https://doi.org/10.47278/book.vpph/2021.028

EMERGENCE OF ANTIMICROBIAL RESISTANCE AND INTERACTION BETWEEN HUMANS, ANIMALS AND ENVIRONMENT

Aayesha Riaz[1*], Arfan Yousaf[2], Muhammad Ali Abdullah Shah[1] and Imtiaz Ahmad Khan[3]

[1]Department of Parasitology and Microbiology, Faculty of Veterinary and Animal Sciences, Pir Mehr Ali Shah, Arid Agriculture University Rawalpindi 46300, Pakistan; [2]Department of Clinical Studies, Faculty of Veterinary and Animal Sciences, Pir Mehr Ali Shah, Arid Agriculture University Rawalpindi, 46300, Pakistan; [3]Department of Veterinary Pathology, Faculty of Veterinary and Animal Sciences, Pir Mehr Ali Shah, Arid Agriculture University Rawalpindi, 46300, Pakistan

***Corresponding author:** aayeshariaz@uaar.edu.pk

INTRODUCTION

Antimicrobial resistance (AMR) is defined as the newly found resistance of a group of micro-organisms to an antimicrobial agent against which they were originally sensitive. Unnecessary usage of antimicrobials in the treatment of infectious diseases and as growth promoters in animals may result in the development of resistant microbial strains (Holmes et al. 2016). Micro-organisms acquire resistance to antimicrobials via genes' mutations and through acquisition of new antimicrobial resistant genes from other bacteria. Transmission of this resistance can also occur from animals to humans and from humans to humans (Jindal et al. 2015). Resistant bacteria may be transmitted from food animals, either through the food chain, the environment or through direct contact with these animals. Such transmission may lead to the emergence of potentially challenging infections (Lekshmi et al. 2017).

AMR is a natural evolutionary process normally observed in bacteria, however, antimicrobial abuse, including extensive use, misuse or overuse can lead to an acceleration of this natural phenomenon, and an exacerbation of unwanted effects (Hwang and Gums 2016). Poor management practices in the treatment of infectious diseases also lead to the emergence of AMR in both animals and humans (Ayukekbong et al. 2017). To tackle the issue of AMR in micro-organisms and to combat its threat to public health, a complete understanding of the mechanisms underlying the emergence of AMR is essential. Such an understanding will aid in the development of better diagnostic and therapeutic approaches to bacterial infections (Lammie and Hughes 2016).

This chapter presents a review of number of factors attributing to the emergence and dissemination of AMR among micro-organisms, as well as how natural interactions between these micro-organisms, animals, humans and the environment lead to the spread of such resistance. To limit the emergence of AMR, drivers of AMR in the animals, humans, and environment should be recognized and controlled. For this purpose, it is essential to develop appropriate interventional policies through action plans, both at national and international levels, aided by the principles of the *one health* approach and the involvement of multiple disciplines (Smith et al. 2019).

Mechanism of Acquisition of AMR

Pathogens acquire antimicrobial resistance in two ways: (a) vertical acquisition of AMR through mutations in pre-existing or previously acquired genes, and (b) horizontal acquisition of AMR through acquiring new resistant genes from other bacteria, also called the horizontal gene transfer (HGT) (Lawrence 2005). Depending on the antimicrobials, resistance can develop through either of the two mechanisms.

Vertical Acquisition of AMR

Mutations are one of several mechanisms by which bacteria become resistant to antibiotics. Division of a bacterium results in the creation of two identical copies of DNA. With each bacterial division there is a possibility of the emergence of mutation(s) in the DNA strands. These mutations can give rise to antibiotic resistance genes (Bos et al. 2015). An antibiotic resistant bacterium is then able to survive and multiply, even in the presence of the specific antibiotic to which it had become resistant (Darwinian natural selection), giving rise to a population of mainly resistant bacteria (Lenski 2017) (Fig. 1).

Natural selection of resistant bacteria can occur when an antibiotic is given to a sick animal or human as a part of the treatment of the infection. The antibiotic is unable to kill both the resistant pathogenic bacteria, as well as any commensal bacteria with resistance genes (Boerlin and Reid-Smith 2008). The use of narrow spectrum antibiotics can decrease the possibility of the selection antibiotic resistance commensal bacteria (McAdams et al. 2019).

Acquisition of AMR through Horizontal gene transfer (HGT)

Horizontal gene transfer (HGT) is the most common method by which bacteria acquire AMR. This may possibly occur through the acquisition of resistance genes and/or the exchange of genetic material of one bacterium with that of other bacteria. Plasmid-mediated conjugation is recognized as the most common mechanism by which HGT occurs. Genome sequence analysis of bacteria can confirm HGT (Husnik and McCutcheon 2018).

So, how does HGT work and what does it mean for bacterial populations? HGT is a strong and helpful tool by which bacteria are able to evade the toxic effects of antimicrobials (Gupta et al. 2019). HGT occurs through three mechanisms: conjugation, transformation and transduction (Fig. 2).

Conjugation is a mechanism by which a bacterial cell comes in contact with another bacterial cell and donates its plasmid DNA through a cell-membrane structure called sex pili. Transformation is a mechanism by which a bacterium uptakes DNA directly from its immediate environment. Transduction is a mechanism by which bacteriophages (viruses) inject their viral DNA into a bacterium.

Thus, specific AMR genes can be exchanged among bacteria in close proximity to each other through any of the aforementioned mechanisms. Those bacteria which acquire resistance genes can then transmit resistance through vertical inheritance to the upcoming generations. Unlike vertical gene transfer, mutation is not an essential part of HGT. The lack of a mutation component in HGT is advantageous for bacteria because mutations can sometimes be harmful. Transfer of plasmid through the process of conjugation is the major contributor to HGT among bacteria (Boerlin and Reid-Smith 2008). HGT occurs between the same species of bacteria, strains of the same species and between bacteria belonging to different species as well. It has also been reported that HGT can also take place among different bacterial families and orders. Factors that contribute to the success of HGT include the degree of taxonomical similarity between involved bacteria and the level of compatibility between the (donor and recipient) organisms (Rodriguez-Beltran et al. 2021).

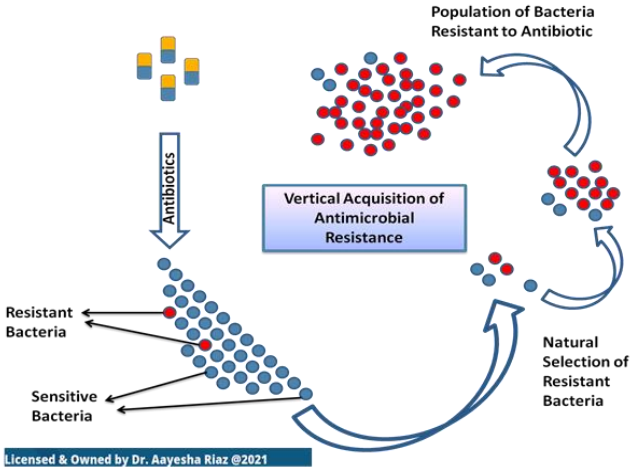

Figure 1: The process of emergence of AMR through natural selection (vertical acquisition) of resistant bacteria. Antibiotic kills most of the antibiotic sensitive bacteria, however, antibiotic resistant bacterium survives. Due to the presence of antibiotic, the sensitive bacteria no longer remain alive in the medium, and their number reduces gradually, whereas resistant bacteria increase in number over time.

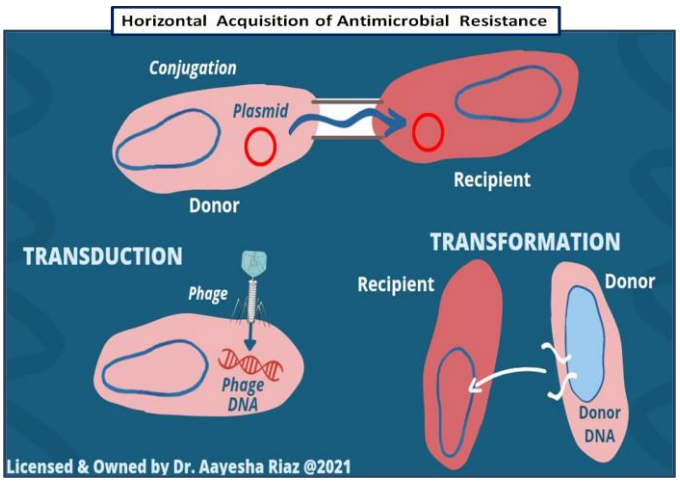

Figure 2: Horizontal acquisition of AMR by acquiring genes from outside through conjugation (from other bacteria), transduction (from a bacteriophage DNA), or transformation (directly from the bacterial surroundings).

Emergence and Transmission of AMR

Emergence and Transmission of AMR within a Micro-organism

Through the mechanisms described above, AMR eventually emerges among bacterial species. These robust mechanisms help them to evade the toxic bactericidal or bacteriostatic effects of antimicrobials. Resistance to antimicrobials was identified soon after the discovery of antimicrobials themselves (Fig. 3). Today, the menace of AMR complicates the treatment of almost all major infectious diseases afflict both animals and humans, including zoonotic diseases (Holmes et al. 2016).

Bacteria elude the effect of antimicrobials by preventing the drug from entering the bacterial cell (Reygaert 2018). They also produce enzymes (the products of AMR responsible genes), which either destroy the antimicrobial or modify the antimicrobial binding or target sites. Studies that aimed at characterizing population structures, AMR and virulence genes of bacterial spp. that afflict both animals and humans, have indicated a wide diversity of genetic determinants of resistance (Hirt et al. 2018; Panzetta et al. 2018). One study reported the emergence of AMR in a group of companion animals with urinary tract infection (UTI). They were shown to be having been infected with high-risk *Klebsiella pneumoniae* clonal lineages with resistance and virulence genes (Marques et al. 2019). In another study, variants of the tet(X) gene were identified. Bacteria with tet(X) gene can modify the structure of tigecycline, which is considered a last-resort antibiotic in the treatment of severe infections caused by extensively resistant bacteria. Two unique variants of this gene, tet(X3) and tet(X4), were also reportedly found in numerous isolates of Enterobacteriaceae and Acinetobacter collected from animals (including food animals), as well as from humans. Tet(X3) and tet(X4) were found to give bacteria the ability to inactivate all tetracyclines, including tigecycline and the newly FDA-approved eravacycline and omadacycline (He et al. 2019).

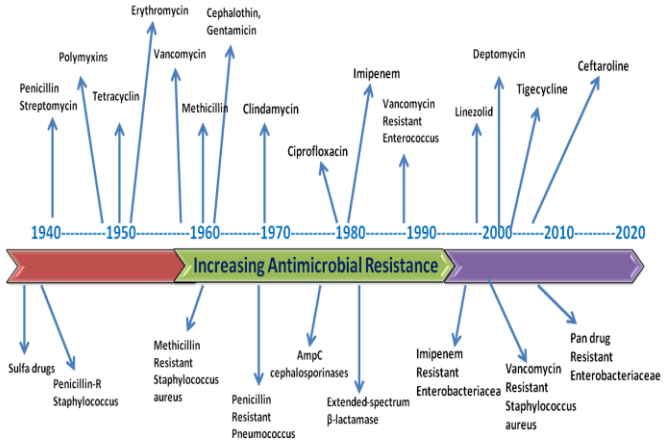

Figure 3: Timeline of antimicrobial discovery and antimicrobial resistance. Each antibiotic class is indicated above the timeline and the time when resistance was first observed for each class is shown below the timeline.

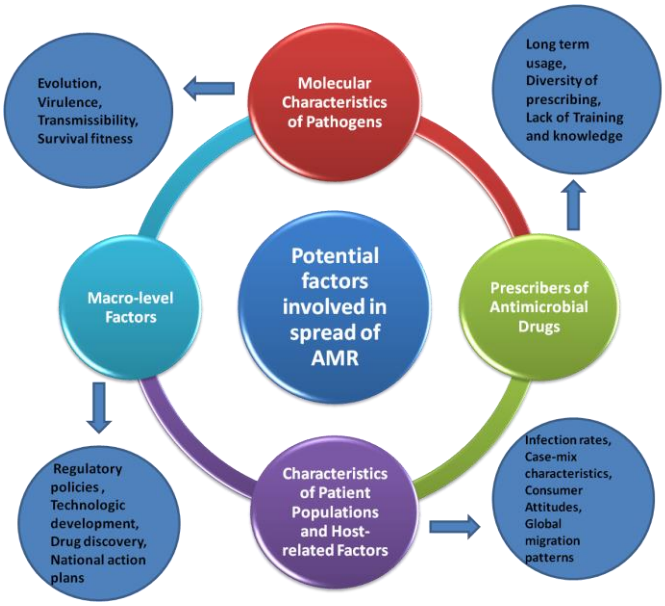

Figure 4: Potential factors involved in dissemination of antimicrobial resistance. The potential factors are indicated in inner circles and their examples are indicated in outer circles.

Other examples include the development of resistance against β-lactam antibiotics by β-lactamases producing micro-organisms that inactivate β-lactam (Sparbier et al. 2012; Worthington and Melander 2013). As widely known, most antimicrobials are produced by saprophytic organisms. The antimicrobial molecules production by saprophytic micro-organisms can affect the growth of other bacteria in the surrounding environment, even in sub-lethal concentrations. These antimicrobial molecules may influence expression of the bacterial and host genes (Andersson and Hughes 2014; Holmes et al. 2016). Emergence of resistance to synthetic antimicrobials also occurs. One example in the emergence of such resistance is resistance to fluoroquinolones. Such resistance emerges through several mechanisms. The structure of target sites may be altered, or "protection" may be "given" to the sites with DNA binding proteins. Bacterial cells may become capable of exporting the drug out at increased rates, leading to a reduction in the amount of damage caused by these fluoroquinolones. Cells may also acquire the capability to produce enzymes that inactivate fluoroquinolones (Redgrave et al. 2014; Osei Sekyere and Amoako 2017). Emergence of AMR is a continuous process in the life of micro-organisms and, thus continuous and diligent global attention is needed for both; the surveillance of AMR gene variants in both clinical and animal settings, as well as those resulting from the use of antimicrobials in food production.

Emergence and transmission of AMR within Human beings

The misuse or overuse of antimicrobials in clinical practice is a major determinant of the emergence and development of AMR in human populations. Reservoirs of AMR genes lie among the commensal microflora present in the gastrointestinal tract (GIT) and other body systems of humans and animals (Taft et al. 2018). *In vitro* and *in vivo* transfer of AMR genes between commensal microflora and pathogenic micro-organisms in the GIT has already been reported in different studies (Walsh and Fanning 2008; Scott et al. 2009). Due to a vast reservoir of commensals in humans, transfer of resistance genes from commensals to pathogens tends to be much more frequent in comparison with the *de novo* development of resistance to a pathogen, leaving the latter mechanism less impactful (Bag et al. 2019). Emergence of AMR as a result of this transfer of AMR genes to pathogens is another global health threat.

The environment, drinking water and food are also major reservoirs of microbes and determinants of AMR emergence. The irrational use of antimicrobials, or the prescription of the needless antimicrobials, is one of the main attributes of AMR in micro-organisms that afflict humans. It can cause damage to beneficial bacteria and can lead to the development of AMR in them, which may then share their resistance gene with other bacteria. In addition, an opportunity may be created for potentially harmful bacteria to replace the harmless ones (Hernando-Amado et al. 2019; Fouz et al. 2020). Some species of normal flora have "natural" resistant genes to some antimicrobials. Selective pressure allows micro-organisms with resistance genes to survive and proliferate. It has been reported that Enterobacteriaceae rapidly colonize neonatal guts soon after birth. Nearly 14% of these Enterobacteriaceae have resistance enzymes, including the extended-spectrum β-lactamase (ESβL), which inactivates β-lactam containing antibiotics. By 60 days of age, approximately 42% of babies' guts are colonized with such bacteria (Kothari et al. 2013).

Resistance genes can also be transmitted from human to human through hospitals (nosocomial infections), in the community through travel, or extended care facilities. NDM-1 (New Delhi metallo-beta-lactamase 1) is a notable example (Johnson and Woodford 2013). NDM-1 is an enzyme that renders bacteria resistant to a broad range of beta-lactam antibiotics (the carbapenem antibiotic family). Carbapenem antibiotics are considered effective

for the treatment of antibiotic resistant bacterial infections (Doi 2019). NDM-1 gene beta-lactamase enzymes are also called carbapenemases. NDM-1 was first detected in 2008 in a *Klebsiella pneumoniae* isolate from a Swedish patient in India (Yong et al. 2009; Kumarasamy et al. 2010). NDM-1 is most common in gram-negative bacteria, such as *Escherichia coli* and *Klebsiella pneumoniae*, and can transfer from one bacterium to another through HGT. A large-scale multi-national study in 2010 reported the emergence and spread of NDM-1 gene carrying bacteria in United Kingdom, Pakistan and India (Kumarasamy et al. 2010). In the community, the transmission of AMR can also occur through the oral-fecal route. Failure to conduct appropriate biological waste management and adequate WASH (Water, Sanitization and Hygiene) plays an important role in the transmission of bacteria, particularly resistant gram-negative organisms like pathogenic *E. Coli* (WHO 2018). Spread of infection due to ESβL-positive Entero-bacteriaceae and methicillin-resistant *Staphylococcus aureus* (MRSA) is associated with travel, contamination associated with hospitals and healthcare personnel, as well as poor WASH conditions (Holmes et al. 2016). During the last ten years, the collective human microflora has acquired AMR in an unprecedented scale (Bassetti et al. 2017). It is essential to interrupt chain of transmission of resistance from human to human by interventions like mass drug administration and vaccinations (Wegener 2012).

Emergence and transmission of AMR among Animals and Human

Antimicrobials are widely used in domestic animals and livestock for the treatment of infectious diseases. In some countries, these are used in sub-therapeutic doses as growth promoters. In many others, use of antimicrobials as growth promoters is banned (Hosain et al. 2021). Humans can acquire antibiotic resistance genes from several sources of animal origin, including livestock, poultry, wildlife and pet animals. AMR can be transmitted from animal to animal or animal to human by direct infection with resistant organism from an animal source. Other sources of bacterial resistance include HGT of resistance genes from agriculture/livestock to human pathogens. In this regard, food-borne pathogens have a higher impact on health at the population level (Walsh and Fanning 2008).

Direct contact with animals can also be a cause of spread of antibiotic resistant micro-organisms. Persons who are involved in direct handling or management of animals (veterinarians, animal handlers, shepherds, milk men, cleaners, manure handlers, laborers and animal receivers) are typically at high risk (Rao 1998; Tang et al. 2017). Studies have revealed that manure may also contain resistant micro-organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) (Casey et al. 2013). Also called livestock-associated MRSA (LA-MRSA), these resistant bacteria are carried or harbored by livestock (cattle, buffaloes, sheep, goat and poultry) and companion animals (dogs, cats, pet animals) and are easily transmittable to humans (Graveland et al. 2011). Studies have shown that these new lineages are commonly found in the guts of workers and veterinarians dealing with these animals. These workers and veterinarians can then potentially transmit these resistant bacteria to their un-exposed family members, friends and other community/society members. This indicates that exposure to livestock greatly increases the risk of developing (MRSA) infection (van Cleef et al. 2011).

There is a positive but complex association between the consumption of antimicrobials and the emergence, development and transmission of resistance between humans, animals, and the environment. There are direct and indirect routes of AMR transmission, which are associated with the use of antimicrobials in animals and resistance in humans (Graham et al. 2019). Studies examining LA-MRSA, such as CC 398 and mecC MRSA, have reported a shared lineage of AMR genes among humans and farm animals, indicating that at some time point resistance genes were transmitted from humans to farm animals (Lepuschitz 2015). Similarly, sequencing analyses of the ST5 MRSA lineage revealed that they may have originated as a result of human to poultry transmission (Bernier-Lachance et al. 2020). There is also evidence of MRSA lineages that were transmitted from animals to humans (Takano et al. 2013).

Third-generation cephalosporin resistant *Escherichia coli* and *Salmonella typhimurium* DT104 strains have been shown to be spread from livestock to humans via food consumption and their genes shared through conjugation (Dechet et al. 2006; Lin et al. 2019). Animals transfer AMR bacteria to humans indirectly through food. Ingestion and occasional colonization of resistant micro-organisms in the gut can lead to the development of AMR in humans (Marston et al. 2016). Salmonella, *E. coli*, Campylobacter, and Listeria species are the most common food-borne bacterial pathogens.

Milk and other dairy products, as well as meat (beef, mutton, and poultry meat), can carry pathogens that may have developed resistance to antimicrobials. Shiga toxin-producing *E. coli* (STEC) is a food borne pathogen of zoonotic importance that causes outbreaks of diarrhea, hemorrhagic colitis, and hemolytic uraemic syndrome (HUS) in humans. Irshad et al. (2020) reported the presence of STEC in 43.5% of raw meat samples (of cattle and goats) collected from meat shops. They found that positive isolates had one or more of the STEC virulence genes; stx1, stx2, eae and/or ehxA. Antibiotic susceptibility profiles indicated AMR levels ranging from 33.3 to 100% against lincomycine, cephradine, neomycin, streptomycin and doxycycline (Irshad et al. 2020). These antibiotics are widely used for treatment, prevention, and as growth promoters in food producing animals in Pakistan (Rahman and Mohsin 2019). Other studies involving the surveillance of retail meats such as beef, chicken and turkey have detected the presence of Enterobacteriaceae. Handlers, buyers and sellers of these products are thus at serious risk of becoming infected with typical AMR resistant bacteria (Miranda et al. 2008; Gelbíčová et al. 2019; Díaz-Jiménez et al. 2020).

Emergence and transmission of AMR via Environment

The emergence of AMR depends on many environmental factors. Most importantly, these include population densities, the level of health care provided, immigrations, travel, tourism, sanitation, the occurrence of cultural and religious gatherings involving animals (such as Eid-Al-Ad'ha in Islam and worship of cattle in Hinduism) and the presence of animals in close proximity to humans (Berndtson 2020). Some examples of environmental transmission of AMR have been discussed in previous sections. In this section, mechanisms of environment-related spread and transmission of AMR have been discussed. Some antimicrobial drugs (either taken for the treatment of infections or consumed as food source) are not fully digested, absorbed and processed in the animal or human gut. Therefore, 40-90% of these ingested drugs are excreted to environment in urine and/or in faeces (Berndtson 2020; Wang et al. 2020). This means that human sewage and animal manure can both be sources of antibiotic resistant micro-organisms. Animal manure is also used as fertilizer, potentially spreading micro-organisms to crops and into runoff water (Kumar et al. 2013). Different studies have detected the presence of antibiotics in small amounts in crops grown in fields fertilized with animal manure and into runoff water (Hu et al. 2010; Kang et al. 2013). This clearly indicates the importance of waste processing to control environment–human transmission. Many potentially pathogenic resistance micro-organisms and antimicrobial metabolites have been isolated from sewage systems, even after treatment, which indicates the need of preventive measures to be taken (Talebi et al. 2007; Luczkiewicz et al. 2010a; Luczkiewicz et al. 2010b; Heck et al. 2015).

Potential factors involved in spread of AMR and methods of control

Potential factors involved in dissemination of AMR are numerous and diverse. It is very important to control these factors in order to control the AMR transmission and spread. These can be divided into 4 groups, as shown in Fig. 4.

Molecular characteristics of pathogens

Molecular characteristics of pathogenic micro-organisms, including their evolution, pathogenicity, virulence, transmissibility, and survival potential, are key factors in the spread of AMR. These factors can be detected by laboratory diagnostic techniques (Baker et al. 2018). However, uncertainty in diagnosis may lead to misuse or overuse of antimicrobial and higher rates of emergence of resistant microbes (Harbarth and Samore 2005). Evolutionary engineering, inhibition of microbial AMR gene expression, probiotics, and rapid and improved diagnostic tests can help to control the potential determinants of AMR (Andersson et al. 2020; Pollock et al. 2020).

Prescribers of antimicrobial drugs (Physicians)

To control the emergence of AMR, physicians need to change their prescription patterns by avoiding the use of antibiotics in the treatment of non-bacterial infections, as well as avoid any unnecessary long-term use of antimicrobials. These are promising means of reducing antimicrobial selection pressure. Studies have shown that shortening the duration of treatment with antimicrobial agents reduces the risk of development of AMR (Marston et al. 2016). With the increased awareness of prescribers of the emergence of AMR, an overall reduction in prescriptions of antimicrobials has been reported. This has resulted in some reduction in antimicrobial resistance. This also indicates that to overcome antimicrobial misuse or overuse, educating the prescribers and other health care providers is crucial (Abera et al. 2014; Llor and Bjerrum 2014).

Characteristics of patient populations and host-related factors

These factors include rate of infection and case-mix characteristics, consumer behavior and attitude towards usage of anti-microbials and increased immigrations or global migrations (Harbarth and Samore 2005). Host related factors which can increase antimicrobial use and AMR include, increased numbers of surviving immune-compromised patients, longer life expectancies, along with the increased susceptibility to infection of older populations (Yoshikawa 2002). These factors can be controlled through screening, increased surveillance of antimicrobial usage and AMR dissemination, better control of chronic infectious diseases, public information campaigns, vaccination and the implementation of WASH guidelines (WHO 2018).

Macro level factors

These are factors related to the quality of each country's health-care system, as well as its policy making practices. Key measures include, the formulation of regulatory policies designed to control the use of antimicrobial drugs and enforced implementation of infection control practices (Weese et al. 2015). Other factors include technological development and drug discovery. An effective strategy to combat AMR requires both global and national action plans (WHO 2016). Challenges linked to the control of the dissemination of AMR include, poor healthcare regulations, politicization, lack of predictability in decision-making in case of any outbreak, the ability to identify key stakeholders and the ability to implement regulations at smaller and individual levels. If implemented correctly, healthcare regulations would have a powerful influence and help to control antimicrobial drug use in the future (World-Bank 2017). It is also of extreme importance to restrict the purchase of over-the-counter antimicrobial drugs without a medical prescription (Parsonage et al. 2017).

Novel Approaches to control or slow down the Emergence of AMR

There is a dire need of the development of novel approaches to more efficiently curb the emergence and spread of AMR. In recent years, metal nanoparticles (NPs) have gained attention of scientists and researchers due to their high and long-lasting antimicrobial activity (Bogdanović et al. 2014; Kruk et al. 2015). Zinc doped CuO NPs, used against multi-drug resistant (MDR) bacteria, have shown profound antimicrobial effect against both antimicrobial susceptibility and MDR-strains of *E. coli* and *S. aureus* (Malka et al. 2013; Ali et al. 2017).

Commercially available bacteriophages, such as commercial Listeria phage products, (ListShieldTM and ListexTM P100), can be used to reduce the growth of Listeria. It was reported that treatment with ListexTM P100 considerably reduced the growth of *Listeria monocytogenes* (Pietracha and Misiewicz 2016). Also, a mixture of two bacteriophages (P433/1 and P433/2) used to treat infections induced by the *E. coli* strain P433 in pigs was shown to be very promising. Both bacteriophages showed a high capacity to lyse bacteria *in vitro* (Zhang et al. 2015).

Bacteriocins can also be used as potential alternatives to antibiotics. Bacteriocin is a group of ribosomal proteins with antimicrobial properties (Yang et al. 2014). Some of the bacteriocins exhibit narrow spectrum of activity, whereas others exhibit broader spectrums (Cotter et al. 2013). Lantibiotics have been the most extensively studied bacteriocins. They include nisin, lacticin 3147, mersacidin, lacticin 481 and staphylococcin C55, amongst others (Willey and van der Donk 2007). Some lentibiotics have been shown to target vancomycin-resistant Enterococci and MRSA (Alves et al. 2020; Reinseth et al. 2020). Due to their distinct mode of action and wide spectrum of action, bacteriocins have attracted considerable attention in the area of antimicrobial research.

Conclusions

Antimicrobial resistance has become an enormous global public and animal health concern. It is vital that measures be implemented in order to curtail the emergence of AMR in micro-organisms, animals, humans and the environment. Needless use of antimicrobials is the single biggest cause of emergence of AMR, which then is disseminated via animals, humans, agricultural practices and/or environmental contamination. Our understanding of antimicrobial resistance is far from complete. A thorough understanding of factors involved in AMR, such as pathogen-host and pathogen-drug interactions, mutation rates of pathogens and AMR transmission rates is crucial for our ability to prevent the emergence of AMR. AMR cannot be controlled by a single measure. There should be several overlapping and synergistic stern strategies with the involvement of multiple stakeholders at the national and global levels. The prudent and safe use of antimicrobials in humans and animals can only be achieved through the prescription of antibiotics limited to appropriate and fully justifiable cases.

REFERENCES

Abera B et al., 2014. Knowledge and beliefs on antimicrobial resistance among physicians and nurses in hospitals in Amhara Region, Ethiopia. BMC Pharmacology and Toxicology 15(1): 1-7.

Ali SS et al., 2017. Synthesized zinc peroxide nanoparticles (ZnO_2-NPs): A novel antimicrobial, anti-elastase, anti-keratinase, and anti-inflammatory approach toward polymicrobial burn wounds. International Iournal of Nanomedicine 12: 6059-6073.

Alves FCB et al., 2020. Comparative proteomics of methicillin-resistant *Staphylococcus aureus* subjected to synergistic effects of the lantibiotic nisin and oxacillin. Microbial Drug Resistance 26(3): 179-189.

Andersson DI et al., 2020. Antibiotic resistance: Turning evolutionary principles into clinical reality. FEMS Microbiology Reviews 44(2): 171-188. Andersson DI and Hughes D, 2014. Microbiological effects of sublethal levels of antibiotics. Nature Reviews: Microbiology 12(7): 465-478. Ayukekbong JA et al., 2017. The threat of antimicrobial resistance in developing countries: causes and control strategies. Antimicrobial Resistance and Infection Control 6(1): 1-8.

Bag S et al., 2019. Molecular insights into antimicrobial resistance traits of commensal human gut microbiota. Microbial Ecology 77(2): 546-557.

Baker S et al., 2018. Genomic insights into the emergence and spread of antimicrobial-resistant bacterial pathogens. Science 360(6390): 733-738.

Bassetti M et al., 2017. Antimicrobial resistance in the next 30 years, humankind, bugs and drugs: A visionary approach. Intensive Care Medicine 43(10): 1464-1475.

Berndtson AE, 2020. Increasing globalization and the movement of antimicrobial resistance between countries. Surgical Infections 21(7): 579-585.

Bernier-Lachance J et al., 2020. Prevalence and characteristics of livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) isolated from chicken meat in the province of Quebec, Canada. PloS One 15(1): e0227183.

Boerlin P and Reid-Smith RJ, 2008. Antimicrobial resistance: its emergence and transmission. Animal Health Research Reviews 9(2): 115-126.

Bogdanović U et al., 2014. Copper nanoparticles with high antimicrobial activity. Materials Letters 128: 75-78.

Bos J et al., 2015. Emergence of antibiotic resistance from multinucleated bacterial filaments. Proceedings of the National Academy of Sciences of the United States of America 112(1): 178-183.

Casey JA et al., 2013. High-density livestock operations, crop field application of manure, and risk of community-associated methicillin-resistant *Staphylococcus aureus* infection in Pennsylvania. JAMA Internal Medicine 173(21): 1980-1990.

Cotter PD et al., 2013. Bacteriocins—a viable alternative to antibiotics? Nature Reviews Microbiology 11(2): 95-105.

Dechet AM et al., 2006. Outbreak of multidrug-resistant *Salmonella enterica* serotype Typhimurium Definitive Type 104 infection linked to commercial ground beef, northeastern United States, 2003-2004. Clinical Infectious Diseases 42(6): 747-752.

Díaz-Jiménez D et al., (2020). Chicken and turkey meat: Consumer exposure to multidrug-resistant Enterobacteriaceae including MCR-carriers, uropathogenic *E. coli* and high-risk lineages such as ST131. International Journal of Food Microbiology 331: 108750.

Doi Y, 2019. Treatment options for carbapenem-resistant gram-negative bacterial infections. Clinical Infectious Diseases 69(Supplement_7): S565-S575.

Fouz N et al., 2020. The contribution of wastewater to the transmission of antimicrobial resistance in the environment: Implications of mass gathering settings. Tropical Medicine and Infectious Disease 5(1): 33.

Gelbíčová T et al., 2019. Dissemination and comparison of genetic determinants of MCR-mediated colistin resistance in Enterobacteriaceae via retailed raw meat products. Frontiers in Microbiology 10: 2824.

Graham DW et al., 2019. Complexities in understanding antimicrobial resistance across domesticated animal, human, and environmental systems. Annals of the New York Academy of Sciences 1441(1): 17-30.

Graveland H et al., 2011. Livestock-associated methicillin-resistant *Staphylococcus aureus* in animals and humans. International Journal of Medical Microbiology 301(8): 630-634.

Gupta A et al., 2019. Combatting antibiotic-resistant bacteria using nanomaterials. Chemical Society Reviews 48(2): 415-427.

Harbarth S and Samore MH, 2005. Antimicrobial resistance determinants and future control. Emerging Infectious Diseases 11(6): 794-801.

He T et al., 2019. Emergence of plasmid-mediated high-level tigecycline resistance genes in animals and humans. Nature Microbiology 4(9): 1450-1456.

Heck K et al., 2015. Pattern of multiresistant to antimicrobials and heavy metal tolerance in bacteria isolated from sewage sludge samples from a composting process at a recycling plant in southern Brazil. Environmental Monitoring and Assessment 187(6): 328.

Hernando-Amado S et al., 2019. Defining and combating antibiotic resistance from One Health and Global Health perspectives. Nature Microbiology 4(9): 1432-1442.

Hirt H et al., 2018. A D-enantiomer of the antimicrobial peptide GL13K evades antimicrobial resistance in the Gram positive bacteria *Enterococcus faecalis* and *Streptococcus gordonii*. PloS One 13(3): e0194900.

Holmes AH et al., 2016. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet 387(10014): 176-187.

Hosain MZ et al., 2021. Antimicrobial uses for livestock production in developing countries. Veterinary World 14(1): 210-221.

Hu X et al., 2010. Occurrence and source analysis of typical veterinary antibiotics in manure, soil, vegetables and groundwater from organic vegetable bases, northern China. Environmental Pollution 158(9): 2992-2998.

Husnik F and McCutcheon JP, 2018. Functional horizontal gene transfer from bacteria to eukaryotes. Nature Reviews: Microbiology 16(2): 67-79.

Hwang AY and Gums JG, 2016. The emergence and evolution of antimicrobial resistance: Impact on a global scale. Bioorganic and Medicinal Chemistry 24(24): 6440-6445.

Irshad H et al., 2020. Occurrence and molecular characterization of Shiga toxin-producing *Escherichia coli* isolates recovered from cattle and goat meat obtained from retail meat shops in Rawalpindi and Islamabad, Pakistan. Pakistan Veterinary Journal 40(3): 295-300.

Jindal AK et al., (2015). Antimicrobial resistance: A public health challenge. Medicine Journal Armed Forces India 71(2): 178-181.

Johnson AP and Woodford N, 2013. Global spread of antibiotic resistance: The example of New Delhi metallo-beta-lactamase (NDM)-mediated carbapenem resistance. Journal of Medical Microbiology 62(4): 499-513.

Kang DH et al., 2013. Antibiotic uptake by vegetable crops from manure-applied soils. Journal of Agricultural and Food Chemistry 61(42): 9992-10001.

Kothari C et al., 2013. Community acquisition of beta-lactamase producing Enterobacteriaceae in neonatal gut. BMC Microbiology 13(1): 1-6.

Kruk T et al., 2015. Synthesis and antimicrobial activity of monodisperse copper nanoparticles. Colloids and Surfaces B: Biointerfaces 128: 17-22.

Kumar RR et al., 2013. Application and environmental risks of livestock manure. Journal of the Korean Society for Applied Biological Chemistry 56(5): 497-503.

Kumarasamy KK, 2010. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: A molecular, biological, and epidemiological study. Lancet Infectious Diseases 10(9): 597-602.

Lammie SL and Hughes JM, 2016. Antimicrobial resistance, food safety, and one health: The need for convergence. Annual Review of Food Science and Technology 7: 287-312.

Lawrence JG, 2005. Horizontal and vertical gene transfer: The life history of pathogens. In: Russel W, Herwald H, (eds) Contributions to Microbiology, Basel, Karger. Vol.12, pp: 255-271.

Lekshmi M et al., 2017. The food production environment and the development of antimicrobial resistance in human pathogens of animal origin. Microorganisms 5(1): 1-15.

Lenski RE, 2017. What is adaptation by natural selection? Perspectives of an experimental microbiologist. PLoS Genetics 13(4): e1006668.

Lepuschitz S, 2015. Subtyping of livestock-associated methicillin-resistant *Staphylococcus aureus* CC398 isolates by next generation sequencing. Master's Thesis, University of Vienna.

Lin WP et al., 2019. Prevalence of and risk factor for community-onset third-generation cephalosporin-resistant *Escherichia coli* bacteremia at a medical center in Taiwan. BMC Infectious Diseases 19(1): 245.

Llor C and Bjerrum L, 2014. Antimicrobial resistance: Risk associated with antibiotic overuse and initiatives to reduce the problem. Therapeutic Advances in Drug Safety 5(6): 229-241.

Luczkiewicz A et al., 2010. Diversity of fecal coliforms and their antimicrobial resistance patterns in wastewater treatment model plant. Water Science and Technology 61(6): 1383-1392.

Luczkiewicz A et al., 2010. Antimicrobial resistance of fecal indicators in municipal wastewater treatment plant. Water Research 44(17): 5089-5097.

Malka E et al., 2013. Eradication of multi-drug resistant bacteria by a novel Zn-doped CuO nanocomposite. Small 9(23): 4069-4076.

Marques C et al., 2019. *Klebsiella pneumoniae* causing urinary tract infections in companion animals and humans: Population structure, antimicrobial resistance and virulence genes. Journal of Antimicrobial Chemotherapy 74(3): 594-602.

Marston HD et al., 2016. Antimicrobial resistance. Journal of American Medical Association 316(11): 1193-1204.

McAdams D et al., 2019. Resistance diagnostics as a public health tool to combat antibiotic resistance: A model-based evaluation. PLoS Biology 17: e3000250.

Miranda J et al., 2008. Antimicrobial resistance in Enterobacteriaceae strains isolated from organic chicken, conventional chicken and conventional turkey meat: A comparative survey. Food Control 19(4): 412-416.

Osei Sekyere J and Amoako DG, 2017. Genomic and phenotypic characterisation of fluoroquinolone resistance mechanisms in Enterobacteriaceae in Durban, South Africa. PloS One 12(6): e0178888.

Panzetta ME et al., 2018. Chlamydia persistence: A survival strategy to evade antimicrobial effects *in-vitro* and *in-vivo*. Frontiers in Microbiology 9: 3101.

Parsonage B et al., 2017. Control of antimicrobial resistance requires an ethical approach. Frontiers in Microbiology 8: 2124.

Pietracha D and Misiewicz A, 2016. The use of products containing a phage in food industry as a new method for *Listeria monocytogenes* elimination from food (*Listeria monocytogenes* phages in food industry)-A review. Czech Journal of Food Sciences 34(1): 1-8.

Pollock J et al., 2020. Alternatives to antibiotics in a One Health context and the role genomics can play in reducing antimicrobial use. Clinical Microbiology and Infection 26(12): 1617-1621.

Rahman UrS and Mohsin M, 2019. The under reported issue of antibiotic-resistance in food-producing animals in Pakistan. Pakistan Veterinary Journal 39(3): 323-328.

Rao GG, 1998. Risk factors for the spread of antibiotic-resistant bacteria. Drugs 55(3): 323-330.

Redgrave LS et al., 2014. Fluoroquinolone resistance: mechanisms, impact on bacteria, and role in evolutionary success. Trends in Microbiology 22(8): 438-445.

Reinseth IS et al., 2020. The increasing issue of vancomycin-resistant Enterococci and the bacteriocin solution. Probiotics and Antimicrobial Proteins 12(3): 1203-1217.

Reygaert WC, 2018. An overview of the antimicrobial resistance mechanisms of bacteria. AIMS Microbiology 4(3): 482-501.

Rodriguez-Beltran J et al., 2021. Beyond horizontal gene transfer: The role of plasmids in bacterial evolution. Nature Reviews: Microbiology 19(6): 347-359.

Scott L et al., 2009. Detection of numerous verotoxigenic *E. coli* serotypes, with multiple antibiotic resistance from cattle faeces and soil. Veterinary Microbiology 134(3-4): 288-293.

Smith KM et al., 2019. Infectious disease and economics: The case for considering multi-sectoral impacts. One Health 7: 100080.

Sparbier K et al., 2012. Matrix-assisted laser desorption ionization-time of flight mass spectrometry-based functional assay for rapid detection of resistance against beta-lactam antibiotics. Journal of Clinical Microbiology 50(3): 927-937.

Taft DH et al., 2018. Bifidobacterial dominance of the gut in early life and acquisition of antimicrobial resistance. mSphere 3(5): e00441-18.

Takano T et al., 2013. A new local variant (ST764) of the globally disseminated ST5 lineage of hospital-associated methicillin-resistant *Staphylococcus aureus* (MRSA) carrying the virulence determinants of community-associated MRSA. Antimicrobial Agents and Chemotherapy 57(4): 1589-1595.

Talebi M et al., 2007. Prevalence and antimicrobial resistance of Enterococcal species in sewage treatment plants in Iran. Water, Air and Soil Pollution 185(1): 111-119.

Tang KL et al., 2017. Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: A systematic review and meta-analysis. Lancet Planet Health 1(8): e316-e327.

van Cleef BA et al., 2011. Persistence of livestock-associated methicillin-resistant *Staphylococcus aureus* in field workers after short-term occupational exposure to pigs and veal calves. Journal of Clinical Microbiology 49(3): 1030-1033.

Walsh C and Fanning S, 2008. Antimicrobial resistance in foodborne pathogens--a cause for concern? Current Drug Targets 9(9): 808-815.

Wang Q et al., 2020. Occurrence and distribution of clinical and veterinary antibiotics in the faeces of a Chinese population. Journal of Hazardous Materials 383: 121129.

Weese J et al., 2015. ACVIM consensus statement on therapeutic antimicrobial use in animals and antimicrobial resistance. Journal of Veterinary Internal Medicine 29(2): 487-498.

Wegener HC 2012. Antibiotic resistance—linking human and animal health. Paper presented at the Improving

Food Safety Through a One Health Approach: workshop summary, National Academies, Press 331.

WHO 2016. Antimicrobial resistance: a manual for developing national action plans. World Health Organization Report, Rome, Italy.

WHO 2018. WHO Water, Sanitation and Hygiene strategy 2018-2025. (No. WHO/CED/PHE/WSH/ 18.03). World Health Organization, Rome, Italy.

Willey JM and van der Donk WA, 2007. Lantibiotics: Peptides of diverse structure and function. Annual Review of Microbiology 61: 477-501.

World-Bank 2017. Drug-resistant infections: A threat to our economic future: World Bank doi.org/10.1596/ 26707.

Worthington RJ and Melander C, 2013. Overcoming resistance to beta-lactam antibiotics. Journal of Organic Chemistry 78(9): 4207-4213.

Yang SC et al., 2014. Antibacterial activities of bacteriocins: Application in foods and pharmaceuticals. Frontiers in Microbiology 5: 241.

Yong D et al., 2009. Characterization of a new metallo-beta-lactamase gene, bla(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in *Klebsiella pneumoniae* sequence type 14 from India. Antimicrobial Agents and Chemotherapy 53(12): 5046-5054.

Yoshikawa TT, 2002. Antimicrobial resistance and aging: Beginning of the end of the antibiotic era? Journal of the American Geriatrics Society 50: 226-229.

Zhang J et al., 2015. Bacteriophages as antimicrobial agents against major pathogens in swine: A review. Journal of Animal Science and Biotechnology 6(1): 1-7.