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No Action Today, No Cure Tomorrow - A Review of Agricultural Factors Predisposing Humans at The Risk of Antimicrobial Resistance and Its Preventive Strategies

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ABSTRACT

One of the most significant public health issues today is AMR (AMR), which poses significant difficulties in controlling and treating infectious diseases. It is believed that the abuse and overuse of numerous antibacterial agents in the healthcare and agriculture industries led to the emergence of antimicrobial resistance. Even though irrational prescriptions have been blamed for the rise in resistance among microbes to various antimicrobial drugs, a variety of environmental factors have also been linked to the development of multidrug-resistant (MDR) organisms. Several studies have stressed the significance of using a one-health approach, or a holistic strategy, to combat antibiotic resistance that takes into account people, animals, and the environment. Models describing how resistance starts and spreads could be created with a better understanding of the environmental factors that encourage its development. Yet, preventing the establishment and spread of mobile resistance elements is challenging since it is unclear how and when the environment favors resistance growth. Hence the current review focuses on the agricultural factors predisposing humans to the risk of AMR and preventive strategies.

Keywords: Antimicrobial Drug Resistance, Agriculture, Prevention and Control.

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INTRODUCTION

Antimicrobial resistance (AMR) is now being considered among significant public health concerns, providing substantial barriers to infectious disease treatment and prevention. Despite various efforts being made in current times to address this issue, global AMR trends display no sign of abating[1]. AMR is assumed to have evolved as a result of the inappropriate and overuse of numerous antibacterial drugs in both the medical and agricultural sectors. AMR is additionally impacted by the process of bacterial evolution, bacterial mutation, and the

horizontal gene transfer of resistant genes[2]. Though the increase in resistance among microorganisms towards various antimicrobial agents has been attributed to irrational prescriptions, however, various environmental factors are responsible for the development of multi-drug resistant (MDR) organisms[3]. Several researchers have emphasized the importance of taking a holistic approach to tackle antibiotic resistance that considers animals, humans, and the environment—a so-called one-health approach. An increased understanding of the environmental elements that facilitate the development of resistance could lead to the generation of models for how resistance originates and spreads. However, mitigating the creation and spread of mobile resistance elements is difficult due to a lack of understanding of how and under what conditions the environment favors resistance development. Furthermore, irrational and unmonitored use of antibiotics in various fields of agriculture (Plants, Livestock, Crops) facilitates in development of AMR[4, 5]. Therefore, the current review focuses on the agricultural factors that are responsible for predisposing humans to the risk of AMR and strategies to combat it [6, 7].

This review study discusses the agricultural factors predisposing humans at the risk of antimicrobial resistance and strategies to combat it. The related literature was explored by using public search engines and electronic databases like MEDLINE, PUBMED, Google Search, and Google Scholar. The proper keywords for the topic-specific search were "Antimicrobial resistance, Agricultural factors, Improvements in prevention, ways to combat antimicrobial resistance established as a result of agricultural goods, etc.

DISCUSSION

AMR has become a serious public health risk around the world, with 10 million fatalities anticipated by 2050. AMR emerges when antimicrobial treatments are ineffective against various pathogens such as "viruses, bacteria, fungi, and parasites", allowing the microorganism to survive within the host. AMR has been referred to as the "Silent Pandemic" and AMR is a concern that requires immediate attention and should be controlled more effectively rather than being seen as an issue that might arise in the future[8]. One of the primary contributors to the existing problem can be the consequences of antibiotic abuse or irresponsible usage in a range of situations, mostly clinical treatment, but also agricultural use, animal healthcare, and the food system[9]. Several recent researchers have found that the use of antimicrobials in food systems and agriculture may have a substantial influence on AMR. According to reports, 70% of antibiotics used for treating humans are also being used in veterinary medicine in the United States. Recognizing the broad use of antibiotics in global agriculture, several organizations, notably the World Health Organization (WHO), the European Union (EU), and the United Nations (UN) have taken initiatives to minimize and limit antimicrobial use in animals. Furthermore, legal restrictions on the use of various antibiotics in agri-food systems for growth promotion have been imposed, along with initiatives regarding antimicrobial stewardship programs in the treatment of food animals and small companies. However, such limitations may be hard to apply in emerging countries where demand for food animals continues to climb year after year. Hence, the review focuses on the agricultural factors that are responsible for predisposing humans to the risk of AMR and strategies to prevent it[8, 10, 11].

Mechanisms of Development of Resistance in Bacteria

To evaluate the environmental factors that are causing the increase in antimicrobial resistance, it is important to understand the mechanisms that are responsible for the resistance development in bacteria [12]. These mechanisms can be categorized as, (i) Intrinsic resistance, where the resistance is because of the bacterium's inherent features such as enzyme (penicillinase) production by gram-positive organisms and the presence of glycopeptide layer in bacterial cell envelope's outer membrane that prevents the entry of drugs inside the organism. (ii) Acquired resistance i.e., an earlier sensitive bacterium becomes resistant through the acquisition of new genes by gene transfer horizontally or through mutation, and (iii) Adaptive resistance i.e., antibiotic resistance triggered by a specific environmental stimulus. It subsides once the trigger is removed [7, 13, 14].

There are three approaches used by bacteria to acquire genetic material, (a) Transformation: This is a type of genetic recombination in which free DNA pieces from a dead bacterium are incorporated into the chromosome of a recipient bacterium. Only a few microorganisms can naturally change. (b) Transduction, A bacteriophage transfers genetic material from a donor to a recipient bacterium and (c) Conjugation, horizontal gene transfer is most likely accomplished using this technique. It includes the direct physical genetic material transmission from one cell of bacteria to another. A plasmid is transferred from the donor cell to the receiving cell through a sex pilus produced by the two bacterial cells. Multiple resistance genes are often located on a single plasmid, allowing for multidrug resistance to be delivered in a single conjugation event[13, 15-17].

Agricultural Factors

Soil has been considered to be a rich source of antibiotics and antibiotic-resistant genes due to natural and anthropogenic activities. Anthropogenic pressure may be caused by antibiotics used in healthcare or livestock that are discharged into the

marine environment via wastewater treatment plants. Current water waste treatment plant systems only partially remove antibiotics, as well as other organic contaminants hence increasing the antibiotic concentration in the agricultural fields and providing exposure of different antibiotics to organisms that leads to the initiation of the resistance generation process. We found evidence that antibiotic-resistant genes can reach edible parts of commercial crops, and their concentrations and presence are affected by agricultural practices. Animal manure application has become a significant environmental concern [21]. According to one study, when compared to mineral fertilizer, the usage of commercial organic fertilizer and composted manure significantly increased the abundance of antibiotic-resistant genes and pathogens, particularly in surface soil and pakchoi roots. The results of this study highlighted the vertical migration of antibiotic-resistant genes and pathogens in vegetables and soil and indicated that how the mutant genes or pathogens are transferred from agricultural fields to human hosts [22].

The antibiotics used in agricultural fields and grass or food used by animals as their chow are also thought to be a connective link between the transfer of resistant genes from agricultural fields to human hosts [23]. The animals play a crucial role in this cycle. The grass or food used as their chow contain bacterial residue and also antibacterial compounds, the presence of both of these in animal-derived products (kidney, muscles, fat, liver, egg, and milk) leads to the transfer of resistant genes or organisms to human host as well as antibacterial residue in animal products also exposes the bacteria to suboptimal concentrations of antibiotics that further increases the resistance development risk [24, 25].

Understanding the cycle of transfer of resistant microorganisms and antibacterial residue at suboptimal doses from agricultural fields to humans can help in establishing policies to overcome the current scenario and also can be used to plan interventions to break this cycle that may help in reducing the burden or resistant organisms as well as antibiotic resistance that is posing a serious risk to society and if not intervened at right time this will lead us to era before 1928 when we were not having antibiotics to treat the infections [26-28].

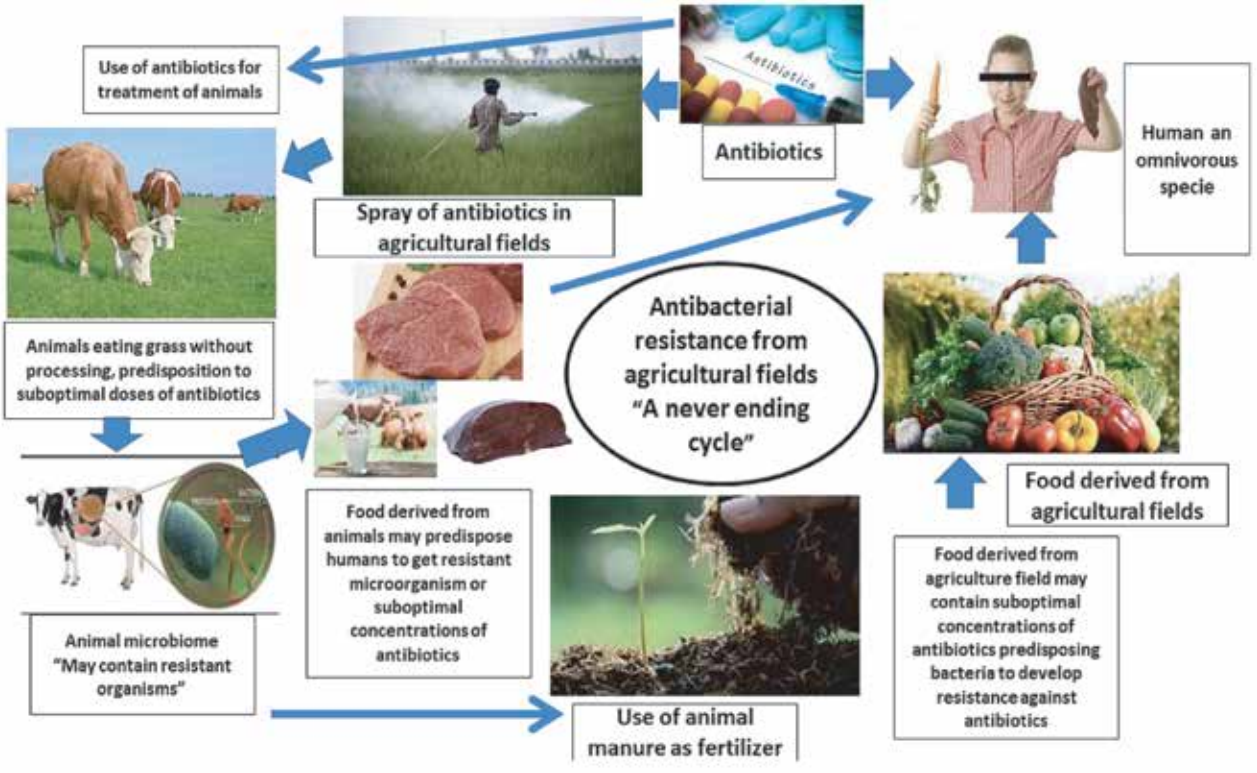

Figure 1. Agricultural factors predisposing humans towards antibacterial resistance

Alternative Strategies to Encounter Antibiotic Resistance in the Agricultural Sector

As discussed earlier, the imprudent and widespread use of antibiotics in agriculture to boost crop output and in animals as growth promoters has resulted in the emergence of AMR to a large extent[29]. Keeping in view the extent of this major public health concern, numerous programs have been initiated

and implemented worldwide by various government and public health specialists. Their recommended options include setup up of nationwide target for reduction in antibiotic use, good health practices, tracking down antimicrobial usage, tracking veterinarians and other healthcare professional who prescribe antibiotics, reliable diagnostics, and managing practices to reduce the spread [29-31].

Along with that, various strategies have been outlined to achieve advancements in the field of biotechnology which includes the use of carbohydrate-modified compounds, antimicrobial peptides, combination therapies, or the use of non-antimicrobials to develop new antibiotics with the potential to solve the global AMR problem[32, 33].

Farming Practices

Carefully controlled extensive farming techniques using a slight amount of chemical substances that are good for animal health whilst preventing the occurrence of infectious diseases and lessening antibiotic usage should be encouraged instead of ancient farming practices[34]. Organic farming practices have been deemed as an appropriate way to satisfy global food requirements while minimizing the excessive use of antimicrobial agents; nevertheless, further research is required to determine the features associated with such practices and boost production. [35]. In 1986, Sweden implemented a complete ban on growth promotors in their food production industry and it is one of the World's references to restrict the use of antibiotics in the food chain through well-regulated and adequate farming [32].

Immunization in Livestock

Due to increased global food requirements Farmers' reliance on antibiotics or growth promoters to generate significant amounts of animal protein at a low cost has grown. However, evidence suggests that enhancing animal health and well-being can minimize antibiotic reliance without affecting cost or production. Utilization of vaccines is highly endorsed in livestock to prevent them from infections which eventually leads to a reduction in antibiotic consumption. To protect animal health, mass vaccination programs should be initiated, the higher the usage of vaccines, the lower the incidence of infections[37, 38].

Ban on Unrestricted Antibiotic Use and Legislative Regulation

The unrestricted usage of antibiotics should be banned and only be allowed when it's under a veterinary prescription. When classes of antibiotics permitted to prevent infectious disease in humans as well as animals are employed, substantial veterinary control should be emphasized 39. It is also essential to create ways for justifying antibiotic use, as well as indicators to track success and guidelines for taking veterinary medicines. However, the global burden of antibiotic resistance has outpaced the rate of new antibiotic development for clinical use, resulting in a drastic rethinking of antibiotic use [40]. According to WHO, all LMICs should identify their annual consumption of antibiotics in animal food and prohibit the use of "critically, high, and important antimicrobials in human medicine" as well as those that are not currently approved for veterinary use. Achieving stability between minimized antibiotic use in the farming sector and fulfilling the unprecedented global food demand is very challenging as well and defining target goals to limit the use of antibiotics in the food chain is also a crucial step. It is therefore crucial that every country must involve all the stakeholders from different sectors to set realistic and achievable goals to reduce this burden [41-43].

Integrated Surveillance and Monitoring Systems

The determination of resistance load from diverse ecological niches in the food chain (farm, market, and human consumption) is a critical step in addressing this worldwide concern. A monitoring system for the integrated food chain is obligatory to develop. Therefore, to conduct sustainable epidemiological studies from farm to fork complying with one health approach, and reporting active, passive, and different outbreak data sources are important to fill these information gaps. Furthermore, to evaluate and monitor the impact of public awareness campaigns on antibiotic use and its adverse consequences on human health should be initiated [44, 45]. The information that will be generated through such surveillance systems will eventually help the decision-makers and authorized people to make evidence-based decisions and effectively allocate the resources to prevent and reduce food chain-associated ABR[46].

To cope with the situation, in November 2012, Pakistan formed its national body, the "Division of Pharmacy Services of the Drug Authority of Pakistan (DRAP)", but the laws drafted have not yet been properly followed. Similarly, Pakistan has enacted a policy restricting the use of antibiotics in animal husbandry; however, the regulation has yet to be strictly enforced. Further to this, As part of its commitment to the global action plan to combat AMR, Pakistan has recently produced its national strategy framework for AMR containment, to convert it into an AMR National Action Plan (NAP) using the "One-Health" approach however, till date no outcome of any policy has been reported in this regard[47].

CONCLUSION

The irrational use of antibiotics in agriculture has contributed to the development of MDR organisms. Hence, antibiotics usage in agriculture has a link to

causing life-threatening infections in humans that are difficult to treat. Therefore, the usage of antibiotics in agriculture should be rationalized and policies for monitoring evaluation should be developed to precheck the agricultural products before distribution in the markets. Furthermore, awareness among the farmers regarding the use of antibacterial products should be promoted.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHORS CONTRIBUTION

Author AA conceptualized the study, and formatted the draft facilitated in writing and literature search. Author NK and SWS managed the literature search and facilitated in writing of discussion and referencing. Author SHD critically reviewed the article and facilitated in finalization of the manuscript.

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