THE ROLE OF ANTIMICROBIALS IN FOOD ANIMALS IN THE EMERGENCE OF RESISTANT HUMAN PATHOGENS

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ABSTRACT Resistance to antibiotics is one of the most pressing issues facing the globe today. Antibiotics have saved many lives and have revolutionized medicine by making many procedures such as organ transplant possible. However, the development of resistance is threatening to bring us to a post-antibiotic era. Many factors contributed by different industries cause the rise in resistance. Human medicine is one sector in which the manner of antibiotic use causes resistance. Also, the veterinary sector also holds great accountability in resistance since most antibiotics are used in food animals and mostly for non-therapeutic purposes. It is also important to understand the mechanism of resistance at a molecular level to combat this problem more efficiently. A tremendous amount of effort must be put forth in finding alternatives to antibiotics, many have been proposed, but none hold much promise in being an absolute replacement. Fortunately, these alternatives can be used in tandem with antibiotics to slow down the advance of resistance. A multi-pronged approach should be adopted to tackle this global phenomenon, which includes cooperation between different countries, the different sectors (agriculture, food animal production and human medicine) and between scientists and governments.

KEYWORDS: Antimicrobial Resistance, Food Animal, Human Medicine, Antibiotics

INTRODUCTION

Antibiotics are drugs used in the prevention and treatment of disease by killing or limiting the replication of microorganism. They usually accomplish this by inhibiting the synthesis of bacterial cell walls, proteins, deoxyribonucleic acid and ribonucleic acid Antibiotics (Cureus Inc., 2017). The golden era of antimicrobial drug discovery began in the 1950s and spanned three decades; it was during this time that the major antibiotic classes were identified and developed (Frontiers Media SA, 2010).

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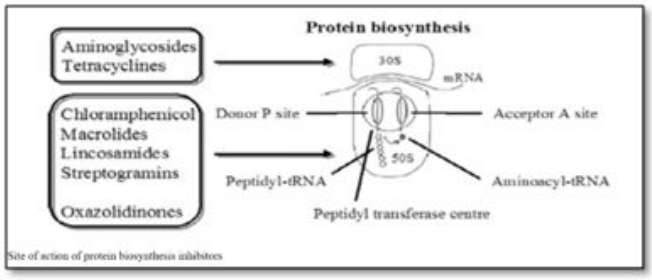
Unfortunately, not much progress has been made since and the search for new classes stalled. Several of the main classes of antibiotics are beta-lactams, sulfonamides, aminoglycosides, tetracyclines, chloramphenicol, macrolides, glycopeptides, oxazolidinones, ansamycins, quinolones, streptogramins and lipopeptides.

Before explaining the different mechanisms of action of antibiotics, it is beneficial to understand the basic structure of the bacterial cell. Bacteria are classified according to cell structure into Gram-positive bacteria and Gram-negative bacteria. Both possess a plasma membrane. However, gram-positive bacteria are further enveloped by a rigid cell wall. On the other hand, Gram-negative bacteria lack a cell wall and instead are surrounded by an additional lipid outer membrane. The outer membrane of Gram-negative bacteria is capable of blocking harmful substances, but it is also embedded with porins (water filled channels) that can be utilized by drugs to destroy the bacterium (Kapoor et al., 2017).

There are several mechanisms of action implemented by an-

timicrobials. Some antibiotics are only effective against Gram-positive bacteria because they target the cell wall. The building blocks of the bacterial cell wall are long sugar polymers called peptidoglycans (Kapoor et al., 2017). Beta-lactams inhibit the synthesis of the peptidoglycan layer of the cell wall and glycopeptides inhibit the synthesis of peptidoglycan by binding to amino acids, e.g. penicillin-binding proteins (PBP) in the cell wall which prevents the peptidoglycan from growing (Boundless. "Boundless Microbiology." Lumen Learning, Lumen Learning,courses.lumenlearning.com/boundless-microbiology/chapter/functions-of-antimicrobial-drugs/).



Although it is evident that resistance to antimicrobials is directly proportional to its use and encouraged by its irresponsible administration. It is essential to understand that bacterial resistance is intrinsic since the source of antimicrobials co-existed with bacteria in the environment, so they had to adapt by developing resistance. Another mode is the inhibition of protein synthesis by targeting either its 30S or 50S nucleoprotein subunits of the 70S ribosome. As we know, messenger mRNA is transcribed from the bacterial DNA, and then the mRNA is translated to protein by the ribosomes. The 30S unit is inhibited by aminoglycosides and tetracyclines and the 50S unit by chloramphenicol, macrolides and oxazolidinones. Fluoroquinolones inhibit bacterial DNA replication by targeting the bacterial DNA gyrase or in the case of gram-positive bacteria, topoisomerase-IV. The last mechanism is inhibition of folic acid synthesis needed for the synthesis of purines that is accomplished by sulfonamides alone or synergistically with trimethoprim (Kapoor et al. 2017).

EPIDEMIOLOGY OF ANTIBIOTIC RESISTANCE

The threat of multi-drug resistance is rising and spreading all over the world and will soon make antibiotic therapy obsolete. The first step to solving any problem is to identify and understand the driving forces behind it. Misuse of antibiotics is not limited to its utilization in the treatment of humans. Antibiotics are used extensively and on a much larger scale in animal production. It is used as a growth promoter, as treatment, metaphylaxis (treatment of the whole flock to prevent disease transmission when a few individual animals exhibit clinical signs) (Dove Press, 2015) and prophylaxis (preventative treatment involving long term administration of low doses of antimicrobial) (Dove Press, 2015) which are often mass administered (Hudson et al., 2017). However, antibiotics are also beneficial in animal farms. Because they are an important part of animal welfare since they prevent and treat many maladies, they reduce the risk of exposing the public to zoonotic and foodborne diseases, and they even benefit the environment, since ionophores, e.g. monensin reduce the production of the greenhouse gas methane (Hudson et al., 2017). Unfortunately, there is a possibility that the use of antimicrobials in livestock contributes to the appear-

Major group	Sub groups	Site of action	Examples
β-lactams	Penicillins	Cell wall synthesis	ampicillin, methicillin, penicillin G, amoxicillin
	Cephalosporins		1st generation: cefalothin, cefalonium
			2nd generation: cefuroxime
			3rd generation: cefotaxime, ceftriaxone, ceftiofur, ceftazidime
			4th generation: cefquinome
	Monobactams		aztreonam
	Carbapenems		ertapenem, imipenem, meropenem
Aminoglycosides		Protein synthesis	kanamycin, streptomycin, tobramycin, gentamicin, neomycin, amikacin,
Sulphonamides		Folic acid synthesis	sulphonamide, sulfamethoxazole, sulfamethazine, sulfamerazine, sulfadimethoxine
Quinolones/Fluoroquinolones		DNA synthesis	enrofloxacin, ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, nalidixic acid, flumequine, pefloxacin
Macrolides		Protein synthesis	azithromycin, clarithromycin, dirithromycin, erythromycin, azithromycin, clindamycin, tylosin, spiramycin, carbomycin, oleandomycin, kitsamycin, tiamulin
Polypeptides		Cell membranes	colistin, polymixin B, bacitracin
Other:			
Glycopeptides		Cell wall synthesis (Gram + ve)	avoparcin, vancomycin, teicoplanin, ardacin
Rifampin/Rifampicin		RNA synthesis	
Linezolid		Protein synthesis (Gram + ve)	Tetracycline, doxycycline, oxytetracycline, chlortetracycline
Tetracyclines		Protein synthesis	
Trimethoprim/sulfamethoxacole		Folate synthesis	
Coccidiostats		Ionophore	Lasolacid, monensin, salinomycin, narasin. Not used in human medicine.
Streptograminins		Protein synthesis	virginiamycin, quinupristin, dalfopristin (last two combined = synercid)

(John A. Hudson, Lynn J. Frewer, Glyn Jones, Paul A. Brereton, Mark J. Whittingham, Gavin Stewart, 2017)

ance of antimicrobial resistance in bacterial pathogens of both humans and animals. For instance, tetracycline-resistant Campylobacter jejuni has emerged in Canada due to the incorporation of chlortetracycline in feedlot calves. Manheimia haemolytica a pathogen of strictly veterinary importance, causing respiratory disease in cattle, has also developed resistance (Hudson et al., 2017).

Antibiotics are used extensively in livestock and poultry to improve feed efficiency, prevent and treat illnesses. In Cattle, amoxicillin, penicillin, erythromycin, quinolones, gentamicin, novobiocin, tylosin, tilmicosin and tetracyclines are given to treat common bovine diseases, most notably shipping fever, pneumonia and diarrhoea, but in mastitis cases, narrow-spectrum antibiotics such as beta-lactams for streptococcal mastitis or penicillin for those caused by Staphylococcus are used. In swine production, the animals are grouped according to age, making it feasible to deliver antibiotics via water and feed. Due to the stressful conditions associated with specific procedures, e.g. castration and vaccination and overcrowding, antibiotics are often

used prophylactically.

Ceftiofur, tetracycline, tiamulin, lincomycin and enrofloxacin are given to prevent and treat enzootic pneumonia and penicillin, tetracyclines, quinolones, and aminoglycosides are used for bacterial enteritis. Lincomycin, tetracyclines and macrolides are also used in cases of swine dysentery and ileitis. In poultry, antibiotics for treatment is often delivered via drinking water and those used for prophylaxis and growth promotion in the feed. The range of poultry antibiotics includes penicillin, quinolones, tetracyclines, macrolides, aminoglycosides, potentiated sulfonamide, colistin and tiamulin. In small ruminants, amoxicillin with or without clavulanic acid, ampicillin, ceftiofur, enrofloxacin, lincomycin, oxytetracyclines, sulfonamides, potentiated sulfonamide, tylosin and tilmicosin, the last of which can only be used in sheep (Dove Press, 2015)

Despite the conflicting results of studies concerning different species of antimicrobial resistant bacteria in various hosts. In 1997, the world health organization concluded at the end of the consultation on "The Medical Impact of the Use of Antimicrobials in Food Animals" that antimicrobial use in food animal does contribute to resistance in animal and human pathogens, especially foodborne pathogens like Salmonella and Campylobacter. Isolates of antimicrobial resistant pathogens are identical from both human and food sources. Which suggests that agricultural antibiotic use and the emergence of resistance in farms pose a threat to public health. For example, gentamicin resistance has been found in Campylobacter species that are clinically relevant in human medicine and found in poultry production (Hudson et al., 2017). Despite finding bacterial isolates in human and animal production settings to be indistinguishable, this does not give us information on the direction of the transmission of resistance. Fortunately, other studies have elucidated the direction of the flow of resistance transmission, and the evidence points to them spreading from the agricultural sector to the human population. Since a more significant population of resistant pathogens have been found in the agricultural environment. An alarming example of antimicrobial resistance is the transfer of plasmid-encoded resistance to the antibiotic Colistin for Escherichia coli in China. Because in China and other countries, Colistin which is considered a "last resort drug" in the treatment of refractory infections in humans, is also used in the treatment of animals (Hudson et al., 2017).

However, the link between the provision of antibiotics to farm animals and the emergence of antimicrobial resistance of human pathogens is still considered by many to be inconclusive and in need of further investigation. A widescale inquiry spanning seven European countries has established a connection, although findings conflicting with this general trend has been found. In order to establish a causal relationship between the use of antibiotics in food animals and the emergence of resistance in human pathogens. It is beneficial to look at foodborne pathogens individually and see if those isolated from human patients are resistant to the antibiotics used in the animal from which the pathogen originated from. According to WHO, the most common etiological agent in human gastroenteritis is Campylobacter with the two most common isolate being C. jejuni followed by C. coli. A significant concern is the resistance of Campylobacter to many antibiotics, most of which are common between human and veterinary medicine, like quinolones, macrolides, lincosamides, chloramphenicol, aminoglycosides, tetracycline, beta-lactams, cotrimoxazole and tylosin (Dove Press, 2015). The emergence of fluoroquinolone-resistant Campylobacter infections in humans appeared with their use in the veterinary field two decades earlier. The Netherlands noticed the rise of poultry-origin fluoroquinolone-resistant campylobacteriosis after using the antibiotic in the poultry industry (Dove Press 2015). Resistance to the aminoglycosides is also beginning to be noted, especially towards gentamicin even though it is still considered to be low, representing only 2% of isolates. In Spain, almost 14% of isolates turned out to be resistant, and in the US gentamicin-resistant C. coli increased by approximately 12% and 17% in human and chicken isolates respectively in a span of four years from 2007 to 2011. Salmonella is another agent of food poisoning in humans that is characterized by its worrisome ability to spread across the globe and attain resistance to multiple drugs (Dove Press, 2015). The use of antibiotics and the appearance of resistant isolates in food animals have been confirmed to be harmful to human health in the case of Salmonellae.

Multi-drug resistance in Salmonellae has been recognized for around six decades. Multi-drug resistance to tetracyclines, sulfonamides, streptomycin, kanamycin, chloramphenicol, penicillin and cephalosporin exist but has not gotten any worse since 1996. The situation differs with resistance to combinations of amoxicillin and clavulanic acid, ceftriaxone, ceftiofur and nalidixic acid, which are increasing. From 1998 to 2005, resistance to amoxicillin with clavulanic acid and ceftiofur has increased by 13%. Presently, the most abundant phenotype of multi-drug resistant salmonellae is to ampicillin, chloramphenicol, streptomycin, sulfonamides and tetracyclines (Dove Press, 2015).

Methicillin-resistant S. aureus is the most notorious superbug today, and its resistance to antibiotics has been known since the late forties. The highest MRSA rates in Europe, which is approximately 50% are even higher in other countries, including the USA, Taiwan, Hong Kong, Singapore and Japan (Gould, 2008). Staphylococcus species cause diseases in both humans and animals, only 10% of human isolates remain susceptible to penicillin, and even though it is considered a nosocomial infection, it has started appearing in community settings as well. Most of the world has witnessed a rise in MRSA cases, and glycopeptides are used more often for treatment than in the past. Resistance to the glycopeptides vancomycin (Vancomycin-resistant S. aureus or VRSA) and teicoplanin has been reported, and there is a minor drop in daptomycin susceptibility that should be monitored (Gould, 2008). S. aureus is also present in animal farms, the extensive use of penicillin to treat staphylococcal mastitis for several decades has resulted in S. aureus strains that are no longer susceptible to penicillin with some being isolated from cow milk. A novel variant of S. aureus has appeared in food animals and is known as MRSA clonal complex 398 (CC398) which has been isolated from a wide range of hosts including cattle, dogs, horses, chickens and to a lesser extent swine. MRSA CC398 is also proven to be carried in the nasal mucosa of humans that come in contact with farm animals, especially farmer.

A significant issue is the use of growth promoters in animal production, in which subtherapeutic doses of antimicrobials are given to enhance weight gain. These low and continuous dosing does not kill the target bacteria allowing the more resistant microorganisms to survive and proliferate, which is known as selection pressure. The majority of antibiotics is used in animal production and of that, only 20% to 40% is used for therapy (Milanov et al., 2016). Since 2006, the use of antibiotics, excluding ionophores, has been prohibited in the EU in food animals to cur-

tail the emergence of resistance (Dove Press, 2015). The rest of the major consumers of antibiotics have yet to adopt such laws despite the proof that subtherapeutic administration is a primary driver of resistance. The use of antibiotics as growth promoters was first authorized around seven decades ago at 1% to 10% of the therapeutic dose. Administering antibiotics at below the minimum inhibitory concentration leads to resistance.

Nevertheless, it does increase feed efficiency and increase the average weight gain by 4% to 8%. The way it accomplishes this is uncertain, it is believed that the drugs reduce the normal intestinal flora that competes with the host cells for nutrients, produce harmful compounds, e.g. ammonia, amines, indole and phenols that are growth stunting, cause thickening of the intestinal wall reducing the absorption and stimulate energy-consuming local immunity. The reduction of the intestinal microbiota is harmful to the animal because it represents a primary non-specific immune mechanism, which is colonization resistance. In which the normal flora competes with pathogens for space and nutrients not giving and not giving them the chance to gain a foothold to begin an infection. Denmark, an EU member, has monitored the consequences of the ban on growth promoters. The relevant information was collected and analyzed by the Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP), and it was concluded that there were no adverse results, except for a temporary rise in the use of antibiotics for treatment. Prohibiting the use of human antibiotics as animal growth promoters is not enough because of the chemical similarities and the shared drug targets between human antibiotics and strictly veterinary ones (monensin, salinomycin, virginiamycin, tylosin, spiramycin, avoparcin and carbadox) which makes cross-resistance a serious possibility. A historical example of this is the emergence of vancomycin-resistant enterococci (VRE) from poultry due to the use of the glycopeptide avoparcin in farms, this connection is proved by the cross-resistance between vancomycin and the glycopeptide teicoplanin and the fact that VRE prevalence in broilers decreased in the EU after it was banned (Milanov et al., 2016).

Other sources of antibiotics resistance are the environment, aquaculture and plant agriculture. Antibiotic resistomes are present in the environment; the resistome is the collection of all antibiotic resistance genes (Wright G.D., 2007). Treated animals excrete unmetabolized antibiotics in their faeces, which can also be used as fertilizer. Therefore, these antibiotic molecules can be spread to humans through contaminated agricultural soil and water. Another environmental source is effluent resulting from the manufacturing of antimicrobials that seeps into the environment, making it a source of resistance transmission. This has been the case in China, where the manufacturing waste has leaked into the environment (Hudson, 2017).

Aquaculture is another sector where antibiotics are used, and it has risen rapidly over the last three decades. Unfortunately, the industry's use of antimicrobials has not been as well regulated or as closely monitored as in animal production (Hudson et al., 2017). Even more concerning is that many classes of antibiotics fundamental to human medicine are used in aquaculture, which includes sulfonamides, penicillin, quinolones, tetracyclines and phenicol (Dove Press, 2015). In the early 1960s, aquaculture represented 5% of fish consumption, and by 2002 that figure rose to almost half of all fish consumed. However, the growing demand has led to unsanitary conditions and high stocking density that encourage an over-reliance on antibiotics (Watts, J.E. et al., 2017). This raises the important question of whether antimicrobial resistance of fish pathogens can be transmitted up the food chain to the human consumer (Hudson et al., 2017). An additional food production sector that uses antibiotics, albeit to a much lesser extent, is planted agriculture. There are two ways in which plants can be exposed to antibiotics. Firstly, antibiotics were used to treat bacterial infections of valuable edible and ornamental plants since the fifties. Secondly, antibiotic contaminated animal manure used as fertilizer or contaminated irrigation water.

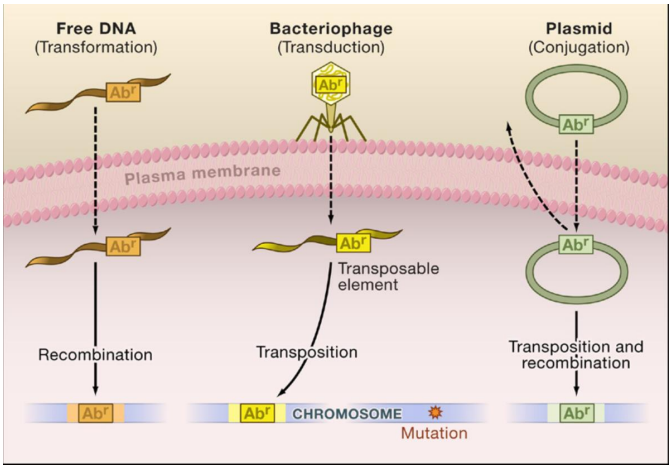
MECHANISMS OF ANTIMICROBIAL RESISTANCE

Bacteria can obtain antibiotic resistance by intrinsic or acquired mechanisms. Intrinsic mechanisms are encoded by the bacterial chromosome and usually help bacteria survive by circumventing the antimicrobial agents' mechanism of action. Examples of intrinsic mechanisms are gram-negative bacteria's AmpC type beta-lactamase and efflux systems of MDR pathogens (Indira T. Kudva, Qijing Zhang 2016). Acquired mechanisms result from mutations of the genes that antibiotics target and are transferable via mobile genetic materials through horizontal gene transfer (HGT) (Alekshun and Levy 2007, p. 1038). Mobile genetic materials bearing resistance determinants are plasmids, transposons and bacteriophages and are exchanged and disseminated amongst microorganisms via transduction, conjugation and transformation which are the main modes of HGT (Indira T. Kudva, Qijing Zhang, 2016).

Plasmids are circular double-stranded DNA molecules that are independent of the chromosomal DNA. They carry many genes coding for various traits in addition to resistance, and an individual bacterium can possess multiple plasmids. Transposons are discrete DNA pieces, also known as jumping genes due to their ability to change location within the genome (Alekshun and Levy 2007, p. 1038). They are found on plasmids or integrated into other transposons or the host's chromosome and assist in plasmid exchange between microorganisms. Bacteriophages are viruses infecting and replicating within microbes (Indira T. Kudva, Qijing Zhang, 2016).

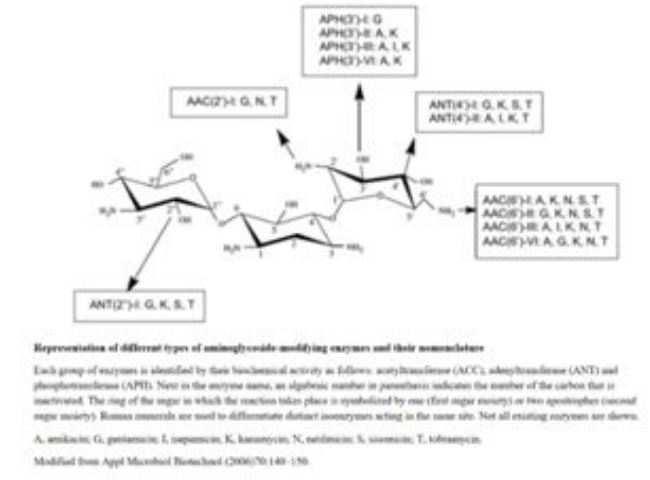
Transformation is the uptake and incorporation of naked DNA left behind by dead and lysed germs directly from the environment by bacteria. Conjugation is the direct transfer of DNA, usual plasmids on cell-to-cell contact. It is a highly efficient process and takes place commonly in the gastrointestinal tract of patients undergoing antibiotic therapy. Finally, transduction involves the transfer of DNA via bacteriophages. Another mechanism driving antibiotic resistance are integrons, which are mobile DNA made of a collection of genes known as a gene cassette. They integrate into other DNA, inserting multiple genes into the bacterial chromosome along with the tools required to express them (Indira T. Kudva, Qijing Zhang, 2016) (Alkeshun and Levy, 2017).

Biochemical routes involved in the mechanisms of resistance can be grouped into four major routes. Firstly, modification of the antibiotic molecule either by chemically changing or destroying it using enzymes, to prevent it from interacting with its target. Gram-negative and gram-positive bacteria produce enzymes that reduce the drug's affinity to its target by chemically altering the antibiotic through acetylation, adenylation or phosphorylation. Resistance resulting from enzymatic modification often affects antibiotics that hinder protein synthesis on a ribosomal level. The prevailing mechanism of aminoglycoside resistance are aminoglycoside modifying enzymes or AMEs and are an excellent illustration of this type of mechanism of



Molecular mechanisms of antibacterial multidrug.jpg (Alekshun and Levy 2007, p. 1038).

resistance. AMEs are classified according to the biochemical reactions they carry out into acetyltransferase, adenyltransferase and phosphotransferase. They exert this modification on the hydroxyl or amino group of the aminoglycoside molecule. Resistance to chloramphenicol is also caused by enzymatic alteration by chloramphenicol acetyltransferase (CATs) of which there are two types. Type A that is associated with high levels of resistance and type B that causes low levels of resistance. Both AMEs and CATs are encoded by mobile genetic elements or are encoded by the bacteria's chromosomes (Indira T. Kudva, Qijing Zhang, 2016).



(Kudva and Zhang, 2016)

On the other hand, antimicrobials can be destroyed to prevent them from carrying out their function. A good example of this is beta-lactam resistance resulting from the severing of the amide bond present in the beta-lactam ring by beta-lactamases. Interestingly, beta-lactams were the answer to the problem of penicillin resistance to plasma encoded penicillinase. However, plasma encoded beta-lactamases appeared afterwards beginning in Gram-negative microorganisms against ampicillin in the sixties. The nomenclature of beta-lactamase encoding genes is bla preceding the specific name of the enzyme. These genes are found as a part of core chromosomes or on MGEs and on integrons which promote its spread. As of today, there are over a thousand beta-lactamases described and are categorized using two systems. One is the Ambler Classification that groups these enzymes into four groups (A, B, C and D) based on their amino acid sequence. The other is the Bush-Jacoby Classification also consists of four categories, each having multiple subgroups and is divided according to their biochemical routes (Indira T. Kudva, Qijing Zhang, 2016).

Class A beta-lactamases are diverse and include penicillinase, carbapenemase and extended-spectrum beta-lactamase (ESBLs). They use a serine residue to break the amide bond and induce resistance to monobactams but not cephamycin and are susceptible to clavulanic acid inhibition. Class B enzymes differ from those of class A in the fact that they are not susceptible to clavulanic acid or tazobactam and in the way they destroy the beta-lactam ring using a metal ion usually zinc as a cofactor, which is why they are called metallobeta-lactamases. Type B lactamases confer resistance to an extended spectrum of beta-lactams encompassing carbapenems with ten metallo-carbapenemases identified. Class C is not inhibited by clavulanic acid and is active against penicillin and cephalosporins. The most prominent example of class C is the AmpC; a cephalosporinase often encoded by the core chromosome. AmpC expression is tightly regulated and only occurs in the presence of beta-lactams. Class D is a diverse group of enzymes encoded on an array of MGEs and are easily spread within and between species throughout the world. They are called OXA because unlike class A, they were able to hydrolyze oxacillin (Indira T. Kudva, Qijing Zhang, 2016).

Secondly, decreasing antibiotic penetration and efflux pumps. Antibiotic targets are often intracellular or found on the inner cytoplasmic membrane of gram-negative bacteria. That is why decreasing the influx of antibiotics into the cell or periplasmic membrane and preventing it from reaching its target is beneficial to the bacteria. For example, Pseudomonas and Acinetobacter baumanii are naturally resistant to hydrophilic beta-lactams, due to the low number of water-filled channels known as porins through which the antibiotic must traverse to work. Other drugs that are influenced by changes in membrane permeability are hydrophilic tetracyclines and a few fluoroquinolones. Permeability is lowered by changing porin type, lowering porin expression or interfering with its function, all of which cause low-level resistance and is often occurs alongside other resistance mechanisms, e.g. efflux pumps. Two organisms that utilize this mechanism are Pseudomonas aeruginosa and Klebsiella pneumoniae (Indira T. Kudva, Qijing Zhang, 2016).

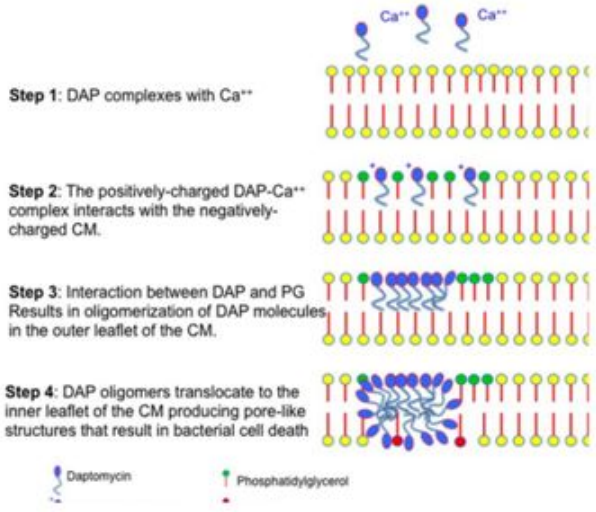
Efflux pumps are used by the bacteria to eject toxins out of their cells, including antibiotics. These pumps are present in both the core chromosome and on MGEs, Gram-positive and Gram-negative bacteria and can be either substrate specific (effective against a single class of antibiotics) or can affect several substrates which are the case in multi-drug resistant bacteria. Efflux pumps are divided amongst five leading families. They are the major 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 (MATE). The families are different in terms of the source of energy they use, their conformational structure and in which bacterial species do they induce resistance and to which antimicrobial compounds. Genes encoding efflux-mediated resistance to tetracycline are mostly found on MGEs and are generally found in Gram-negative bacteria. They lower the susceptibility of tetracycline and doxycycline, but minocycline and tigecycline are not affected. RND pumps

play a major role in multi-drug resistance in clinical settings involving infections with Gram-negative bacteria. Two RND pumps causing tetracycline efflux as a part of their MDR are AcrAB-TolC in Enterobacteriaceae and MexAB-OprM in P. aeruginosa. RND pumps are responsible for resistance not only to many antibiotics, including tetracycline, chloramphenicol, beta-lactams, novobiocin, fusidic acid and fluoroquinolones. They can pump out bile salts, cationic dyes, disinfectants and other toxins as well. Mef genes encode another group of efflux pumps that extrude macrolides are found in Gram-positive organisms, primarily in Streptococcus pyogenes and Streptococcus pneumoniae (Indira T. Kudva, Qijing Zhang, 2016).

Thirdly, changing the target site through protection which prevents the antimicrobial from contacting it or by alteration of the site in a manner decreasing its affinity to the drug. Two notable examples of resistance due to target protection occurs in tetracycline and fluoroquinolones. Genes conferring this type of resistance are often found and disseminated by MGEs. Tet(M) and Tet(O) are resistant determinants borne on plasmids and transposons, causing resistance to tetracycline. Tet(O) was initially discovered in Streptococcus species, and it interacts with the ribosome, displacing the antibiotic and causing conformational changes to the ribosome which prevents rebinding. Tet(M) that was first discovered in Campylobacter jejuni also interacts with the ribosome through competitive inhibition with the antibiotic molecule. Therefore, both Tet(M) and (O) protect the ribosome from the drug allowing it to resume bacterial protein synthesis. Quinolone resistance protein Qnr causes low-level resistance to fluoroquinolones. This is achieved by reducing the formation of DNA-DNA gyrase or DNA-topoisomerase IV complex that the antibiotic targets due to Qnr acting as a DNA homologue that binds these enzymes (Indira T. Kudva, Qijing Zhang, 2016).

Modification of the target site is a resistance mechanism that is prevalent and effective against a wide range of antimicrobials. This can be done by point mutations, enzymatic alteration or by the replacement/bypass of the target site. Rifampin and fluoroquinolone resistance have emerged due to point mutations of the target site. Rifampin binds to DNA-dependent RNA polymerase to inhibit bacterial transcription and resistance develop due to a mutation in the gene that encodes the rifampin binding site on the RNA polymerase. Fluoroquinolone resistance is due to mutations in the genes encoding subunits of the antimicrobial targets (DNA gyrase and topoisomerase). Macrolide resistance has emerged due to the methylation of its a ribosomal target that is catalyzed by an enzyme encoded by erythromycin ribosomal methylation erm gene. These genes are carried by MGEs and are distributes in about thirty genera encompassing aerobic and anaerobic as well as both gram-positive and gram-negative organisms. Despite the effectiveness and commonality of erm encoded methylase, this mechanism comes at a fitness cost because a methylated ribosome does not perform optimally. Therefore, this mechanism is tightly regulated, and methylase is only expressed in the presence of antibiotics (Indira T. Kudva, Qijing Zhang, 2016). An old target could also be replaced by a new one that carries out the same function as its predecessor but is not inhibited by the antibiotics. The most infamous example of target replacement is methicillin-resistant Staphylococcus aureus that obtains a foreign gene that expresses an exogenous PBP. Target bypass is achieved by excessive production of the target with the intent of overwhelming the antibiotic. The target of trimethoprim-sulfamethoxazole is two enzymes of the folic acid synthesis pathway, dihydrofolate reductase and dihydropteroic acid synthase, respectively. Bacteria can become resistant to trimethoprim-sulfamethoxazole as a result of mutations in the promoter region of the gene encoding theses enzyme leading to overexpression and overproduction of these enzymes (Indira T. Kudva, Qijing Zhang, 2016).

Lastly, resistance due to global cell adaption, bacteria have evolved, sophisticated mechanisms enabling them to execute vital cellular processes in the face of severe circumstances and the most hostile environments. Daptomycin and vancomycin resistance are both examples of loss of sensitivity due to global cell adaption in clinical settings. Daptomycin resistance is uncommon, and so it is used in the treatment of multi-drug resistant infections. Daptomycin causes cell death by causing leakages in the cellular envelope, which interferes with homeostasis. It is a peptide antibiotic whose mode of action is similar to cationic antimicrobial peptides or CAMPs of the innate immune system; it is believed that resistance to daptomycin is due to the co-evolution of bacteria and CAMPs of the host they infect (Indira T. Kudva, Qijing Zhang 2016).



Mechanism of Action of Daptomycin. (Indira T. Kudva and Quijing Zhang, 2016)

THE IMPLICATION OF ANTIMICROBIAL RESISTANCE

The economic cost of AMR is narrowly defined as the incremental cost of treating patients with resistant infections as compared with sensitive ones, and the indirect productivity losses due to excess mortality attributable to resistant infections (Shrestha et al., 2018). In the United States, 20 billion dollars a year is spent due to infections by multi-drug resistant organisms, and the global cost is estimated to be 100 trillion dollars (Indira T. Kudva, Qijing Zhang 2016). Resistant infections are more expensive than susceptible one due to the additional costs associated with second-line treatment, need for further investigation and more extended hospital stays (Shrestha et al., 2018).

According to the Center for Disease Control, at least 23,000 deaths annually can be attributed to the resistant microorganism in the US, and it is predicted to cause 300 million deaths by 2050 (Indira T. Kudva, Qijing Zhang 2016). In Europe, the number of fatalities due to multi-drug resistant infections is 25,000 yearly (Cureus Inc. 2017). Multi-drug resistant infections inflict a substantial financial burden on the healthcare; the European

Union spends 1.5 billion euros per annum because treatment of multi-drug resistant infections are lengthier and costlier (Frontiers Media SA, 2010). The treatment of nosocomial infection caused by six species of multi-drug resistant alone costs 1.87 in 2006 dollars (Frontiers Media SA, 2010).

Infections with multi-drug resistant microorganisms is a serious, rapidly evolving and dynamic issue. Resistance to penicillin was noticed soon after discovering the antibiotic itself, and Acinetobacter baumannii is another example of how fast bacteria can gain resistance. In just three decades, A. baumannii developed from an opportunistic pathogen susceptible to all antibiotics to one possessing over 40 resistance genes via horizontal gene transfer (Milanov et al. 2016). If a pathogen is resistant to a single antibiotic, then it is more likely to be resistant to other classes of antibiotics compared to a susceptible pathogen of the same species (Gould, 2008). The use of one antimicrobial can result in selection for resistance to a different antimicrobial class (Scott et al., 2018). Moreover, Patients infected with methicillin-resistant Staphylococcus aureus are prone to developing infections with other multi-drug resistant pathogens (Gould, 2008).

As we know, a significant bulk of antibiotics are used in food animals for both treatment, prophylaxis and to promote growth. This has led to public concern since the sixties, over the possible ramifications of these agricultural practices on human and consumer health. The question was raised again in the nineties as a result of introducing fluoroquinolones and third generation cephalosporin administration to animals. These concerns prompted the world health organization to investigate; the WHO committee found that it does lead to the appearance of resistant human pathogens, notably in foodborne pathogens, e.g. Salmonella and Campylobacter (Scott et al., 2018). Concerns are even higher when it comes to antibiotics shared by both humans and animal, data on the classes of antibiotics used in human versus veterinary medicine in England has been noted. Although many classes can be used in both fields, penicillin, fluoroquinolones and the first two cephalosporin generations are mostly human drugs. On the other hand, tetracycline, lincosamides and sulfa drugs are more common in veterinary medicine. Strictly human antibiotics included glycopeptides and monobactams/carbapenems (Hudson et al., 2017).

This begs the question as to whether antibiotic in livestock can increase resistance in human as well as animal pathogens. A study carried on pig farms in the Netherlands involving both the animals and people residing in these farms established a dose-response relationship. An increase in the dose of antimicrobial given causes an increase in the prevalence of livestock-associated MRSA. A twofold increase in the dose resulted in a 16% and 1.2% rise in pigs and human, respectively (Scott et al. 2018). Another study found similar results, after the introduction of fluoroquinolones in food animals, the US and Spain have seen a rise in resistant Campylobacter infections in the human population with the cases in Spain rising by approximately 70% (Scott et al. 2018). Resistance can spread from animals to humans through meat and animal product consumption, close contact with these animals (farmers and veterinarians), contaminated crops and the environment. Another more surreptitious mechanism of the transfer of resistance is horizontal gene transfer of resistance encoding genes from bacteria, viruses and DNA fragments (Dove Press, 2015).

Transmission of resistance through the food chain has been established, and more recent studies have demonstrated that workers on farms using antimicrobial growth promoters and their families have more resistant bacteria than the general population. Those who work closely with animals, e.g. farmers and veterinarians have a higher chance of being colonized by resistant microorganisms from the animals. They then become a source of transmission to their families and the larger community. A study demonstrated that caretakers of chickens fed tetracycline for growth promotion became carriers of tetracycline-resistant E. coli, which was the same strain in the chicken they were in close contact with. In the US, gentamicin is used in broilers more than any other antibiotic and poultry workers were proven to be over thirty times more likely to be colonized with E. coli resistant to gentamicin.

Moreover, people who work closely with animals given growth promoters are more likely than others to be colonized with multi-drug resistant bacteria. Homologous genes are shared by animal and human pathogens providing genetic evidence of the emergence of resistant human pathogens originating from animals. This link has been found in foodborne pathogens such as E. coli and Salmonella as well as in enterococcal spp. Moreover, methicillin-resistant S. aureus (Marrshall and Levy, 2011).

LIMITING ANTIMICROBIAL RESISTANCE

The problem of antimicrobial resistance transcends nations and is a product of certain practices of several sectors, mainly human medicine and agriculture. Therefore, it is crucial for all those working in these industries to come together to bring about change, not just in the regulation of antibiotic use but also in their attitude towards this public health issue (Cureus Inc. 2017). There are promising studies regarding the effectiveness of antimicrobial withdrawal or reduction on lowering the prevalence of resistance. In Canada, the cessation of in ovo ceftiofur injections of chicken eggs in 2005 and its partial reintroduction a couple of years later, presented an opportunity to investigate the effect of antimicrobial withdrawal in food animals on the prevalence of resistance in foodborne zoonoses. Isolates of S. Enterica serovar Heidelberg were collected from both retail chicken meat and faecal samples of infected humans. After ceftiofur withdrawal, the isolates in both human and chicken meat showed increased susceptibility, and on reintroduction, the prevalence of resistance increased again (Scott et al. 2018). On the other hand, in the United States, enrofloxacin use was prohibited in poultry, yet there was no reduction in ciprofloxacin resistance of zoonotic Campylobacter species (Hudson et al., 2017).

Proposed alternative therapies include phage therapy, in which bacteriophages are utilized to combat bacterial infections and combination therapy, which consists of pairing antibiotics with antibiotic-enhancing phage (Cureus Inc. 2017). The history of phages goes further back than most would expect, and their potential to treat bacterial infections was recognized before antibiotics. They were discovered in 1915 by the English bacteriologist Frederik Twort. Six years after this discovery, Richard Bruynghe and Joseph Maisin were the first to apply phage therapy in Belgium. They used phages to successfully treat cutaneous staphylococcal infections by injecting the phages in and around the skin lesions. A couple of decades later, commercial preparations of phages were manufactured by French and American companies (Cheng et al. 2014). There are several conditions that must be met for phage therapy to be effective.

The identity of the target bacteria must be identified because phages have a very narrow target spectrum. Accessibility to the

target bacteria should be comfortable and straightforward, and the population of the bacteria should be substantial. In a study using lytic phages to treat Salmonella serovar Typhimurium infections in poultry and swine concluded that it did not manage to completely resolve the infection yet did reduce the number of organisms. The possible reason put forward is that phages were no longer available once the bacterial numbers dropped. This type of treatment must be immediately implemented after infection as well, mice that were experimentally infected with E. coli were given an intramuscular injection of K1 phages soon after bacterial inoculation recovered completely, however, once 16 hours have lapsed from the time of inoculation the phage therapy ceased working. A significant advantage of phage therapy is that unlike antibiotics, it does not disrupt the normal microbiota of the patient. Although phage therapy is proposed as an alternative therapy to antibiotics, it can cause the resistance of bacteria to the phage and transmit virulence and resistance factors to the target bacterium. That is why a combination of various phages are used and rotated, and resistance-associated gene transfer can be avoided by using purified phage gene products that can kill bacteria, e.g. phage lysins (Stanton 2013, p. 116). Despite most phage therapies still requiring further research and testing, there are already success stories. There are reports of phages being somewhat capable of preventing infections with severe foodborne pathogens (E. coli O157: H7, Salmonella and Campylobacter).

Moreover, bacteriophages are currently being used in livestock feed to minimize meat contamination with foodborne pathogens. In 2006, the FDA approved the use of LMP-102TM, which is composed of six types of pure phages specific against Listeria. A year later, the United State Department of Agriculture green-lit a similar product to disinfect E. coli in cattle (Cheng et al. 2014).

Lysins, also known as endolysins, are enzymes known since the fifties, produced by the bacteriophage at the lytic stage to cause bacterial cell lysis by disrupting the peptidoglycan layer to release the viral progeny. Lysins have many advantageous over the phages from which they are obtained from. Lysins cause bacterial cell lysis much faster, so fast in fact that it does not allow time for resistance to develop, it has a wider spectrum of activity, and we can monitor its mechanism of activity with relative ease. There are also drawbacks, mainly the cost, they are more expensive to produce than bacteriophage treatment, it degrades quickly in storage and with use, and it is only effective against Gram-positive species. In the 1990s, lysins were discovered to be deadly to Staphylococcus, Bacillus anthracis, L. monocytogenes and Clostridium butyricum. They are also used in the treatment of septicemia caused by the Gram-positive organisms, Enterococcus faecalis, Clostridium perfringens and Streptococcus belonging to group B. Also, there are different lysins available that can treat a variety of infections caused by group A Streptococcus, staphylococcal infections including MRSA, local and systemic pneumococcal infections and vancomycin-resistant E. faecalis (Cheng et al. 2014).

Feed additives (prebiotic, probiotics and organic acids) are promising alternatives to antibiotics, and they are currently available on the market and used in the field. Nevertheless, the way these additives work needs further clarification and the results so far have not been consistent. Prebiotics are fermented carbohydrates indigestible by the host that stimulate the beneficial commensal bacteria in the intestinal flora preventing colonization via competitive exclusion. Examples are polysaccharides, oligosaccharides such as fructooligosaccharides and mannan-oligosaccharides, plant extracts and dietary fibres (Cheng et al. 2014)(Stanton, 2013). Prebiotics selectively multiply the numbers of beneficial intestinal bacteria, improve host immunity and have even demonstrated antiviral activity and have been used in livestock since the eighties (Cheng et al. 2014). Organic acids such as lactic acid are added to feed to lower the pH to prevent spoilage, which reduces the pathogen load in the gastrointestinal tract. Probiotics possess the same function as prebiotics except they are living organisms like yeast, Lactobacillus, Bacillus, Streptococcus and Bifidobacterium and even some fungal species like Saccharomyces cerevisiae and kluyveromyces (Cheng et al. 2014). The definition of probiotics, as proposed by the World Health Organization, is "microorganisms which, administered live and in adequate amounts, confer a benefit to the health of the host".

Ways in which probiotics wipe out pathogens is by synthesizing antibacterial substances such as bacteriocins and organic acid, stimulating the local mucosal immunity in the intestines and increase nutrient digestion and absorption in addition to encouraging competitive exclusion by normal flora (Cheng et al. 2014). Certain criteria must be met to be an effective probiotic. They must be able to survive gastric acid and bile, colonize the intestines and synthesize nutrients; they cannot be capable of causing disease, they must be devoid or at least very low in genes encoding resistance and have reduced potential of transferring them. Feed additives are a lucrative business with probiotics sales in animal feed, reaching 186 million dollars globally. Unfortunately, unlike antibiotics, this industry has issues with verifying the efficacy and safety of products and with regulating its use. In China, no less than 50 probiotics are used despite only a dozen products being approved by the ministry of agriculture. Occasional incidences of poisoning, allergic reactions and gastrointestinal upset have been reported. It may even have detrimental effects on the intestinal microbiota, and its use in immunodeficient animals can be damaging (Cheng et al. 2014). Potentiated probiotics are combinations of probiotics with other treatment such as vaccines or organic acids, so they can work synergistically to fight disease. The most typical example is symbiotic, which are probiotics potentiated with prebiotics. The results of symbiotic studies are inconsistent with only some noting an improvement in weight gain and a reduction in foodborne pathogen loads (Stanton 2013, p. 116).

Immunity modulating agents are those used in immunotherapy, which is the manipulation of the immune system by activating, enhancing or suppressing it. Immunostimulants are a type of immunomodulator that improves the innate immune system making the host less susceptible to disease in general. Certain immunostimulants accomplish this by mobilizing the innate immune system that will trigger intracellular genes that will express antimicrobial products. Immunostimulants are an expansive and diverse class with hundreds of types belonging to more than twelve categories. Many added in animal feed such as nucleotides, probiotics and herbs are reported to aid animals in resisting infection by enhancing innate immunity, especially during a time where immunity is suppressed due to stress like reproduction, transfer and vaccine administration.

A good example is beta-glucan, a polysaccharide extracted from the cell wall of yeast that improves the animal's defence against disease by stimulating the immune cells. There are downsides to immunostimulants as well, they are not effective in all species of animals, there is no direct correlation between the

dose given and the effects produced, and it is not suitable for treatment since it is effective only if administered before or at the time infection occurs. The biggest drawback is the possibility of immune-mediated disease because of the prolonged stimulation of the immune system, and if given to young animals whose immune systems are still in development, it can impede the formation of a normal healthy immune system. In the case of immunostimulants, there is still no set standards, and some marketed products may not be as efficacious as claimed to be. For instance, a known immunostimulant composed of Propionibacterium acnes extracts, Ochrobactrum intermedium lipopolysaccharides and Proclin did not affect when used in goats (Cheng et al. 2014).

Vaccination, an immunomodulating agent, is an obvious yet underappreciated method of limiting antimicrobial use in animals as it can be used to reduce both animal pathogens and foodborne pathogens of humans. Vaccination also lowers the prevalence of the clinical disease, which will aid in cutting down therapeutic antibiotic use. Pigs in Denmark immunized against Lawsonia intracellularis, an enteropathogen of swine, showed a reduction in need of antibiotic therapy with oxytetracycline (Stanton 2013, p. 116). Attenuated live Salmonella vaccines have been tested with inconsistent results, and they do not induce cross-protection against other non-host adapted serovars (Cheng et al. 2014). Even though vaccination against viral infections is ubiquitous, the same cannot be said of antibacterial vaccines which still require development, testing and commercialization. Conferring protection against both C. jejuni and E. coli, two important foodborne pathogens of humans have been done, yet there is still no available vaccines on the market (Cheng et al. 2014). Salmonella vaccines used in combination with competitive exclusion cultures have a synergistic protective effect (Stanton 2013, p. 117). There are even reports of a vaccine against swine dysentery, caused by Brachyspira hyodysenteriae, that needs to be tested for effectiveness and safety (Cheng et al. 2014).

THE SITUATION IN THE GULF COOPERATION COUNTRIES

As of 2012, the majority of the member countries of the Gulf Cooperation Countries lack definite regulations regarding the sale and use of antibiotics, and the situation is less clear concerning veterinary antibiotics (Aly and Balkhy, 2012). The emergence of resistant isolates in the GCC is attributable to several factors: many broad-spectrum antibiotics are readily available, e.g. quinolones, carbapenems, third and fourth generation cephalosporins, etc. The layout of many hospitals does not allow for proper quarantine of patients infected with resistant organisms, and most importantly, there is a shortage of highly skilled professionals in the fields of infectious disease control and pharmacology. In addition to the misuse of antimicrobials in human medicine, the problem of using antibiotics in farm animals without the supervision of a veterinarian is rife in many countries, and there is also proof of its use for growth promotion (Balkhy et al., 2016).

The two most common resistant pathogens reported in the GCC between 1990 and 2011 were E. coli and K. pneumoniae. Other pathogens identified include bacteria that produce extended-spectrum beta-lactamases (ESBLs) and carbapenemases, pan-resistant-drug resistant Gram-negative bacilli and multi-drug resistant tuberculosis. They have grave ramifications in clinical settings, ESBL providing K. pneumoniae increase mortality by 40% and account for the majority of isolates (60% to 90%), ventilator-associated pneumonia caused by Acinetobacter is resistant to antimicrobials with a prevalence of 60% to 90% and multi-drug resistant infections results in 20% mortality in bloodstream infections in children (Balkhy et al., 2016).

Country	Gram Negative				Gram Positive			
	Acinetobacter	*Escherichiacoli*	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*	*Clostridium difficile*	Enterococcus	MRSA	*Streptococcus pneumoniae*
Bahrain	N.R	14.0%	13.9%	N.R	N.R	76.5%	8.5%	N.R
Kuwait	16.7%	77.0%	36.2%	2.6%	70.0%	N.R	3.3%	66.3%
Oman	N.R	N.R	0.1%	0.3%	0.0%	N.R	58.3%	N.R
Qatar	N.R	1.1%	0.8%	0.6%	N.R	N.R	N.R	N.R
Saudi Arabia	83.3%	7.6%	48.3%	92.3%	30.0%	23.5%	29.9%	30.7%
UAE	N.R	0.3%	0.7%	4.2%	N.R	N.R	N.R	3.0%

GCC = Gulf Corporation Council; N.R = not reported; MRSA = *methicillin resistant Staphylococcus aureus*; UAE = United Arab Emirates.

Figure 1: Aly, Balkhy 2012 - The prevalence of antimicrobial resistance.jpg (Aly and Balkhy 2012)

Country	Population	Population %	Reports (*n*)	Reports%	Isolates (*n*)	Isolates%	References
Bahrain	1,106,509	2.9%	3	9.1%	2841	7.6%	[4-6]
Kuwait	2,583,020	6.7%	9	27.3%	20339	54.5%	[7-15]
Oman	3,173,917	8.2%	3	9.1%	882	2.4%	[8,16,17]
Qatar	1,608,903	4.2%	2	6.1%	570	1.5%	[7,18]
Saudi Arabia	25,373,512	65.7%	14	42.4%	12174	32.6%	[19-32]
UAE	4,765,000	12.3%	2	6.1%	491	1.3%	[33,34]
GCC total	38,610,861	100.0%	33	100.0%	37295	100.0%	*n* = 33 articles

GCC = Gulf Corporation Council; UAE = United Arab Emirates.

Figure 2: Aly, Balkhy 2012 - The prevalence of antimicrobial resistance.jpg (Aly and Balkhy 2012)

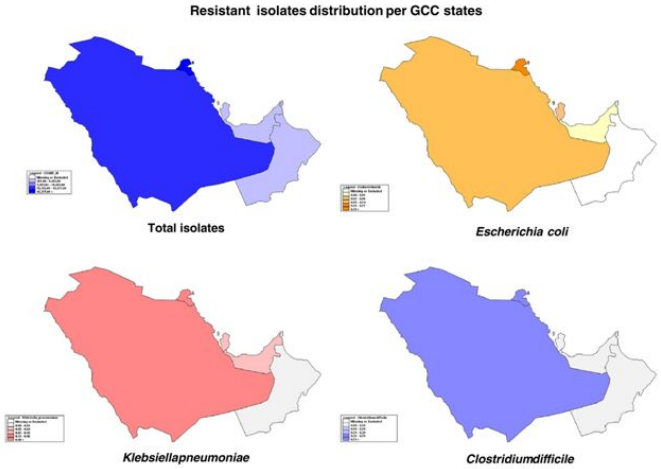


Figure 3: Aly, Balkhy 2012 - The prevalence of antimicrobial resistance.jpg (Aly and Balkhy 2012)

Fortunately, the emergence of resistance in the GCC has not gone unnoticed, and in 2014, the Gulf Cooperation Countries Center for Infection Control (GCC-IC) has drafted a plan to fight antimicrobial resistance. This plan is part of WHO's Global Action Plan on Antimicrobial Resistance using the "One Health" concept. This global plan consists of five main goals:

- Raise awareness about antimicrobial resistance.
- Gain the knowledge and collect data via surveillance.
- Lower the incidence of resistant infections.
- Optimize antimicrobial use.
- Convince countries that it is financially beneficial to invest in limiting resistance and developing alternative therapies.

The two principal priorities of the GCC-IC are to establish a standardized practice method in surveillance and reporting and

to increase the presence of competent healthcare professionals. The centre has already published the revised a second edition of the infection control manual that serves as a reference for the member countries to unify guidelines regarding practice and surveillance, prompt identification of multi-drug resistant organisms and in improving collaboration in antimicrobial resistance research between the human, veterinary and environmental sectors. The GCC's plan strives to gain a better understanding of the nature and scope of resistance in the region and the interplay between humans, animals, agriculture and the environment and to limit the availability and overuse of antimicrobials (Balkhy et al., 2016).

DISCUSSION

Resistance to antimicrobials has been recognized since the advent of antimicrobial use, and in 1945 Alexander Fleming himself warned about the possibility of resistance development when the drug is not used responsibly. Although the misuse of antibiotics in human medicine and by human patients has been long recognized as a driving factor of resistance. Veterinary use of antimicrobials in food animals has only recently been a topic of focus, and its role in the emergence of resistant pathogens, which could pose a threat to public health requires further research.

The emergence of resistant foodborne pathogens due to the use of antibiotics in food animals is indisputable, and it is proven to transfer to humans through the consumption of contaminated animal meat and products or close contact. The biggest issue seems to be the use of antibiotics for growth promotion. Because it involves long periods of antibiotic administration at sub-inhibitory concentration, both are factors in the emergence of resistance in both target pathogens and commensal bacteria. The situation is complex because one must consider the animal, drug and environmental factors. Meaning not all animal species will develop resistance in the same manner, and this is mostly due to the differences in the composition of their natural flora and their external environment and not all drugs develop the same extent of resistance over the same period.

Current recommendations to limit and maybe reverse antimicrobial resistance that stems from veterinary use includes, prohibition of the use of antimicrobials in growth promotion, withdrawing or restricting the use of antibiotics to which resistance has developed and banned the use of mainly human drugs especially those known as 'reserve antibiotics' from being used in veterinary medicine. Although these interventions are beneficial, they are insufficient and should not expect to work in all circumstances. One major problem is co-selection, meaning that certain bacteria can develop resistance to several antibiotics, even if only one is used. An example is when tetracycline given to poultry targeting caecal coliforms resulted in resistance not just to tetracycline, the coliforms became resistant to ampicillin, streptomycin and sulphonamides. Also, limiting or completely stopping the use of an antibiotic in any given species to reverse the resistance that emerged from their intensive use is not always successful. In swine and cattle, the resistance of E. coli to tetracycline persisted longer than resistance to gentamicin (Catry et al., 2003).

Putting a stop to non-essential use of antibiotics in both human and veterinary medicine is an essential step in the right direction. However, will this be sufficient considering that many resistance determinants have already taken hold and have disseminated widely amongst different bacteria and across borders? Bacteria's ability to rapidly evolve and survive the onslaught of antibiotics seems to suggest that a replacement for antibiotics is sorely needed. Presently, many other therapies could slow down the development of resistance by using them in conjunction with antibiotic therapy such as feed additives, phage therapy and immunization against bacteria. Unfortunately, these methods need further development and commercialization, and as of now, none are feasible as total replacements of antimicrobials.

The three greatest hindrances seem to be firstly, our present attitude towards antibiotic use and our overreliance on these drugs in animal food production since we use them to maximize our profits using as little effort and financial investment as possible. Secondly, the lack of interest by scientists and pharmaceutical companies to find alternatives to the already available and relatively inexpensive antimicrobials due to a lack of financial incentives. Thirdly, is the absence of a comprehensive approach encompassing the fields of human medicine and veterinary medicine as well as agricultural and environmental sciences in solving this issue.

CONCLUSION

The link between antibiotic use in food animal production and the emergence of resistant human pathogens is inconclusive and requires further research to prove, disprove or to determine the strength of this link. The review contains overwhelming support to the transmission of resistance from animal farm settings to the human population, especially in foodborne pathogens with only a few contradictions. There is contention regarding this issue. However, all agree on one matter. The need for further investigation to clarify the situation and obtain accurate data so that governments and relevant authorities can be responsible and unbiasedly informed to make the right decisions. More than half of all antibiotics are used in food animals, which puts excellent accountability and responsibility when it comes to antibiotic resistance in the veterinary profession. Transmission of resistance has occurred through the consumption of animal meat and their products and direct or indirect contact with these animals and their excretions. Another more elusive method of transmission is via resistance carrying mobile genetic elements via HGT that needs further investigation. There are four main ways of metabolic mechanisms of antibiotic resistance that bacteria may employ. 1) modifying the antibiotic molecule, 2) decreasing antibiotic penetration into the cell and increasing efflux of intracellularly present drug molecules, 3) changing the target site, 4) global cell adaption. Alternatives to antibiotic therapy have been proposed, such as phage therapy or using their endolysin, immunotherapy, e.g. vaccination and feed additives. None of these alternatives can serve as a complete replacement to antibiotics have their own set of challenges. In conclusion, further research and alternative therapies are vital in fighting antimicrobial resistance; this requires international cooperation and communication between the human, veterinary, agricultural and environmental sectors.

AUTHORS CONTRIBUTION

Khaja Mohteshamuddin conceived and designed the topic of the study as it was relevant to the local needs. Ahmad al Aiyan provided key inputs in the concept and overall design of the study. Fatema Rashed Almuhairi executed the concept and was the primary author involved in the study and was supported by Asma Mahmood Bulshawareb in this task, Aisha Al Nuami & Maryam examined the review and provided with critical feedback to improve the quality of work. All authors interpreted the

data, critically revised the manuscript for remarkable intellectual contents and approved the final version.

CONFLICT ON INTEREST

The authors declare no conflict of interest.

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