NDM-1 generating strain, which may happen in the community or in a hospital environment (Bogaerts P et al.,2010). NDM-1 strains are particularly dangerous because: (i) the majority of plasmids found in these bacteria are transferable and capable of wide rearrangement, implying widespread horizontal transmission and flexibility among bacterial populations; (ii) there is no routine standardised phenotypic test for metallo-beta-lactamase (MBL) detection; and (iii) there is a likely high prevalence of uti in these bacteria (Rolain JM et al.,2010). The spread of metallo β-lactamase poses a significant challenge for both individual patient care and infection control strategies, and reveals the significant unpreparedness of national public health structures in dealing with this emergency (Miyajima Y et al.,2008).

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1.10. Objectives of the study:

I. REVIEW OF LITERATURE:

Antimicrobial resistance (AMR):

Antimicrobial resistance (AMR) is becoming a greater threat to human and animal health, reducing the ability to treat bacterial infections and increasing the risk of morbidity and mortality from resistant bacteria. Antimicrobial efficacy in the treatment of bacterial infections is still a major concern in both veterinary and human medicine (Tang, K.L et al.,2017,Schwartzet al.,1988, Vieira, N et al.,2007, Chantziaras et al.,2014). Antimicrobial resistance has developed as a result of the use of antimicrobials to treat and prevent diseases in animals or to encourage their development. Resistance can be transmitted from animals to humans through a number of routes, the most important of which is possibly through food. Reduced antimicrobial use has been shown to reduce the prevalence of antimicrobial resistance in humans, and the use of sub-therapeutic doses to gain weight has been prohibited in the European Union since January 2006 (Regulation 1831/2003/EC). Animal antimicrobial treatments can spread resistant strains to humans through other animals, sewage, or humans, such as farmers or slaughterhouse workers (Phillipset al., 2003; Miranda et al., 2008).

Antimicrobial use in broiler chicken processing has been linked to a rise in the risk of antimicrobial-resistant pathogens infecting humans via food (WHO, 1997).There are concerns that the normal flora of poultry staphylococci and enterococci could serve as a reservoir for antimicrobial-resistant bacteria and resistance genes (Lu et al., 2003),Antimicrobial usage in poultry processing has been linked to the incidence of antimicrobial-resistant bacteria and resistance genes in samples of fresh poultry litter, according to study (Nandi et al., 2004). Antimicrobials were first used in broiler production to improve growth, livability, and feed conversion efficiency around 50 years ago (Libby and Schaible, 1955; Stokstad and Jukes, 1958–1959; Waibel et al., 1954) and while some producers claim to have stopped using growth-promoting antimicrobials in feed, the extent of use is unknown because producers can potentially switch the basis for use from growth promotion to disease prevention (Weise, 2006).

2.1 Modes of Antimicrobial resistance:

Antimicrobial agents function as selective toxins, inhibiting enzymes that are either specific to the prokaryotic cell or sufficiently distinct from the mammalian host to cause minimal toxicity. Based on their mode of action, most antimicrobials fall into one of four groups. Inhibition of cell wall synthesis, protein synthesis, nucleic acid synthesis, or cell membrane integrity disruption are examples.There are several excellent articles on the mechanisms by which bacteria establish antimicrobial resistance (Bradford 2001; Chopra and Roberts 2001; Fluit, Visser, and Schmitz 2001; Ouellette and Kundig 1997; Poole 2001).

2.1.1 Inhibitors of Cell Wall Biosynthesis:

Many antimicrobial agents work by inhibiting the formation of bacterial cell walls. Mammalian cells do not have cell walls, and bacterial organisms have different cell walls. As a result, cell wall synthesis offers a range of possible therapeutic targets in the production of anti-infective drugs. Resistance to β-lactams is caused by one or more of the mechanisms mentioned below: (1) mutations in the target PBP or acquisition of new PBPs with lower drug affinity; (2) development of one or more β-lactamases that inactivate the drug; (3) changes in cell wall porins that restrict drug movement to the target site; and (4) active efflux of the drug out of the cell by energy-dependent pumps. The most effective mechanism of resistance among gram-negative bacteria is via production of β-lactamases, which inactivate the drug by hydrolysis of the β-lactam ring (Bradford 2001).The second major group of agents that inhibit cell wall synthesis are the glycopeptide antibiotics, the foremost examples being vancomycin and teicoplanin. Resistance to glycopeptides arises in cells that synthesize a dipeptide terminus consisting of D-Ala-D-Lac in place of D-AlaD-Ala. Six vancomycin resistance types in enterococci have been described: VanA, VanB, VanC, VanD, VanE, and VanG(Schouten et al.,2001). The van gene cluster has long been feared to spread from Enterococcus to Staphylococcus, where vancomycin is a last-resort treatment for multiresistant infections. The first case of a glycopeptide-resistant Staphylococcus isolate from Michigan in a strain carrying the vanA gene was published in 2002 (Centers for Disease Control and Prevention 2002).

2.1.2 Inhibitors of Nucleic Acid Metabolism:

Antimicrobials that disrupt DNA and RNA synthesis generally do so by interacting with

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the cell's nucleotide (e.g., sulfonamides) or nucleic acid (e.g., quinolones, rifamycins) biosynthesis processes. Genes encoding resistance to sulfonamides and trimethoprim are widespread among both commensal and pathogenic gramnegative bacteria and are often located on extrachromosomal DNA mobile elements (White et al.,2001; Zhao et al.,2001). Compounds that inhibit RNA polymerase (rpoB) or DNA topoisomerase feature in nucleic acid synthesis usually target RNA polymerase (rpoB) or DNA topoisomerases (gyrA, gyrB, parC, parE). The rifamycins, which include the antituberculosis drug rifampin, bind to the bacterial RNA polymerase, inhibiting bacterial transcription initiation selectively. Mutations in the structural gene (rpoB) for RNA polymerase cause resistance in Mycobacterium tuberculosis (Spratt 1994). Fluoroquinolones are antimicrobials that target DNA topoisomerase II (DNA gyrase) and DNA topoisomerase IV, two associated enzymes. DNA topoisomerases are enzymes that catalyse DNA supercoiling, which is an important step in cellular metabolism (Drlica and Zhao 1997; Hooper 1999). For both veterinary and human agents, resistance to one fluoroquinolone sometimes leads to decreased susceptibility and/or resistance to other members of the class(Hooper, 1999). While some fluoroquinolones can diffuse directly across the lipid bilayer, it appears that most fluoroquinolones cross the gram-negative outer membrane through porin channels in the outer membrane (Drlica and Zhao, 1997). Resistance due to decreased drug influx is generally low-level resistance. For example, mutations of the E. coli porin OmpF showed about a twofold increase in resistance to quinolones (Alekshun and Levy 1999). In both gram-negative and gram-positive bacteria, efflux is a process of fluoroquinolone tolerance. Also in the presence of efflux pathways, absolute clinical resistance is thought to require gyrA mutations. Recent studies on E. coli showed that in cells with topoisomerase mutations, deletion of the gene encoding the AcrAB efflux pump reduced ciprofloxacin MICs to near-wild-type levels (Oethingeret al.,2000).

2.1.3 Inhibitors of Protein Synthesis:

Proofreading is disrupted, resulting in certain mRNAs being misread. Furthermore, some aminoglycosides tend to inhibit the translocation step in polypeptide synthesis while others appear to block the development of a functional initiation complex.

Streptomycin resistance can occur as a result of structural mutations in the 30S ribosomal subunit or the development of modifying enzymes. Resistance to aminoglycoside antibiotics is often linked to the presence of modifying enzymes that can phosphorylate, adenylate, or acetylate these drugs (Wright 1999). Chloramphenicol resistance is often mediated by chloramphenicol acetyltransferases (CATs) in bacteria, and several cat genes have been found in a variety of bacteria (Trieu-Cuot et al.,1993; VassortBruneau et al.,1996). Inactivation of the drug by acetylation of the two hydroxyl groups is the most common cause of resistance. A number of bacteria have also been found to have chloramphenicol resistance efflux mechanisms (Bissonnette et al.,1991; White et al.,2000). Antimicrobial macrolides (e.g., erythromycin) bind to the tRNA binding site on the 50S subunit and cause the tRNA molecules to dissociate from the ribosomes, preventing protein synthesis. Resistance in Gram-positive bacteria is usually caused by mutations or methylation of the 23S ribosomal RNA subunit, but efflux is becoming more common (Zhong and Shortridge 2000). High-level streptogramin resistance is due to inactivation by acetylation, although ribosomal mutations can confer low-level resistance (Simjee et al.,2001).

2.1.4 Enzymatic Degradation:

2.1.4 Hydrolysis

The integrity of many antibiotics' hydrolytically prone chemical bonds (e.g., esters and amides) is crucial to their biological function. As a result, many enzymes have evolved to attack and cleave these weak bonds, resulting in the destruction of antibiotic activity. Amidases, which cleave theβ-lactam ring of penicillin and cephalosporin groups of drugs, are among the most important. Esterases related to macrolide antibiotic resistance and fosfomycin resistance ring-opening epoxidases are two other examples. Since these enzymes only require water as a co-substrate, they can also be excreted by bacteria, preventing antibiotics from reaching the bacteria.

2.1.4.1 β-Lactamases:

The development of penicillinase by pathogenic Escherichia coli was likely the first antibiotic resistance mechanism published in the literature (E.P. Abraham et al., 1940). To hydrolytically cleave the β-lactam ring of penicillins and cephalosporins, β-lactamases use one of two molecular strategies: an active site Ser nucleophile or a Zn2+ centre to activate water (fig

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1). Ser-β-lactamases, also known as metallo-β-lactamases, can be further divided based on their three-dimensional structures, which include amino acid sequences, substrate preferences, and inhibitor sensitivities. The β-lactamase family has been split in a variety of ways, but (Bush et al.,(K. Bush 1995)nomenclature has risen to prominence. Ser-β-lactamases work through a covalent catalytic mechanism similar to Ser proteinases and esterases, in which an active site Ser attacks the lactam ring with a ring opening nucleophilic attack (fig 1). The mechanism of peptidoglycan peptidases and Ser-β-lactamases is similar, and it has been suggested that they are evolutionarily related(J.R. Knox et al.,1996). The metallo-β-lactamases are part of the larger Zn-dependent hydrolase family (H. Daiyasu et al.,2001) and they were once thought to be of minor clinical significance, but they have emerged in the last decade as major sources of carbapenem resistance in Gram-negative bacteria (P. Nordmann et al.,2002).

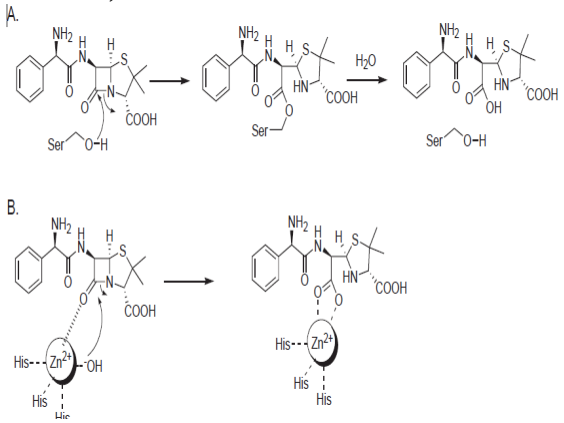

Fig 1. General mechanism of Ser-h-lactamases and metallo-h-lactamases. The hydrolysis of the penicillin amoxicillin is shown catalyzed by a Ser-h-lactamase (A) and a metallo-β-lactamase (B).

2.1.4.2 Metallo-beta-Lactamases (MBLs):

Metallo-beta-Lactamases (MBLs) are class B β-lactamases that hydrolyze almost all clinically accessible β-lactam antibiotics and have the metallo-hydrolase/oxidoreductase superfamily's distinctive / sandwich fold. MBLs have a shallow active-site groove with one or two divalent zinc ions and versatile loops surrounding it (Mojica MF et al.,2016). This versatile hairpin loop in NDM-1 passes over the zinc ion for hydrolysis and then is removed after the catalysis is complete(Aitha M et al.,2016). According to sequence identity and zinc ion dependency, MBLs are divided into three subclasses (B1, B2, and B3), with the B1 subclass containing the majority of clinically important enzymes. Because of the existence of zinc ligands, catalytic mechanisms, and variations in active site architecture, few inhibitors have been successfully developed (Mojica MF et al.,2016).β-Lactamase inhibitors (BLIs), which could play an important role in combating β-lactam resistance in Gram-negative bacteria, have lost their effectiveness due to the development of a diverse and harmful class of β-lactamases. A triple combination of meropenem/piperacillin/tazobactam β-lactams, has been proved as one of the strategies to kill Methicillin-resistant Staphylococcus aureus (MRSA) in vitro as well as in a mouse model through a novel synergistic mechanism of action(Bush K. A, 2015). Multi-resistant bacteria, also known as "super bacteria" or "super bug," are bacteria that bear many antibiotic-resistant genes; infections caused by them are difficult to treat (Padhi S. 2011). Most likely, a very rare “genetic fusion” occurred between two previously identified antibiotic-resistant genes, resulting in the NDM-1 mutation. The bla NDM-1 gene produces NDM, an enzyme that hydrolyzes a wide variety of antibiotics, including carbapenems, which are antibiotics of last resort. In the last few years, 17 new NDM-1 variants have been generated by modifying one or two residues at various positions (Kaase M et al.,2011,Khan AU et al.,2012,Williamson DA et al.,2012,Khan AU et al.,2014). A number of New Delhi metallo-β lactamase-1 (NDM-1) variants have been discovered. In A. baumannii, NDM-2 had a Cysteine to Glycine substitution at position 82, and an amino acid substitution of alanine at position 28 in place of proline.16S RNA methylase and extended-spectrum-lactamases, on the other hand, were not found. Furthermore, plasmids were not detectable in strains carrying bla NDM-2, and the bla NDM-2 was not seen to be moved by conjugation (Du H et al.,2016).

II. ANTIMICROBIAL RESISTANCE IN POULTRY FARMING:

Antimicrobial resistance (AMR) remains an increasing problem for human and animal health, lessening the opportunity to treat bacterial infections and furthering the risk associated with morbidity and mortality caused by resistant bacteria. Ensuring the efficacy of antimicrobials to treat bacterial infections remains a pressing problem for both veterinary and human medicine (Tang K.L et al.,2017,Schwartz B et al.,1988, Vieira N. et al., 2007, Chantziaras I. et al.,2014).In recent years, enough evidence highlighting a link

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between excessive use of antimicrobial agents and antimicrobial resistance from animals as a contributing factor to the overall burden of AR has emerged (Marshall BM, Levy SB 2011).Due to the intensification of farming practises in most developed countries, the extent of consumption is expected to rise dramatically in the coming years (Van Boeckel TP et al.,2015). Antibiotics are commonly used in food-producing animals for a variety of purposes, including infection prevention, treatment, growth promotion, and increased productivity (Mathew AG et al.,2009, Castanon JIR 2007). Poultry is one of the most widely consumed foods on the world. With over 90 billion tonnes of chicken meat processed each year, chicken is the most widely farmed animal (C Agyare, VE Boamah 2018). In most countries, a wide range of antimicrobials are used to raise poultry (Landers TF et al.,2012, Sahoo KCet al.,2010, Boamah VE et al.,2016). In human medicine, a large number of these antimicrobials are considered important (World Health Organization 2018, World Health Statistics 2017). The widespread use of such critical antimicrobials in animal production is likely to hasten the emergence of AR in pathogens and commensal species. This will result in treatment failures and financial losses, as well as serving as a source of gene pool for human transmission. Furthermore, there are questions about antimicrobial residues in meat posing a threat to human health (Mirlohi M et al.,2013, Darwish WS et al.,2013, Goetting V et al.,2011, Addo KK et al.,2011, Mehdizadeh S, et al.,2010).When an antibiotic is used in any environment, it generally destroys susceptible bacterial species, leaving those with drug-resistant traits behind. These resistant bacteria then multiply and become the dominant species, allowing them to transmit the genes responsible for their resistance to other bacteria (both horizontally and vertically) (Madigan MT et al.,2014, Laxminarayan R et al.,2013).Through eating or handling pathogen-contaminated meat, resistant bacteria may be transmitted from poultry products to humans (Van, den Bogaard AE, 2011). Once in the human system, these pathogens can colonise the intestines, where resistant genes can be exchanged or transmitted to the endogenous intestinal flora, jeopardising potential treatments for infections caused by these species (Marshall BM et al.,2011, Hall MAL et al.,2011, Jakobsen L et al.,2010, De Leener E et al.,2005). Antimicrobials were first used in animal processing in 1910, when workers across America staged strikes and disturbances due to a lack of meat products(Ogle M. 2013). At the time, scientists were searching for ways to produce more meat at a lower cost, which led to the use of antibiotics and other antimicrobial agents (Dibner JJ et al.,2005). Antibiotics for non-therapeutic use in animal agriculture has been banned in several countries due to the global challenge of antibiotic resistance and growing treatment failures (Castanon JIR 2007, Cogliani C et al.,2011, European Union 2006, Choct M 2001). Antibiotic use in poultry and livestock production benefits farmers and the economy because it has generally improved poultry performance effectively and economically. However, the likely dissemination of antibiotic resistant strains of pathogenic and non-pathogenic organisms into the environment, and their subsequent transmission to humans via the food chain, could pose a threat to humans (Apata DF 2009).

III. ANTIBIOTIC RESISTANCE OF SOME SELECTED ORGANISMS IN POULTRY:

4.1 Staphylococcus species:

The bacterial genus Staphylococcus is a Gram-positive cocci and a facultative anaerobe which appears in clusters when viewed under the microscope(Barrow GI, 2009). Staphylococcosis, pododermatitis (bumblefoot), and septicaemia are caused by them, and they mostly affect chickens and turkeys. Infections in humans and animals have also been linked to coagulase-negative organisms(Koksal F et al.,2009, Boamah VE et al.,2017). β-lactams were once considered the first line of defence against staphylococcal infections, but due to the advent of high levels of resistance to these and other medications, there are still very few options for treating these infections (Mamza SA et al.,2009) prone to the antibiotic methicillin MRSA (methicillin-resistant Staphylococcus aureus) is a superbug that is resistant to almost any antibiotic used to treat Staphylococcus aureus(Stapleton PD, Taylor PW 2007). In a study in Germany to detect the presence of MRSA in broilers, turkeys, and the ambient air, MRSA was found in 77 percent of broilers and 54 percent of turkeys in the air. There are ten different spa types, with spa type t011 and clonal complex (CC) 398 being the most common. It was also discovered that the same sequence forms were found in both the birds and the atmosphere for each farm (Friese A et al.,2013). This pattern of resistance was also observed in India, where the mecA resistant gene was found in 1.6 percent of staphylococcal isolates (Bhedi KR et

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al.,2018).In Africa, studies in Ghana and Nigeria found that livestock-associated Staphylococci are susceptible to amoxicillin/clavulanic acid, amikacin, ciprofloxacin, gentamycin, and cephalexin (Boamah VE et al.,2017, Suleiman A et al.,2013), while most staphylococcal isolates in the United States were susceptible to rifampin, cotrimoxazole (Waters AE et al.,2011, Abdalrahman LS et al.,2015). Most of these species had high levels of resistance to oxacillin and tetracycline, which would be devastating if these oxacillin-resistant strains were transmitted to humans (Boamah VE et al.,2017, Suleiman A et al.,2013, Waters AE et al.,2011).

4.2 Pseudomonas species:

Pseudomonas is a Gram-negative, aerobic bacteria genus belonging to the Pseudomonadaceae family (Skerman SV et al.,1989). Pseudomonas is a genus of bacteria that can be found in soil, water, and on plants. P. fluorescens, P. pertucinogena, P. aeruginosa, P. chlororaphis, P. putida, P. stutzeri, and P. syringaeare among the 191 subspecies that make up the genus. Pseudomoniasis, an opportunistic P. aeruginosa infection, is widespread in poultry birds such as chickens, turkeys, ducks, geese, and ostriches, where infections in eggs cause embryos to be destroyed (De Vos et al.,2009).Pseudomonas aeruginosa causes respiratory infections, sinusitis, keratitis/keratoconjuctivitis, and septicemia, as well as pyogenic infections, septicemia, endocarditis, and lameness, among other diseases.Infections may be spread by skin wounds, infected vaccines, antibiotic solutions, or injection needles. In poultry birds, the disease may be systemic, affecting various organs and tissues, or localised in tissues such as the infraorbital sinus or air sacs, causing swelling of the head, wattles, sinuses, and joints. Many poultry farms and birds have been found to have P. aeruginosa(Sams AR. 2001). According to a study conducted in Ghana, P. aeruginosa isolated from poultry litter was susceptible to levofloxacin in the range of 20–100%, with approximately 75% showing intermediate susceptibility to aztreonam. Cephalosporins, carbapenems, penicillins, quinolones, monobactam, and aminoglycoside resistance were all found in the bacteria. Metallo-Lactamase encoding genes (blaIMP, blaVIM) were not found in any of the isolates, but the class 1 integron, which is known to bear many antibiotic resistant genes, was found in 89.4% of multidrug resistant strains (Odoi H. 2016).P. aeruginosa isolates were found to be highly resistant to β-lactams, tetracycline, tobramycin, nitrofurantoin, and sulfamethoxazole-trimethoprim in a Nigerian study, while ofloxacin, imipenem, and ertapenem were highly effective against bacterial pathogens (Aniokette U et al.,2016).

4.3 Escherichia species:

Escherichia coli is a Gram-negative bacterium that has long been known to easily and frequently exchange genetic information with other bacteria through horizontal gene transfer. As a result, depending on the source of isolation, it can exhibit those characteristics. E. coli is a commensalbacteria that lives in both human and animal intestines. Some strains, however, have been linked to gastrointestinal issues (Tenaillon O et al.,2010).Tetracycline, a popular antibiotic used in poultry, has been identified as one of the drugs to which bacteria are most resistant. Even without the use of this antibiotic, tetracycline resistance has been identified in poultry (Van, den Bogaard AE et al.,2000).

4.4 Salmonella species:

Salmonella spp. are Gram-negative, facultatively anaerobic, non-spore-forming, motile rods of the Enterobacteriaceae family found in animals' gastrointestinal tracts(Barrow GI, Feltham RKA 2009, Bell C, Kyriakides 2007). Salmonella can be spread among flocks of birds by faeces shedding. Salmonella spp. is common in the poultry industry. The prevalence varies greatly depending on the region, form of output, and detection methods used. Salmonellosis is caused by Salmonella spp., and it is considered to be the etiological agent in both humans and animals. Food-borne salmonellosis is still a problem all over the world (Bell C, Kyriakides 2007).Contaminated chicks, farm size, and contaminated feed are all risk factors for Salmonella infections and contamination in broiler chickens, and these risks are amplified when feed trucks are parked near the workers' change room and chickens are fed meals (Marin C et al.,2011, Arsenault J et al.,2007). Salmonella can be spread among flocks of birds by faeces shedding.Salmonella spp. is common in the poultry industry. The prevalence varies greatly depending on the region, form of output, and detection methods used. Salmonellosis is caused by Salmonella spp., and it is considered to be the etiological agent in both humans and animals. Food-borne salmonellosis is still a problem all over the world(Arsenault J et al.,2007).The risk factors associated with Salmonella infections and

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contamination in broiler chickens include contaminated chicks, size of the farm and contaminated feed and these risk increase when feed trucks are parked near the entrance of the workers' change room and when chicken are fed with meals (Marin C et al.,2011, Arsenault J et al.,2007). It also depends on age of the chicken, animal health, survival of organism in the gastric barrier, diet and genetic constitution of the chicken could also affect the colonization ability of Salmonella spp. in poultry (Cosby DE et al.,2015).The S. pullorum causes pullorum disease in poultry. Vertical (transovarian) transmission of the disease in birds is possible, but it can also happen through direct or indirect contact with infected birds through the respiratory path, faeces, or polluted feed, water, or litter. Furazolidone, gentamycin sulphate, and antimetabolites (sulfadimethoxine, sulfamethazine, and sulfamerazine) are antimicrobials used to treat pullorum disease(Msoffe PL et al.,2009). Salmonella spp. have been increasingly isolated from poultry in Brazil, with a prevalence of 2.7 percent. The most common isolates were Salmonella enteritidis (48.8%), Salmonella infantis (7.6%), Salmonella typhimurium (7.2%), and Salmonella heidelbergii (7.2%). (6.4 percent). Streptomycin (89.2%), sulfonamides (72.4%), florfenicol (59.2%), and ampicillin (59.2%) were all resistant to at least one antimicrobial class, and 53.2 percent demonstrated multidrug resistance to three or more groups, with streptomycin (89.2%), sulfonamides (72.4%), florfenicol (59.2%), and ampicillin (59.2%) being the most common (44.8 percent) (Medeiros MAN et al.,2011).

4.5 Streptococcus species:

Streptococcus is Gram-positive bacteria. Streptococcus gallolyticus is a common member of the gut microbiota in animals and humans; however, being a zoonotic agent, it has been reported to cause mastitis in cattle, septicemia in pigeons, and meningitis, septicemia, and endocarditis in humans (De Herdt P et al.,1993). A study carried out in Japan isolated Streptococcus gallolyticus from pigeons with septicaemia. Most of the isolates were susceptible to vancomycin, penicillin G and ampicillin, while some were resistant to tetracycline, doxycycline and lincomycin. All the isolates were resistant to tetracycline had tet(M) and/or tet(L) and/or tet(O) genes(Nomoto R et al.,2013).

4.6 Campylobacter species:

The most common disease-causing Campylobacter species are Campylobacter jejuni and Campylobacter coli. They are primarily responsible for human foodborne gastroenteritis(Sackey BA et al.,2001, Wimalarathna HML et al.,2013, Acheson D et al.,2001).Handling raw poultry or consuming undercooked poultry meat are common causes of campylobacteriosis(AltekruseSFet al.,1999).Cross-contamination of raw poultry with other ready-to-eat foods has been confirmed through the cook's hands or kitchen utensils. In most cases, erythromycin is the medication of choice for treating Campylobacter infections (Acheson D et al.,2001).When antimicrobial therapy is needed, fluoroquinolones, gentamicin, and tetracycline are also clinically effective in treating Campylobacter infections(Moore JE et al.,2005).It has been documented that C. jejuniandC. coli isolates are resistant to fluoroquinolones, tetracycline, and erythromycin. The widespread use of these antimicrobials in animal husbandry, especially in poultry, is contributing to the rise in resistance(Wilson IG et al.,2003,Randall LP et al.,2003).

4.7 Yersinia species:

It's a Gram-negative, non-spore-forming rod that's also psychrotrophic and can survive and multiply at low temperatures. One of the most common causes of Yersinia spp. infections in humans is poultry meat. The most common species is Yersinia enterocolitica, which is often isolated from poultry and poultry products.Y. enterocolitica is an enteric pathogen that causes acute enteritis in humans, which is characterised by fever, bloody diarrhoea, and lymph node inflammation. One of the most common causes of yersiniosis in humans is contaminated food(Annamalai T et al.,2005).Y. enterocolitica isolated from poultry raw meat and retailed meats in Poland were classified as biotype 1A and exhibited moderate ability of producing biofilms and ystB was the predominant virulence gene. In biofilms, a multi-system that include poor antibiotic penetration, nutrient limitation and slow growth, adaptive stress responses, and formation of persister cells are hypothesized to constitute the organisms' resistance to antibiotics(Zadernowska A, Chaje W 2017).

4.8 Clostridium species:

Clostridium is a genus of Gram-positive obligate anaerobic bacteria which includes several

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significant human pathogens. Spore of Clostridium normally inhabits soil and intestinal tract of animals and humans(Péchiné S et al.,2016).Common infections caused by Clostridia include botulism caused by C. botulinum, pseudomembranous colitis caused by C. difficile, cellulitis and gas gangrenecaused by C. perfringens, tetanus caused by C. tetani and fatal post-abortion infections caused by C. sordellii(Num SM et al.,2014).In poultry, C. perfringens is known to cause necrotic enteritis. When administered in the feed or drinking water, bacitracin or virginiamycin is an effective treatment choice. Ulcerative enteritis is caused by C. colinum. The most important medications for treating and preventing this infection are bacitracin and penicillins(Osman KM et al.,2013, Nhung NT et al.,2017).

4.9 Bacillus species:

Bacillus is a phylum firmicutes genus of Gram-positive, obligate aerobic or facultative anaerobic rod-shaped bacteria. Bacillus spp. includes both non-parasitic free-living bacteria and parasitic pathogenic bacteria (Slepecky RA et al.,2009).B. anthracis, which causes anthrax, and B. cereus, which causes food poisoning, are two medically important organisms (Fagerlund A et al.,2012).Pneumonia, endocarditis, ocular, and musculoskeletal infections are among the other infections caused by Bacilli spp. Vancomycin, imipenem, ciprofloxacin, gentamycin, tetracycline, chloramphenicol, clindamycin, and erythromycin are common antibiotics used to treat Bacillus infections. The majority of Bacillus spp. are immune to broad spectrum cephalosporins and ticarcillin-clavulanate(Reboli AC et al.,1989).All 18 strains of B. cereus isolated from raw and processed poultry meat from supermarkets in Iasi County were found to be resistant to penicillin, amoxicillin-clavulanate, colistin, cefoperazone, sulfamethizole, and metronidazole, but sensitive to erythromycin, cotrimoxazole, tylosin, flumequine, kanamycin, gentamycin, enrofloxacin, Almost half of the antibiotics used to screen B. cereus isolates were immune(Florişteanu V et al.,2007).This resistance pattern was also found in 44 B. cereus strains isolated from chicken and chicken products in India's Jammu area. Penicillin G resistance was found in all isolates, but streptomycin sensitivity was found in all. Amoxicillin, ampicillin, and carbenicillin resistance was found in over 60% of the isolates(Bashir M et al.,2017).

4.10 Mycobacterium species:

Mycobacteria are bacteria of the genus Mycobacterium that are acid-fast, aerobic, and nonmotile (Rastogi N, Legrand E, Sola C 2001). Mycobacteria are common organisms that live in water and food sources, and they can colonise their hosts without causing any symptoms. Tuberculosis is caused by pathogenic mycobacterial species such as M.tuberculosis, M. bovis,M. africanum, and M. macroti, while leprosy is caused by M. leprae. Penicillin-resistant Mycobacteria spp. are mostly susceptible to clarithromycin and rifamycin(Barrow WW 2001).

4.11 Klebsiella species:

Klebsiella belongs to the Enterobacteriaceae family and is a non-motile,Gram-negative, oxidase-negative, rod-shaped bacteria with a prominent polysaccharide capsule (Podschun R et al.,1998). Klebsiella species can be found in a variety of environments, including soil, plants, insects, people, and other animals (Ajayi AO, Egbebi AO 2011). Septicaemia, meningitis, urinary tract infections, pneumonia, and diarrhoea are all infections caused by Klebsiella spp.(Podschun R et al.,1998).K. pneumoniae, K. oxytoca, and K. variicolaare common pathogenic Klebsiella in humans and animals (Fielding BC 2012). Third-generation cephalosporins, carbapenems, aminoglycosides, and quinolones are among the antibiotics widely used to treat Klebsiella infections (Van Duin D, Bonomo RA 2016).

IV. ANTIMICROBIAL USE IN POULTRY PRODUCTION:

Antimicrobials fed to poultry at subtherapeutic concentrations accelerated their development, which was discovered by chance. Antimicrobial growth promoters (AGPs) were first used on chickens in 1946 (Moore P., Evenson A 1946).Farmers in the postwar United States and Europe struggled to meet rising demand for poultry food products soon after(Laxminarayan R et al.,2015). The Food and Drug Administration (FDA) of the United States approved the delivery of antimicrobial agents in feed without veterinary prescription in 1951(Jones F.T., Ricke S.C 2003).The European Union regulation No. 1831/2003, which came into effect in 2006, restricted the use of antimicrobials in animal nutrition to the treatment of coccidiostats and histomonostats(Laxminarayan R 2015).Following

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that, in 2014, the Canadian government modelled its ban on such AGPs after FDA policy(Diarra M.S et al.,2014).Several Organization for Economic Cooperation and Development (OECD) countries have banned APGs (for example, Mexico, South Korea, and New Zealand), while APGs are still legal in others (e.g., Japan)(Laxminarayan R. et al.,2015).Antimicrobial growth promoters (AGPs) are not banned in most non-OECD nations, including China, Brazil, Russia, Argentina, India, Indonesia, the Philippines, and South Africa, which are among the world's leading poultry producers(Schar D et al.,2018).Due to the scarcity of high-quality data outside of a few HICs, determining AGP productivity gains on a global scale remains difficult. AGP bans have marginal economic consequences in HICs with optimised production processes, but they could have greater consequences in lower-income countries with less developed biosecurity and sanitation practises(Laxminarayan R 2015).Antimicrobial usage restrictions in LMICs could theoretically raise animal disease burdens, as antimicrobials are often used as a replacement for good hygiene and sanitation(Laxminarayan R., Duse A 2013).Tetracyclines, aminoglycosides, lincosamides, amphenicols, fluoroquinolones, sulfas, and beta-lactams are among the antibiotics used in poultry farms and are critical for animal health(Thome K et al.,2019).

5.1 The emergence of antimicrobial resistance in bacteria:

Antimicrobial resistance was first identified in Bacillus coli (now known as Escherichia coli) by Abraham and Chain (1940), just a year before the use of penicillin to treat infectious diseases in humans (Chain et al., 1940), and not long after its discovery by Fleming (1929).Since most antimicrobials in clinical use are developed naturally by soil microorganisms, such microorganisms are the source of many resistance genes now found in clinically important bacteria, as shown by Benveniste and Davies more than 40 years ago (Benveniste and Davies, 1973). Further phylogenetic research has shed light on the evolutionary source of resistance, suggesting that bacteria evolved AMR genes long before the “antibiotic era” (Finley et al., 2013, Aminov and Mackie, 2007, Wellington et al., 2013, Martinez and Baquero, 2009), and also developed synthetic compound defences (D'Costa et al., 2011, Bhullar et al. 2012)found growing evidence that AMR is an ancient and common part of the genome of environmental bacteria.Multidrug resistance has been discovered in bacteria that can metabolise antimicrobials and use them as a source of nutrients (APUA, 2008). Resistance genes and determinants from these bacteria are likely to be transmitted to other bacterial organisms, including those that are taxonomically and genetically distant (Aminov and Mackie, 2007).Bacteria originally used several resistance genes to promote essential metabolic processes (Aminov and Mackie, 2007, Martinez and Baquero, 2009, Martinez, 2008).Environmental bacteria's plasmid-encoded β-lactamase enzymes may have originally been involved in the synthesis of peptidoglycans rather than providing resistance to β -lactam antimicrobials (Martinez and Baquero, 2009).(Forsberg et al., 2012, Lupo et al., 2012, APUA, 2008) discovered that environmental soil and water bacteria hold a pool of resistance genes (the "resistome") that can serve as a reservoir of resistance for human pathogens.

5.2 Current scenario of Antimicrobial Resistance in the world:

The demand for animal protein for human consumption is increasing at an unparalleled pace around the world. Regular use of antimicrobials is correlated with modern animal production practises, potentially increasing selection pressure on bacteria to become immune. There has been no objective assessment of global antimicrobial intake by livestock, despite the substantial potential implications for antimicrobial resistance.

Antimicrobial use in food animal production was estimated to be 63,151 (1,560) tonnes in 2010 and is expected to increase by 67 percent by 2030, to 105,596 (3,605) tonnes. The increasing number of animals raised for food production accounts for two-thirds (66%) of the global increase (67%) in antimicrobial consumption. The remaining third (34%) can be attributed to changes in agricultural methods, with a greater proportion of animals expected to be raised in intensive farming systems by 2030.Shifts in production processes are expected to account for up to 46% of the rise in antimicrobial use in Asia by 2030. Antimicrobial consumption in Asia is expected to reach 51,851 tonnes by 2030, accounting for 82% of global antimicrobial consumption in food animals in 2010.

China (23%) was the country with the highest share of global antimicrobial consumption in food animal production in 2010, followed by the United States (13%), Brazil (9%), India (3%), and Germany (3%).(Fig 3)

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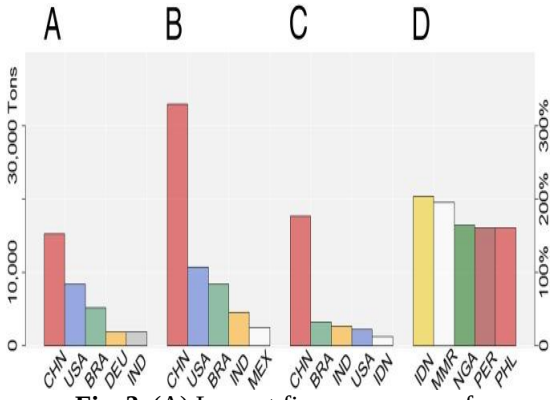

Fig. 3. (A) Largest five consumers of antimicrobials in livestock in 2010. (B) Largest five consumers of antimicrobials in livestock in 2030 (projected). (C) Largest Increase in antimicrobial consumption between 2010 and 2030. (D) Largest relative increase in antimicrobial consumption between 2010 and 2030. CHN, China; USA, United States; BRA, Brazil; DEU, Germany; IND, India; MEX, Mexico; IDN, Indonesia; MMR, Myanmar; NGA, Nigeria; PER, Peru; PHL, Philippines.

By 2030, this ranking is projected to be China (30%), the United States (10%), Brazil (8%), India (4%), and Mexico (2%). Among the 50 countries with the largest amounts of antimicrobials used in livestock in 2010, the five countries with the greatest projected percentage increases in antimicrobial consumption by 2030 are likely to be Myanmar (205%), Indonesia (202%), Nigeria (163%), Peru (160%), and Vietnam (157%).China and Brazil are currently among the largest antimicrobial users, but they are not the countries with the fastest-growing antimicrobial consumption projections. This suggests that these two countries have already begun to move toward more intensive livestock production systems that depend on antimicrobials to keep animals healthy and increase productivity.Antimicrobial use for animals is expected to increase by 99 percent in the BRICS countries by 2030, while human populations are only expected to increase by 13 percent(World Bank 2015).

Antimicrobial use was found to be highly geographically diverse across continents. Antimicrobial consumption hotspots in South and Southeast Asia include China's southeast coast, Guangdong and Sichuan provinces (Fig. 4, top), Vietnam's Red River delta, Bangkok's northern suburbs, and India's south coast, including Mumbai and Delhi.Antimicrobial use was strongest in the Americas in the south of Brazil, the areas of Mexico City, and the midwestern and southern United States. The Nile delta and Johannesburg and its surrounding townships were the only significant hotspots of antimicrobial consumption in Africa. Figure 4(Bottom) shows the uncertainty bounds associated with antimicrobial consumption spatial predictions.

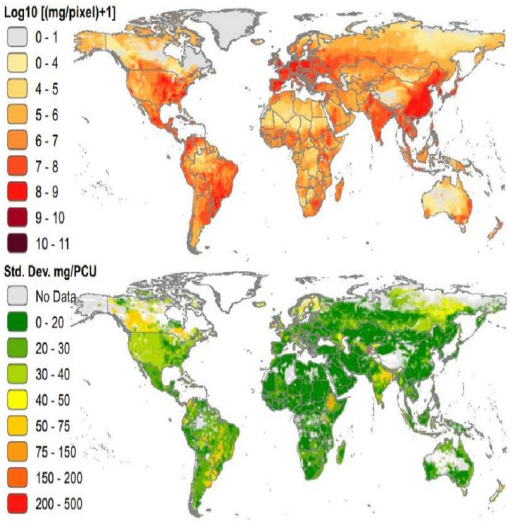

Fig. 4: Global antimicrobial consumption in livestock in milligrams per 10 km2 pixels (Top) and average SD of estimates of milligrams per PCU (Bottom).

Antimicrobials were used in commercial poultry feed for a long time as growth promoters or to treat bacterial infections, which led to the proliferation of resistant bacterial strains around the world. Between 2009 and 2015, 3544 avian pathogenic Escherichia coli strains were isolated from commercial broilers in South Africa and screened for susceptibility to eight antimicrobial groups. Antibiotic resistance was studied using time series methods to determine seasonal and overall patterns.Tetracycline resistance showed seasonal patterns, with increases in the winter months when respiratory diseases are at their highest. Quinolone resistance peaked in 2012, after which there was a downward trend in resistance. Colistin resistance has steadily risen since 2009, peaking at 12.08 percent in 2015, but its use in feed was phased out in 2016.Florfenicol resistance has also risen dramatically, from 2.36 percent in 2009 to 6.63 percent in 2015. Trimethoprim-sulphadiazine resistance, as well as spectinomycin, fosfomycin, and amoxicillin resistance, had sharply decreased by the end of 2015. The overall prevalence of multidrug resistance (MDR) was 80.6 (95 percent confidence interval, 0.743–0.819), but MDR levels were substantially lower in 2013, 2014, and 2015 than in 2009(Theobaldet al.,2018).

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Antibiotics are widely used in veterinary and human medicine today for disease prevention and treatment, as well as for their growth-promoting effects as feed additives. This complicated situation has resulted in the rapid spread of multidrug-resistant bacteria in livestock and humans. Bacteria that produce extended-spectrum beta-lactamase (ESBL) are immune to a broad variety of β-lactam antibiotics. They are currently regarded as one of the most serious threats to human and animal infection treatment.The most common ESBL-types in poultry are CTX-M-1, TEM-52, and SHV-12, with CTX-M-1, TEM-52, and SHV-12 being the most common ESBL-types in livestock and animal products. The bacteria that bear ESBL genes most commonly in poultry are Escherichia coli and Salmonella spp. ESBL-producing bacteria can be found in the meconium of newly hatched chicks and can be found at any step of the poultry production pyramid.The presence of these bacteria in the environment near poultry barns is high, contributing to an ongoing infection pressure with additional ESBL-types. Probiotics have been shown to minimise ESBL-producers as well as ESBL-gene transfer in chickens. When other feed additives, such as zinc and copper, are fed to livestock, they increase the prevalence of ESBL-producing bacteria.Despite the fact that antimicrobial resistance is not a new phenomenon, the prevalence of ESBL-producing bacteria in poultry increased dramatically following the use of ß-lactam antibiotics (Dierikxet al., 2013).Apart from mutations in ESBL-coding genes, selective pressure affects other genes, promoters, and the number of ESBL-genes, increasing antibiotic resistance. Porin protein mutations can alter antibiotic permeability in the outer membrane, for example. The advent of resistance to other antibiotic classes can contribute to co-selection, and stronger promoters can boost ESBL gene expression (Gniadkowski, 2001, 2008).

5.2.1 ESBL-producing bacteria and resistance types in poultry products and their transmission to humans

In comparison to other meat sources, poultry meat has the highest contamination of ESBL-producing bacteria (Friese et al., 2013).Different study groups discovered a high prevalence of ESBL-producing bacteria in poultry products, while infection in meat from other animals was significantly lower.In a Danish study conducted between 2009 and 2011, poultry meat had the highest level of contamination among the meat sources tested (human exposure to ESBL-producing bacteria: 83.8 percent from broiler meat, 12.5 percent from pork, and 3.7 percent from beef) (Carmo et al., 2014).Poultry meat was also found to be more infected with ESBL-producing Salmonella spp. than pork meat (De Jong et al., 2014).Feces were obtained from healthy chickens, pigs, and cattle in Germany and Switzerland. Broiler samples revealed the same thing.Cattle (60 percent respectively, 13.7 percent) and pigs (up to 56.3 percent respectively, 15.3 percent) had the highest contamination levels (100 percent respectively, 63.4 percent) by ESBL-producing E. coli (Geser et al., 2012; Friese et al., 2013).

Broilers have the highest ESBL-producing E. coli contamination in Japan (broilers 60.0 percent, laying hens 5.9%, cattle 12.5 percent, and pigs 3.0 percent) (Hiroi et al., 2012b). ESBL-producing E. coli was found in 79.8% of the chicken meat tested in the Netherlands, compared to 4.7 percent in beef and 1.8 percent in pork (Overdevest et al., 2011). Broilers are more likely than laying hens to be infected with ESBL-producing bacteria (Hiroi et al., 2012b;Blaak et al., 2015; Evers et al., 2016).

The most commonly prescribed antibiotic was amoxicillin (76.5 percent), followed by norfloxacin, ofloxacin, ceftriaxone, and oxytetracycline. During the withdrawal period, 75% of farmers used antibiotics on the banned list, while 14.8 percent continued to use antibiotics. Three patterns of antibiotic use were discovered using hierarchical cluster analysis: 1) excessive use of non-prohibited and prohibited antibiotics, or an excessive user; 2) low use of a few forms of non-prohibited antibiotics and moderate use of prohibited antibiotics, or a low user; 3) multiple use of a number of non-prohibited and prohibited antibiotics, or a moderate user.Farmers from medium-sized, family-run farms, as well as those with a low level of education and income, were more likely to abuse antibiotics.Prior formal agricultural training has been linked to a reduction in the use of a variety of antibiotics.

5.2.2 Famers' practice of antibiotic use:

Escherichia coli infection was the most common infection on chicken farms, followed by three viral diseases. Most farmers used traditional medicine as well as antibiotics to immunise their chickens with mandatory and optional vaccines. Antibiotics is overused to prevent infections rather than treat them. Antibiotics were also used as a

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preventative measure on large chicken farms in other developing countries such as Vietnam and Thailand(Carrique-Mas JJ et al., 2015,Wongsuvan G et al.,2018).Antibiotics are not used to avoid infections in accordance with the US Food and Drug Administration's guidelines(Alimentarius C 2005).Only amoxycillin and oxytetracycline are eligible to be used among the five most commonly used antibiotics in this report. While these two antibiotics were previously thought to pose a lower risk, they are now widely used on chicken farms around the world(Carrique-Mas JJ et al.,2015,Wongsuvan G et al.,2018,GuetiyaWadoum RE et al., 2016)The resistance mechanism can be accelerated by frequent and routine usage (WHO. Antibiotic resistance: 2015, WHO. Integrated surveillance of antimicrobial resistance in foodborne bacteria 2017).Despite using non-prohibited antibiotics on a daily basis, three-quarters of farmers used prohibited antibiotics. One aim of farmers using various antibiotics was to reduce the risk of bacteria from chickens developing resistance. They were unaware, however, that this could result in multiple resistant bacterial strains in animals and humans (Lu Y et al., 2014, Huang TM et al., 2009, WHO). Antimicrobial resistance global report on surveillance 2014).Antibiotics on the restricted list have been determined to be dangerous drugs, and their use in China has been prohibited (Ministry of Agriculture and Rural Affairs 2019).Despite the fact that many developed countries have prohibited the use of antibiotics as growth promoters (Maron DF et al.,2013, Teillant A et al.,2015). China has no limits on the direct use of antibiotics as growth promoters. The Ministry of Agriculture recently approved 21 antibiotic products for use as growth promoters in commercial feeds (Ministry of Agriculture and Rural Affairs. 2019).

5.2.3 Factors associated with misuse of antibiotics:

Medium farm size, lower education levels, lower farmer income, and a lack of formal agricultural training were all linked to increased antibiotic misuse.In our research, medium-sized farms had poor sanitation but a high-intensity production model, which increased the risk of infection and, as a result, antibiotic use. Not only in our research, but also in other studies, good hygiene, cleanliness, and waste management on large farms have consistently resulted in reports of low antibiotic use(Christian A, et al.,2018, Laxminarayan R et al.,2013).Farmers with a higher education, especially those who had completed high school, were less likely to misuse antibiotics. Farmers in both developed and developing countries must be trained in order to follow national guidelines (Lhermie G et al.,2017,Laxminarayan R et al.,2013, Tangcharoensathien V et al.,2018).Antibiotics is used more often by low-income farmers to prevent and manage infections (Lhermie G et al.,2017,Chauvin C et al.,2011).Most farmers were unaware of the distinctions between bacterial and antibiotic resistance, according to the descriptive findings on antibiotic awareness and antibiotic resistance.Infections caused by viruses Antibiotics were considered to be a cure-all for all diseases by the majority of them. Furthermore, only one-third of the farmers were aware of the risk of antibiotic resistance spreading from animals to humans.Farmers in other developing countries, such as Cambodia (Om C etal.,2016, Rousham EK et al.,2018), face similar challenges.Farmers in developed countries such as Germany, on the other hand, are more mindful of the possibility of animal-human transmission (Schulze-Geisthovel SV et al.,2016). Multiple antibiotic use will be reduced as a result of training in pharmaceutical awareness and antibiotic stewardship (WHO. Antibiotic resistance: Multi-country public awareness survey 2015,Sirdar MM et al.,2012,Om C et al., 2016).

#. Antimicrobials were often overprescribed without conclusive evidence of the cause of illness or susceptibility testing. Biosecurity and flock management activities were generally poor. Salmonella was found in 45 (or 16.7%) of the 270 samples. Its prevalence was found to be substantially ($p<0.05$) related to the multiplication center's location, with 27 percent at Bonga and 10.6 percent at Hawassa. The bedding (35.3 percent) and staff hand swabs (33.3 percent) sample types were also substantially ($p<0.05$) different from the chicken cloaca (14.8 percent), demonstrating the weak biosecurity and personnel hygienic practises in the centres.Both 45 isolates (100%) were resistant to kanamycin and sulfamethoxazole-trimethoprim, as well as nalidixic acid (97.8%), ampicillin (97.8%), cefoxitin (97.8%), streptomycin (97.8%), tetracycline (97.8%), chloramphenicol (91.3%), ciprofloxacin (31.1%), and gentamicin (0 percent). Alarmingly, 42 isolates (93.4%) had multidrug resistance (MDR) to eight drugs, and all 45 isolates had MDR to three drugs.The high rate of Salmonella isolation from (I) bedding, (ii) staff hand swabs, (iii) chickens, (iv) more MDR isolates,

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(v) and weak biosecurity practises in the centres could pose a risk of pathogens and drug resistant genes spreading to smallholder chicken producers and the general public(Abdi et al.,2017).

V. CURRENT SCENARIO OF ANTIMICROBIAL RESISTANCE IN THE INDIA:

In recent years, India has emerged as a global hotspot for antibiotic resistance (ABR), with increasing resistance rates to most antibiotics in common pathogens and rising number of treatment failures. Apart from the human health sector an additional area of concern in India is the rampant use of antibiotics in the food-animal production sector. There are few regulations governing the use of antimicrobials for cattle, chicken, and pigs raised for domestic consumption in India, with no stringent implementation protocols even when there are regulations.Antimicrobials are widely used as growth promoters, according to several reports. Antibiotics have been used nontherapeutically in poultry production in particular.On the plus side, with the announcement of a National Action Plan, the establishment of a basic surveillance system, intersectoral collaboration projects, and public awareness campaigns sponsored by official health agencies and civil society groups, the issue of ABR has gained high visibility among Indian policymakers in recent years.

6.1 Antibiotics are used by farmers for three primary reasons:

1. As an antidote for animals showing symptoms of an infectious disease.
2. As a metaphylaxis to treat a group of clinically stable animals and reduce the likelihood of a disease outbreak, or as a prophylaxis to protect those who are at risk from infection
3. As a growth booster to help animals gain weight(National Pharmaceutical Regulatory Agency (NPRA) 2017).

6.2 Global trends in antimicrobial use in food animals

According to the Organisation for Economic Cooperation and Development (OECD), the amount of antimicrobials used in food animals will rise by 67 percent from 63,151 tonnes in 2010 to 105,596 tonnes in 2030. The approximate global average annual consumption of antimicrobials needed to produce one kilogramme of meat is as follows:

1. To produce 1kg of beef, 45mg of antimicrobials are used.
2. To produce 1kg of chicken, 148mg of antimicrobials are used.
3. To produce 1kg of pork, 172mg of antimicrobials are used.

(Laximinarayan, R., et al.,2014,VanBoeckel T.P et al.,2015).

6.3 The top five countries in terms of antimicrobial consumption in foodanimal output

1. China (23%)
2. The United States (13%)
3. Brazil (9%)
4. India (3%)
5. Germany (3%)

(Van Boeckel T.P. et. al.,2015).

6.4 Antibiotic use in livestock in India:

In India, there is currently little reliable data on antimicrobial use in food animals or resistant infections linked to animals, as well as their effects on public health. However, it is acknowledged that there is widespread use ofAntibiotics are used in food animals as infection prevention, treatment, and growth promoters. Non-therapeutic antibiotic use has been particularly prevalent in poultry and aquaculture processing.According to a recent report estimating global antibiotic use in poultry, swine, and cattle in 2010, India, along with China, the United States, Brazil, and Germany, accounted for 3% of global antibiotic intake in 2010. Animal antibiotic use is expected to rise by around two-thirds globally by 2030, according to projections.

Antibiotics in animal feed will increase by 82 percent in India by 2030, according to the report. In India, for example, their use in chickens is projected to triple by 2030. Penicillins, tetracyclines, and quinolones are among the most commonly used antibiotics worldwide, according to the report, with use of these antibiotics being higher in countries with meat-heavy diets.

The WHO's list of Critically Important Antimicrobials is made up of antibiotics which are critically important for human health and their use should be restricted in the veterinary sector. These include ampicillin, amoxycillin, cefadroxil, chlortetracycline, doxycycline, erythromycin, flumequine gentamycin, vancomycin, oxytetracycline, spiramycin, sulfadiazine, sulfadimethoxine (Health Action International Asia Pacific (HAIAP) 2013).

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6.5 ABR in Poultry;

A research titled 'Antibiotic Resistance in the Poultry Environment' was published in 2017 by the Center for Science and the Environment, a non-profit based in New Delhi. It collected litter and soil samples from 12 randomly selected poultry farms in four main poultry-producing states in north India: Uttar Pradesh, Haryana, Rajasthan, and Punjab as part of the report.

A total of 217 E. coli, Klebsiella pneumoniae, and Staphylococcus lentus isolates were isolated and screened for antibiotic resistance against 16 antibiotics. The World Health Organization has designated ten of these antibiotics as Critically Important (CI) for humans (WHO).

Antibiotics were found to be used in these poultry farms, and the litter was used as manure on nearby agricultural lands, according to the report. The research also took 12 soil samples at a distance of 10 to 20 kilometres from the farms where the litter was not being used as manure as a control.According to the findings, 100% of E. coli, 92 percent of K. pneumoniae, and 78% of S. lentus isolated from the poultry setting were multi-drug resistant.Approximately 40% of E. coli isolates and 30% of K. pneumoniae isolates were immune to at least 10 of the 13 antibiotics examined. Antibiotic resistance was found in both E. coli and K. pneumoniae, including penicillins, fluoroquinolones, third and fourth generation cephalosporins, and carbapenems, a last-resort antibiotic used in hospitals(Chandra Bhushan et al.,2017).

6.6 Surveillance of ABR in India:

Antimicrobial/antibiotic resistance surveillance was previously limited to small-scale pilot efforts by the state-funded Indian Council of Medical Research (ICMR) and a few private agencies.There was no national-level surveillance for ABR among human pathogens including Salmonella, Shigella, Staphylococcus, Klebsiella, Acinetobacter, and others. However, disease-specific pathogens were monitored as part of national disease control programmes for tuberculosis, HIV, leprosy, and kala-azar.It was agreed as part of the 'National Programme for Antimicrobial Resistance Containment' (2012–2017) to develop a laboratory-based surveillance system by strengthening ABR laboratories across the country and to generate high-quality data on antimicrobial resistance for pathogens of public health concern.The Antimicrobial Resistance Surveillance and Research Network (AMRSN) of the International Centre for Microbiological Research (ICMR) is currently conducting surveillance with a network of ten laboratories across the world. In order to conduct surveillance, a total of 30 laboratories in state medical colleges will be strengthened in stages.Surveillance of ABR in animals, food, and antibiotics, on the other hand, is extremely limited. There have been isolated studies that show high levels of ABR across animal commodities and processes, but they have yet to be consolidated into a national scaled programme. Despite the fact that the Indian National Action Plan on AMR emphasises a One Health strategy, there is no such cooperation in data collection between the human and animal health sectors on the ground. Another flaw in India's current ABR surveillance systems is that they do not account for antibiotic use.The lack of a surveillance system capable of establishing a connection between antibiotic consumption trends and the emergence of AMR makes it difficult to design and evaluate successful interventions. If such a relation can be identified, data on antibiotic use or consumption may be used as a surrogate marker for the risk of AMR emergence(Standard Operating Procedures Bacteriology 2015, Mehndiratta PL et al.,2014, national policy for containment of antimicrobial resistance 2011).

6.7 National Action Plan on AMR:

India, as one of the countries hardest hit by antimicrobial resistance (AMR), is now taking steps to combat the problem.The National Action Plan on Antimicrobial Resistance (NAP-AMR) 2017–2021, published by the Indian Ministry of Health in 2017, describes the numerous problems that must be addressed in order to manage the phenomenon.Six main areas have been listed by the NAP-AMR as strategic priorities for Indian health authorities to address.These include:

1.Improved awareness of AMR through effective communication;

2.Strengthening knowledge and evidence through surveillance;

3.Reducing the incidence of infection through effective infection prevention and control;

4.Optimizing the use of antimicrobial agents in health, animals and food;

5.Promoting investments for AMR activities, research and innovations; and Strengthening India's commitment and collaborations on AMR at international, national and sub-national levels.

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Significantly, all of India's NAP-strategic AMR's priority areas specifically identify the livestock, food, and environment sectors as priority areas for improved surveillance, disease prevention, control, and antimicrobial usage optimization. The NAP-AMR also advocates the One Health approach, which integrates human and animal health.Despite the existence of a recent, ambitious National Action Plan, few measures have been taken to put it into action. For example, no funds have yet been set aside to enforce India's multiyear National Action Plan on Antimicrobial Resistance (AMR).The reality remains that India lacks a well-defined and enforced regulatory system for limiting antimicrobial use in livestock and food animals. The lack of legislation is particularly noticeable when it comes to the use of antimicrobials for non-therapeutic purposes, such as growth promotion, or for routine prevention, both of which have contributed to antibiotic overuse on farms(National action plan on antimicrobial resistance 2017).

Discussion & Conclusion:

Antimicrobial usage (AMU) is mostly used in food animal production. Poultry is the most plentiful and fastest-growing livestock per capita, as well as one of the most common sources of multi-resistant (MDR) bacteria. As countries progress from low- to middle-income status, there will be a greater need for high-quality animal products. Food security challenges could be addressed by promoting intensive chicken production even more. Special attention is required in the context of the BRICS countries (Brazil, Russia, India, China, and South Africa); these countries account for the majority of global cattle output and AMU. Agricultural intensification is also a primary driver of antimicrobial resistance (AMR) and the expansion of the overall resistome. To lessen the burden of bacterial resistance in humans, animals, and the environment, a systems approach is required. National veterinary service standards around the world fall short of international norms. The ability to diagnose, treat, and use prescribed poultry antibiotics can all benefit from access to professional veterinarian services. In order to I provide early identification and diagnoses of AMR and (ii) create efficient biosecurity and biocontamination controls, quality veterinary services are required. Effective veterinary systems are crucial for stabilising economies, enhancing food security and safety, and minimising AMR and harmful microbe exposure, according to the World Organization for Animal Health (OIE). Effective veterinary governance would lower AMR burdens while also improving the burdens of other infectious diseases. Veterinary services are now required to manage animal production, slaughter, food processing, product distribution, retail shop inspection, and foodborne and occupational disease exposure surveillance programmes in a number of nations. Veterinary services in LMIC food animal systems could be strengthened through capital and training investments. Global food safety is not just a natural concern for animal and human health, but also for international trade partners' market viability. Effective veterinary services must collaborate with human medical services as part of a larger public health endeavour, which many scientists refer to as a "One Health" concept. This method establishes a holistic strategy for enhancing surveillance efforts in humans, animals, and the environment. Veterinary services, according to several research, have a high potential to improve human and animal health, as well as household income. Pandemics originating from animal reservoirs, such as COVID-19 (SARS-CoV-2), Influenza A (H1N1), and West Nile Virus (WNV), have highlighted the importance of public health interventions at the human-animal interface in order to prevent zoonotic spillover events into human populations in recent decades. The World Health Organization (WHO) conducted a study that found that the cost efficiency of preventative investments far above the cost of intervention. For example, restrictions on AMU in 17 countries could indicate that antibiotic reductions can be achieved without a significant impact on production. Furthermore, to guide cutting-edge therapies, a greater knowledge of the evolution of antibiotic resistance is required. To collect data for decision-making and exchanging data on AMR on a worldwide scale, research infrastructures and tracking systems (i.e. laboratory networks) must be implemented. To better understand the transmission dynamics and evolution of AMR at the human-livestock-environment interface, sophisticated molecular methods to identify ARGs, MGEs, and bacterial hosts are required. Despite the fact that antibiotic use in livestock is declining and “antibiotic-free” farms are becoming more popular, MDR bacteria remain in such animals, which is a global problem. Because studies have shown that AMR has a fitness cost, reducing bacterial growth rate and pathogenicity, the efficacy of AMU reduction to manage AMR has been recommended. Bacteria, on the other hand, are evolving

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compensatory modifications to lower the cost of AMR.

As a result, limiting antibiotic use could have very minor short-term impact on chicken farms that have previously been exposed to antibiotics. The AMU bans in HICs, on the other hand, indicated that resistance levels dropped over time. The WHO's Global Action Plan on Antimicrobial Resistance, which was supported by member states and affirmed during the UN's 71st General Assembly's high-level conference on antimicrobial resistance, advises that all nations collect and submit antibiotic use data.

The WHO has established critical important antimicrobials for human medicine (WHO CIA list) as part of this doctrine. Quinolones, cephalosporins (third and higher generations), macrolides and ketolides, glycopeptides, and polymyxins are included on the WHO CIA list. In low-resource areas, the administration of critically important antimicrobials to public health is often unregulated. It's vital to have precise antimicrobial use measures, both medicinal and nontherapeutic, available to track AMU in LMICs. In 2017, the World Health Organization (WHO) suggested that associated countries minimise veterinary AMU. Researchers have already recommended for the creation of a uniform, internationally accepted monitoring system for reliably gathering AMU data from food processing plants. Improved AMR surveillance through the development of a standardised framework could lead to: (1) monitoring antimicrobial consumption trends and setting antimicrobial consumption goals, (2) providing a baseline of AMU consumption rates for comparison between countries at the scales of bacterial species, food animals, and human populations, and (3) developing longitudinal studies determining the associations between antimicrobial consumption and human populations. Antimicrobials used in the production of food animals are quickly depleting, despite their importance for animal health, agrarian livelihoods, and public health. Antibiotic use in the context of intensive poultry development should be carefully monitored to prevent the spread of drug resistance. Veterinary medicine initiatives should focus on areas where resistance is already present. Adopting sustainable poultry husbandry practises may help to mitigate the increase of resistance. All governments have an obligation to improve antimicrobial stewardship in order to increase biosafety and biosecurity.

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