Antimicrobial Resistance and Zoonotic Pathogens

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ABSTRACT

The development of antimicrobial resistance (AMR) poses serious threat to the environment, animal and human health in terms of treatment of the diseases especially zoonotic infections. The ability of microorganisms to withstand the action of antimicrobial therapy has serious consequences for treating bacterial infections and has emerged as a global health concern. Antibiotic resistance has been increased by the irrational use of antibiotics in veterinary care, agriculture and human medicine. This irrational use has made antimicrobial ineffective to treat diseases especially diseases of zoonotic importance. The phenomenon of AMR presents a serious risk to public health in addition to impairing the efficacy of medical interventions. The likelihood of spillover events is raised by the interdependence of ecosystems and the growing connection between humans and animals. The management of infectious diseases is made more challenging by the coexistence of zoonotic pathogens and antimicrobial resistance. The transboundary pathogens have infected the environment globally due to their spread and by developing antimicrobial resistance. The growing issue of antibiotic resistance, which has become a serious health hazard in practically every country in the globe, including Pakistan, has been vigorously advocated for by WHO. 'One Health' offers a variety of strategies to stop the transboundary and zoonotic spread of AMR and maintain the efficient use of antibiotics in both human and animal treatment. Resistant zoonotic pathogen strains have the potential to undermine the efficacy of current therapies, resulting in illnesses that worsen and last longer. Implementing ethical and rational use of antimicrobials, surveillance, and control strategies between human medical care, veterinary care and environmental professions can develop effective measures to reduce the threats of AMR and protect the world from this threat. WHO has started to adopt mitigation measures to have fruitful consequences and pleasant results to cope these conditions effectively.

Keywords: Antimicrobial Resistance, Zoonotic Pathogens, transboundary diseases, Public Health

CITATION

Raza AS, Sial AUR, Humayun A, Rahim MF, Khayam U, Hanif K and Zafar MA, 2023. Antimicrobial resistance and zoonotic pathogens. In: Altaf S, Khan A and Abbas RZ (eds), Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan, Vol 4: 241-250. https://doi.org/10.47278/book.zoon/2023.150

CHAPTER HISTORY Received: 05-June-2023 Revised: 10-July-2023 Accepted: 19-Aug-2023

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1. INTRODUCTION

The continuous and misuse of antimicrobials against bacteria, fungi, viruses and parasites had led to the development of resistance in them. Antimicrobial resistance is one the most discussed topic around the globe due to increased risk against disease spread and its cure. It is estimated that around 10 million deaths will occur yearly by 2050 worldwide. The pathogen becomes resistance against the therapeutic effects of antimicrobials and remain inside the body of host intact. It takes time for a pathogen to develop resistance against any specific drug, when microbe is evolved and become resistant it becomes very difficult to eliminate it from the body (Vidovic et al. 2020).

Providing a healthy and disease-free environment for human as well as for animals is now a greater challenge for researchers due to increasing threat of zoonotic pathogens. The transboundary pathogens have infected the environment globally due to their spread and by developing antimicrobial resistance (Jansen et al. 2018). These resistant pathogens are evolved to great extent in recent times, their presence in the hosts vary greatly. Biological host is required for growth and multiplication of these pathogens. Animals are considered as the perfect host for resistant pathogens (Greig et al. 2015).

2. WHAT IS RESISTANCE TO ANTIMICROBIALS?

Antimicrobial resistance is the resistance against antibiotics or any antimicrobials by virus, bacteria and some parasites to inhibit their function. It must be due to their overuse or misuse for a long time against the disease. With the advancement of time, microbes become resistant to different antimicrobials and spread the disease without any hindrance. The widespread use and abuse of antimicrobials in the fields of both animal and human health has caused the expansion of resistant bacteria that are resistant to the wide range of medicines that are currently accessible (Tang et al. 2023).

The growing issue of antibiotic resistance, which has become a serious health hazard in practically every country in the globe, including Pakistan, has been vigorously advocated for by WHO. The Pakistani government has committed to taking on the problem as a top priority on a global scale. The Ministry of National Health Services Regulations and Coordination is collaborating with the provinces, the veterinary industry, and health development partners to increase national capacity in strengthening laboratory diagnostics and surveillance, promoting the prudent use of antibiotics, preventing and controlling infections, and educating communities on the prevention and management of antibiotic resistance (Greig et al. 2015).

Pakistan just finished creating a national action plan to combat antimicrobial resistance with WHO's assistance; this plan will now be converted into priority-based province operational plans (Jansen et al. 2018).

3. MECHANISM OF ANTIMICROBIAL RESISTANCE AND ITS TRANSMISSION

Antimicrobial substances may prevent the growth of different bacterial colonies (bactericidal substances, such as beta-lactams) or kill them (bacteriostatic substances, such as macrolides and lincosamides). Penicillin, aminopenicillins, and cephalosporins, for example, are beta-lactam antimicrobials that prevent the production of the cell wall (peptidoglycan) (Nhung et al. 2017).

Beta-lactamases, which destroy the beta lactam ring of the gram negative bacteria, is one mechanism of beta-lactam resistance. Alterations to the cells, such as penicillin-binding proteins in Gram-positive cocci. The Beta-lactamases can hydrolyze cephalosporins, beta-lactam/beta-lactamase inhibitor combos, and narrow-spectrum penicillin in Enterobacterales (e.g., *Escherichia coli*) (Rodríguez et al. 2019).

AMR can be caused through chromosomal or extrachromosomal gene alterations, as well as by acquiring resistant genes from different organisms. The treatment protocol by the use of antibiotics, encourages the interchange of resistant elements both within and across bacterial growth and results in the formation, survival, and proliferation of resistant clones. The pathogens have certain genome which has the ability to become resistant to certain bacteria and increase the risk of AMR. The antimicrobials like carbapenems and several generations of cephalosporins, plasmids are of particular significance. Bacteriophages can also be used for transformation or transduction of genetic material (Migura et al. 2022).

4. DRIVING FACTORS OF ANTIMICROBIAL RESISTANCE

There are numerous causes for the occurrence, selection, and spread of AMR. Antimicrobial resistance is well known to be stimulated by the continuous and overuse of antimicrobials by the humans. Between 2000 and 2015, usage of antibiotics in people grew by 65%. Different antimicrobial drugs are utilized for prophylactic and growth stimulation in addition to treating animal diseases as a way to sometimes combat poor hygiene. Since resistant bacteria can spread through human and animal interactions, the medicine in humans as well as in animals should be considered to have a therapeutic index and might be used according to requirement of infection (Mader et al. 2021).

5. DISEASES BY ZOONOTIC PATHOGENS

A zoonotic illness is one that spreads spontaneously between humans and vertebrate animals, such as wild animals, domesticated animals, or cattle. According to estimates, these diseases account for roughly 60% of all emerging diseases and 58% of all human infections (Dafale et al. 2020). A foodborne disease is one that is contracted after consuming tainted food, whether it is due to a parasite, viral, bacterial, or chemical agent (Mader et al. 2021).

6. PREVALENCE OF ANTIMICROBIAL RESISTANCE IN BACTERIAL ZOONOTIC PATHOGENS

One of the biggest risks to global food security and human health is the propensity of bacterial diseases to develop resistance to antibiotics. The MIC (minimum inhibitory concentration) value, or the lowest amount of the medicine necessary to stop the growth of a bacterial culture, can be used to measure antimicrobial resistance (AMR) to a certain medication. While bacterial isolates are frequently categorized as sensitive or resistant for practical purposes, MIC is a continually fluctuating feature (measured discontinuously) (Bhat 2021).

6.1. ANTI-MICROBIAL RESISTANCE IN *STREPTOCOCCUS SUIS*

Streptococcus suis is primarily found in pigs as a commensal, colonizing in the gut area, nasopharynx and vaginal region. However, it can also cause severe respiratory and systemic illness, especially in young ones. *S. suis* causes a dangerous zoonotic illness that was also the main reason for bacterial meningitis in Vietnam for a long period of time. Moreover, certain autogenous vaccines are employed in the pig industry, they are serotype-specific and offer patchy cross protection against heterogeneous *S. suis*. Antimicrobials are still the go-to treatment for *S. suis* as a result, and as a result, *S. suis* is a major factor in the use of antibiotics in pig farms (Dafale et al. 2020).

In addition to being a major issue in and of, this also offers special advantages as a model for researching antimicrobial resistance. *S. suis* is present in the majority of pigs, if not all of them, pork is the most widely consumed meat in the world by weight. Furthermore, compared to other animals, such as cattle (45mg) and fowl (148mg), pigs use more antibiotics (172mg per population corrected unit). They are comprised of antibiotics which are taken directly against *S. suis*, whether as a treatment, prophylactic, or meta-phylaxis, but also, and maybe more frequently in relation to different bacterial infections and in certain countries as growth enhancers. It is anticipated that the high selection pressure brought on by the extensive use of antibiotics in pig farming will result in AMR in *S. suis* (Hadjirin et al. 2021).

6.2. ANTI-MICROBIAL RESISTANCE IN *M. TUBERCULOSIS*

In contrast to *M. tuberculosis* (mTB), which primarily affects humans, *M. bovis* (bTB) is the main cause of tuberculosis (TB) in different domestic and wild animals. *M. bovis* can transmit zoonotic TB (bovine tuberculosis) to humans through eating, inhalation, and less frequently contact with mucous membranes and torn skin. Despite having a close genetic link, members of the MTBC, particularly *Mycobacterium tuberculosis* (mTB) and *Mycobacterium bovis* (bTB), have different host preferences and a different geographic distribution for the formation of tuberculosis. The prevalence of *M. bovis*-caused bovine tuberculosis is rising worldwide, especially in poor countries. *M. bovis*-caused bovine tuberculosis is becoming more common worldwide, especially in developing nations. However, there are few researches in Pakistan that concentrate on *M. bovis* illness in humans and its risk factors (Borham et al. 2022).

6.3. ANTI-MICROBIAL RESISTANCE I N ESBL-*E. COLI*

Escherichia coli that produces extended-spectrum beta-lactamases (ESBL) is most commonly found in chicken, therefore there is a chance that ESBL-producing *E. coli* could be imported into Africa through poultry products. Since chicken is the food source of choice for *Escherichia coli* that generates extended-spectrum beta-lactamases (ESBL), there is a possibility that poultry products could be used to introduce ESBL-producing *E. coli* into Africa. Although the proportion of *E. coli* that must be ESBL in aquacultures can be high (27%) the majority of our knowledge of how marine animals affect human health is limited by the generally subpar quality of published studies. *E. coli* that produces ESBLs has a colonization rate of 1-9% or 3-63% in bats and birds, respectively. Since the majority of them are migratory animals, they can spread bacteria resistant to antibiotics over long distances. Said "filth flies" are a significant carrier of resistant bacteria and gastrointestinal disorders in places with poor sanitation systems (Sajeev et al. 2023).

6.3.1. PREVALENCE OF ESBL IN ASIA

In comparison to Africa, Asia has a significantly greater frequency of ESBL-producing E. coli in meat samples and cattle. It is estimated that 54-93% of chicken meat samples and 35-75% of hog meat samples had ESBL-producing *E. coli*. In contrast, research done in Thailand and Cambodia found that contamination rates for both pork and poultry were less than 4%. In addition to ESBL, meat from Asia is frequently infected with microbes that carry the mcr-1 gene (Sajeev et al. 2023).

7. COMMON ZOONOTIC BACTERIA WITH AMR IN THE FOOD CHAIN

Resistance among zoonotic bacteria, which spread through food, has increased as a result of the overuse or rather misuse of antimicrobials combined with poor hygiene in the food production chain. They are the major risk to people's health. Since more than a decade, campylobacteriosis has been the most often reported zoonosis in humans in the European Union and the most common bacterial food-borne infection overall (Álvarez-Molina et al. 2021).

Food-borne outbreaks found in places where salmonellosis is most frequently diagnosed. Fluoroquinolones are regarded as being of vital importance for treating both zoonosis in humans with severe instances. Additionally, the efficacy of treating human Campylobacter infections with fluoroquinolones has been impaired as a result of an extraordinarily high prevalence of resistant isolates, particularly from broilers and meat (Korsgaard et al. 2022).

8. ANTI-MICROBIAL RESISTANCE IN AQUACULTURE

According to Food and Agriculture Organization (FAO), aquaculture is the farming of aquatic species such as fish, mollusks, crustaceans, and aquatic plants in inland and coastal environments. The lack of environmental separation between aquaculture production systems and the environment in many nations causes an increased risk of AMR residues in animal farming and nearby waters that damage wild fish, plants, and sediments (Olaru et al. 2023). This alters the makeup of environmental bacteria and promotes the selection of bacteria resistant to antibiotics. There are significantly varied numbers of antimicrobial compounds authorized for use in aquaculture in different nations. The use of different medication in aquaculture must be based on some clinical and research based knowledge, proper assessment and diagnosis of diseases must be discussed and set some sort of SOPs to cope different ailments at farm level. Any attempts for the administration of antimicrobials on the surrounding or worldwide basis, however, are hindered by the lack of defined AMU indicators for aquaculture (Olaru et al. 2023).

9. ANTI-MICROBIAL RESISTANCE IN VETERINARY MEDICINE AND FOOD ANIMALS

The overuse of antibiotics in veterinary care and in animals raised for food is encouraging the evolution of antibiotic-resistant bacteria in both zoonotic pathogens and the normal bacterial flora. The connection between AMR and animal and human morbidity is a significant issue for contemporary medicine. Even though zoonotic infections are the subject of substantial research, there is still a need for adequate control, regulation, and human usage of antimicrobial agents (Thapa et al. 2020) . Additionally, the use of antibiotics in manure for agricultural purposes spreads the antibiotics throughout several biological niches, including the soil and water. These antibiotics when enters into water bodies cause the proliferation and the chances of AMR spread accordingly. The spread of antibiotic resistance in the environment is seen as a worldwide danger, and AMR is recognized as preeminence in the World Bank's most recent One Health approach framework (Torres et al., 2021).

10. ZOONOTIC PATHOGEN AS AN AMR CARRIER

- Environmental pollution, antibiotic resistance, and chronic diseases have in the past jeopardized the health of both humans and animals, causing significant rates of death and morbidity (Jones et al. 2008).
- The majority of infectious illnesses are regarded as serious health problems with zoonotic origins. The World Health Organization (WHO) defines zoonotic illness or zoonosis as "any disease or infection that are naturally transmitted between vertebrate animals and humans." An infectious agent that causes disease could be a virus, fungus, bacteria, parasite or prions (Alexander et al. 2018).

- Approximately 200 zoonotic pathogens are known to exist in the globe today; some are restricted to a certain region, while others are said to have a global distribution. Transmission methods for zoonotic pathogens include ingestion, inhalation, and other methods that contaminate mucosal membranes (Schmeller et al. 2020).
- Additionally, zoonotic infections can be consumed through undercooked meat, unpasteurized milk, dairy products, shellfish, and infected vegetables, all of which include animal tissue. Anthrax, animal influenza, bovine tuberculosis (BTB), brucellosis, hemorrhagic colitis, zoonotic diphtheria, rabies, and Q fever are additional well-known zoonotic diseases (Shanks et al. 2022).

11. ZOONOTIC PATHOGENS FEATURING ANTIBIOTIC RESISTANCE

According to one health approach, domesticated animals which are frequently linked with humans are the ones that act as a reservoir for zoonotic infections. Animal husbandry is a crucial component of the agricultural economy and supports the rural population's way of life. Milk, meat, eggs, and wool are products of animal husbandry that have a direct impact on the human population. Animal husbandry has a very high risk of transmitting zoonotic diseases to humans from their hosts. Despite the high danger of zoonotic infections, livestock is essential for many farmers' livelihoods, household nutrition, and the consumption of animal products. There have been recently numerous reports of zoonotic illnesses carrying anti-microbial resistant genes that, when contracted, can infect humans (Binot et al. 2015).

The inappropriate use of antibiotics has led to anti-microbial resistant genes in zoonotic diseases. Animal husbandry treats the entire herd with antibiotics for any infectious diseases to stop the spread of illness, even when some animals have clinical symptoms. Meta-phylaxis is the term for the procedure of administering a high dose of antibiotics for a brief course, whereas prophylaxis refers to the blending of antibiotics with the feed in modest doses for an extended period of time, typically for many weeks. Even though the animals are not showing any clinical symptoms at this time, the risk of infection still exists (Chang et al. 2015).

The improper use of antibiotics places microorganisms under a selection pressure that causes antibiotic resistance at concentrations of antimicrobials below the therapeutic range. Various mechanisms, including as mutation, alterations in cell permeability, horizontal gene transfer, drug efflux, and quorum sensing, are used by different bacterial species to acquire resistance. Increased prevalence of resistant bacteria in the intestinal flora of pigs, chickens, and other agricultural animals has been linked to the transmission of anti-microbial resistant genes and heavy antibiotic use (Dafale et al. 2020).

12. VARIOUS METHODS FOR ANTIBIOTIC DEGRADATION

Antibiotic use and disposal have increased, which disrupts other biological processes and water quality. Antibiotic degradation is therefore required to prevent the formation of new resistant bacteria and anti-microbial resistant genes (Wester et al. 2017). Both abiotic and biotic processes break down antibiotics. It is aided by hydrolysis, metal-assisted photolysis, adsorption mechanisms, bio-electrochemical processes, oxidation, and reduction. (Chang et al. 2015).

12.1. ANTIBIOTIC PHYSICAL-CHEMICAL DEGRADATION

- Antibiotics physicochemical characteristics and molecular structure play a significant role in abiotic degradation. Compared to macrolides and sulfonamides, ß-lactam antibiotics are reportedly more vulnerable to hydrolytic breakdown (Liu et al. 2016).

- Fluoroquinolone antibiotics are primarily broken down via photo-degradation. Waste water is decontaminated and its antibiotic content is reduced through chlorination and UV radiation treatment (Robbiati et al. 2023).
- To limit the extent of anti-microbial resistant microorganisms and anti-microbial resistant genes, natural polysaccharide chemical conjugates can be used in addition to degrading antibiotics to stop the growth of resistant bacteria (Collignon et al. 2019).
- An antibiotic's antibacterial capabilities are lost when it attaches to soil particles and forms a complex, according to research. Adsorption and desorption of antibiotics are two terms that describe this process. In this approach, the soil's pH and water holding capacity are crucial factors (Wester et al. 2017).
- The cationic form of antibiotics like sulfonamides transforms to the neutral and anionic form as they are absorbed in soil. Antibiotic breakdown is dependent on abiotic factors. Waste water is decontaminated and its antibiotic content is reduced through chlorination and UV radiation treatment. In order to limit the extent of anti-microbial resistant microorganisms and anti-microbial resistant genes, natural polysaccharide chemical conjugates can be used in addition to degrading antibiotics to stop the growth of resistant bacteria. An antibiotic's antibacterial capabilities are lost when it attaches to soil particles and forms a complex, according to research. Adsorption and desorption of antibiotics are two terms that describe this process (Falenski et al. 2011).
- In the sorption approach, the soil's pH and water holding capacity are crucial factors. The cationic form of antibiotics like sulfonamides transforms to the neutral and anionic form as they are absorbed in soil (McEwen et al. 2018).
- Abiotic antibiotic degradation is influenced by a number of physical and chemical factors. The abiotic treatment may be hampered by pH changes, salt concentrations, and the presence of other compounds in the system. In such circumstances, biotic mechanisms that include the use of microorganisms may be essential for removing lingering antibiotics from the environment (Sajeev et al. 2023).

12.2. BIO AUGMENTATION-INDUCED ANTIBIOTIC DEGRADATION

- Antibiotics are subject to biotic breakdown when they pass via a possible microorganism metabolic pathway. anti-microbial resistant genes are primarily involved in microorganisms that efficiently break down the parent antibiotic or functional group and release the byproducts, which contribute in the bioremediation of antibiotics (Hong et al. 2020).
- It has been demonstrated that bio augmentation can successfully remove antibiotics from industrial wastewater. Numerous bacterial strains have been used to remove antibiotics from soil and wastewater (Xu et al. 2017).
- Similar to this, it has been reported that bio augmentation of membrane bioreactors with Achromobacter dentrificans improves sulfamethoxazole elimination (Falenski et al. 2011).
- An effective way to remove antibiotics from the environment is bio augmentation (Chang et al. 2015).

13. THE WIDESPREAD RESISTANCE: ONE HEALTH APPROACH

AMR can be fatal, yet there are effective, adoptable remedies that are still hidden. Due to its multidimensional, linked, and diverse ecological aspects, understanding the AMR pattern is difficult. The right usage of antimicrobial products in diverse areas must be decided upon by individuals and society as a whole in order to control widespread resistance (Tang et al. 2023).
A multi-sectoral approach to oversight, involving teams from the veterinary, environmental, and healthcare sectors as well as stakeholders, is necessary to understand the complex AMR situation

(McEwen et al. 2018). A method known as "One Health" entails interdisciplinary cooperation between academics, policymakers, and leaders operating at the regional, municipal, national, and worldwide levels. This strategy aims to improve human, animal, and environmental health outcomes. A priority of the "one health" approach is the onset of epidemic illnesses involving AMR (Sajeev et al. 2023). In order to comprehend the AMR issue and identify competent solutions to create appropriate usage guidelines and deliver efficient risk messaging, this strategy brings together many sectors operating in the field. Another issue that requires a broader explanation is the spread of AMR. This problem includes the transfer of germs between human hosts, animals (both domestic and wild), and the environments in which each can thrive (Wester et al. 2017).

Understanding zoonosis-mediated AMR is a problem that affects everyone, including the scientific community, producers of food animals, healthcare workers, patients, and customers. 'One Health' offers a variety of strategies to stop the trans-boundary and zoonotic spread of AMR and maintain the efficient use of antibiotics in both human and animal treatment (Robbiati et al. 2023).

14. ONE HEALTH STRATEGIES TO COMBAT ANTIBIOTIC RESISTANCE

In order to address the antimicrobial resistance challenge, the WHO, other international organizations (such as the Food and Agriculture Organization FAO) and the World Organization for Animal Health (OIE), as well as numerous individual nations, have established detailed action plans. The five main goals of the WHO Global Action Plan are described in the subtitles of the sections that follow. In order to address antibiotic resistance, the WHO Plan adopts a One Health strategy, and it encourages member nations to follow suit when creating their own action plans. The WHO Global Plan is supported by five fundamental pillars (Wester et al. 2017).

1. Enhance Antimicrobial Resistance Awareness and Understanding Through Effective Communication, Education, and Training
2. Using surveillance and research, improve the body of knowledge and evidence
3. Utilize Effective Sanitation, Hygiene, and Infection Prevention Measures to Decrease the Incidence of Infection
4. Improve Antimicrobial Drug Use for Human and Animal Health
5. Increase investment in new drugs, diagnostic tools, vaccines, and other interventions while developing the economic case for sustainable investment that considers the needs of all countries (Álvarez-Molina et al. 2021).

World Health Organization has devised some plans under the umbrella of one help to limit the usage of antimicrobial and to hinder the antimicrobial resistance, some recommendations and strategies are also proposed at domestic and international levels to set some criteria and SOPs to work on minimizing the antimicrobial resistance worldwide. The main difficulty which scientists and researchers face today is the availability of data regarding disease spread and antimicrobial usage hence it’s a long journey to continue and work for the betterment of human as well as for animal health. The concept of one health helps a lot to cope up this condition but still there are many things to do regarding our strategy and still more work needs to be done to minimize the risk of antimicrobial resistance from our ecosystem (Collignon et al. 2019).

15. CONCLUSION

Antimicrobial resistance is still a significant problem for worldwide public health in the twenty-first century. The G7 nations have already made significant political contributions to this issue and is a priority for a number of political conferences. Zoonotic pathogens are of great concern in this regard as they directly affect our lives and their spread leads to pandemic situation. WHO has started to adopt mitigation measures to have fruitful consequences and pleasant results to cope these conditions effectively.

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