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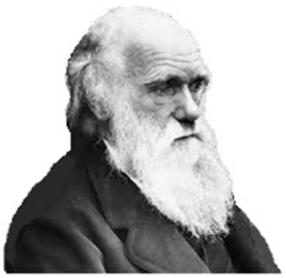

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Vaccine as a remedy for antimicrobial resistance; what are the Pros and Cons?

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ABSTRACT

Before microorganisms were discovered as the causative agents of diseases, it was taught that diseases occur as a result of an imbalance in energy channels within the body system. With the advent of antimicrobials drugs to cure these diseases in both humans and animals, these antimicrobial drugs turn out to be ineffective as a result of overuse and misuse that lead to antimicrobial resistance. Antimicrobials resistance is a silent pandemic having high morbidity and mortality that result in the death of over 1.2 million people worldwide as of 2019. Antimicrobial drugs are meant to prevent and treat disease but as a result of irrational usage, they pose great risks to humans, animals, and also the environment. This resistance is the major cause of persistent diseases and there is a need to avert its transmission and prevent further occurrence through a multidisciplinary approach, approaches to vaccine design and development, and also strengthening health care services delivery.

Keywords: Antimicrobial drugs, Antimicrobial resistance, Vaccines, Pros, Cons

1. INTRODUCTION

Since the existence of life, humans, and animals are afflicted with several diseases caused by various infectious agents or microorganisms such as viruses, bacteria, fungi, and protozoans which are widely distributed in the environment (Morand *et al.*, 2014). Nevertheless, several ways were developed in tackling, preventing, and controlling these infectious agents from

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causing infection (Forder, 2007). These ways include vaccination, implementation of biosecurity, and antimicrobial therapy in both the human and animal populations. Vaccines and antimicrobials showcase a promising result and also play an important role in human, animal, and plants health (Calderon Diaz *et al.*, 2020).

Antimicrobials are agents or substances obtained from plants, animals, or minerals used for the treatment of diseases if they are provided in a sufficient quantity to act at a specific site within the system. They are also used as growth promoters in food animals and also as in antimicrobial prophylaxis. They are usually classified based on their action or effect against particular infectious agents or microorganisms that is, antifungal, antibacterial, antiviral, and antiprotozoal that act against fungi, bacteria, viruses, and protozoans respectively (Stephany, 2010).

These antimicrobials act via various pathways which include: inhibition of cell wall production, damages to the cell membrane, inhibition of synthesis of protein, alteration of protein synthesis, inhibition of enzymes involved in DNA synthesis, inhibition of nucleic acid function, and interfere with the metabolism of the microorganisms.

Antimicrobials are essential in our daily lives because they are used in the treatment of diseases affecting humans, animals, and plants. Some often-used antimicrobials as prophylactic and growth promoters in food animals. Especially in developing countries antimicrobials are randomly used in animals and humans without control, they are been sold anywhere without regulation and irrational use of drugs such as improper dosage, treatment of diseases of unknown origin, continuous treatment of an infection that is non-responsive to drugs, improper laboratory diagnosis and excessive use of drugs on food animals especially poultry, beef cattle, dairy cattle, sheep, and goats. This leads to what's referred to as antimicrobial resistance.

Over nine-decade ago, precisely 1928, a Scottish scientist Sir Alexander Fleming discovered the first antibiotic known as penicillin. Twenty (20) years later there's a development of antimicrobial resistance with the case of microorganisms becoming resistant to penicillin in 1947 (Absar and Asad, 2021). However antimicrobial resistance is a major global challenge faced by public health due to the misuse of antibiotics in agriculture, humans, and animals. Some antibiotics are obtained from soil habitat microorganisms which later become resistant to the antibiotics produced intrinsically, and also a large number of antibiotics are used in municipal water supply, this caused the distribution and spread of antibiotic resistance in the environment (Francesca *et al.* 2015). This way there's a rapid development of antimicrobial resistance by microorganisms. In 2019, Antibiotic resistance accounted for 4.9 million death worldwide (Murray, *et al.* 2022). There's continued discovery and development of new drugs against infectious diseases, and still, the microorganisms keep developing resistance and this is a major dispute to drugs research and developments institutes are facing today. Therefore, more drugs need to be discovered and produced for the treatment of diseases. However, researchers provide a way of addressing antimicrobial resistance by different approaches and strategies such as vaccines, bacteriophage, microbiota transplant etc. So, in this review, we will highlight the pros and cons of using vaccines as a remedy for global antimicrobial resistance.

2. MECHANISM OF ANTIMICROBIAL RESISTANCE

Antimicrobial resistance is often transmitted between microorganisms through the exchange of new genetic materials that encode the antimicrobial resistance gene (Timothy *et*

al., 2011). These genetic materials are transmitted through their different mechanisms which include: transformation, conjugation, and transduction.

Some bacteria become resistant drugs naturally through the transfer of genetic elements from one bacterium to another bacteria, this genetic material responsible for antibiotics resistance is referred to as plasmid.

Plasmids are small circular double-stranded DNA molecules found within the cell of bacteria; plasmids are an important element in bacteria because it's responsible for antibiotic resistance. Plasmids are also found in some fungi (David *et al.*, 2019). It's very essential in the collection and transfer of antibiotic resistance genes, especially in gram-negative bacteria, development of resistance to B- lactams, tetracycline, macrolides, chloramphenicol, and other class antibiotics is an essential function of plasmids (Corneliu *et al.*, 2020). Plasmids assist bacteria in overcoming the effects of antibiotics another poison such as heavy metals. However, plasmids also have the ability to move from one bacterium and another making it causing resistance to multiple antibiotics. (Hughes, and Datta, 1983). Viruses also have the ability to inject resistance genes to any bacteria encountered.

Other mechanism involved in antimicrobial resistance includes Production of enzymes, i.e the microorganisms produce an enzyme that deactivates or destroys the antimicrobial drug. Bypassing of the pathway, where the microbes develop an alternative way to bypass or dodge the effects of the antimicrobial drugs. Decreased cell wall permeability, here there's limiting drug uptake by the organism because cell wall permeability to the drug is decreased. Other mechanisms include enzyme adaptation and altered receptor sites (Aliu, 2011).

3. IMPACT OF ANTIMICROBIAL RESISTANCE IN PUBLIC HEALTH

Antimicrobial resistance is a phenomenon whereby microorganisms particularly infectious agents develop mechanisms or approaches of eluding or avoiding an attack from antimicrobial agents that incline to either kill or inhibit their growth. This resistance mechanism occurs naturally because microorganisms already possess a strong mechanism or way of avoiding destruction from harmful and poisonous substances (Alison *et al.*, 2016). At the individual level, there's a natural development of antimicrobial resistance based on a study conducted in India which shows that neonates are resistant to B- lactam drugs without a history of using any potent antibiotics (Charu *et al.*, 2013). In both human and animal populations, antimicrobial resistance is mainly associated with the uncontrol use of antimicrobial drugs in human hospitals and food-producing animals like poultry, cattle, and fish. Therefore misuse and overuse of antimicrobial drugs instigate the development of antimicrobial resistance (Ramanan *et al.* 2013).

Moreover, the transmission of antimicrobial resistance exists between humans to humans in the community through the fecal-oral route and also as a result of poor sanitation, especially for resistance to enteric bacteria (Elizabeth *et al.*, 2013). The use of antimicrobial growth promoters in food animals is considered to potentiate the transmission of antimicrobial resistance microorganisms from animals to humans and this association was recognized in the 1960s (Anderson *et al.*, 1965). The environment also contributes to the development of antimicrobial resistance as a result of the strong use of fertilizers, fungicides, and other antimicrobials. Other pollution from industries also contributes (Alison *et al.*, 2016). Looking at the driving forces and transmission pathways of antimicrobial resistance in the community,

there's a need to avert its further spread and transmission due to its high morbidity and mortality. Antimicrobial resistance occurs in many ways, it usually occurs naturally as result of genetic alterations of the organism. Normally, the body have normal flora that protects the body from infection and also the pathogenic microorganisms that causes infection. Among these microorganisms both the normal flora and the pathogenic ones, some become resistance to antimicrobials that normally attack them. Some of the resistance microorganisms later on transfer the resistance genes to other organisms, and the condition worsened. This is how resistance to antimicrobials develop naturally.

Moreover, antimicrobials resistance also occurs in the environment when other antimicrobials are contaminated as a result of the release of industrial waste and effluents from pharmaceutical industries in to air, water and land (Mukhlesur, and Satyajit, 2020). Antimicrobials resistance is also transmitted from animals to humans through consumption of either meats, milk, eggs or any animal products that contain the drugs residue a result of poor heating or production process. For example, in some developing countries where humans slaughter animals or consumed animal milk a few days after treatments without considering the withdrawal period of those particular drugs used. However, individuals with drug resistance organisms also spread those organisms to the community or to other individuals nearby.

In developing countries, the major cause of antimicrobials resistance is free access to drugs even without prescription, majority of individuals are involved in self-medication because there's no rules governing prescription and dispensing of drugs. In this regard, policy makers have to implement laws and increase awareness in drugs dispensing.

Antimicrobials resistance varies with countries and geographical regions, resistance microorganisms may be found in a particular country and cannot be found in other country. Therefore, individuals that travels to other regions might contract resistance organisms and spread it to their home country when they are back.

Contaminated environment causes infection and diseases in a community, thereby facilitating the need for antimicrobial drugs. So, keeping the environment free of contamination is an important aspect in preventing the occurrence of antimicrobial resistance.

Other way by which human and animal develop resistance is through food chain, agriculture products that antimicrobials are used on them or trapped resistance microorganisms from the environment also causes antimicrobial resistance to humans or individuals when consumed. The use of antimicrobials in humans, animals, and agriculture needs to be regulated. Public enlightenment and awareness should be increased and also policymakers should also be involved in enforcing and implementing laws concerning the use of antimicrobials drugs and also keeping the environment free from contamination that instigates the occurrence of antimicrobial resistance. In the health sector, proper diagnostic tools with competent scientists involved in diseases diagnoses should be provided especially in developing countries with high cases of antimicrobial resistance, poor diagnosis, and treatment of diseases is the major factor responsible for the resistance.

4. IMMUNE SYSTEM AND VACCINE

The development of vaccines is one of the greatest achievements in the 19th century for the fight against diseases. A vaccine is an important tool used in the prevention of disease outbreaks and eradication of diseases in a population.

In the late 19th century, precisely 1798 Edward Jenner, an English physician was the first to demonstrate the science of vaccine against smallpox disease in humans by inoculation. Furthermore, another scientist called Louis Pasteur in the year 1879 take his footsteps in developing vaccines against several diseases including Rabies, anthrax, and pasteurellosis. The development and production of vaccines are known as vaccinology, while the inoculation of vaccines against specific diseases is referred to as vaccination. Interestingly, vaccine development begins in the laboratory, and with the advancement of science and technology, different methods were developed ranging from attenuation, cell culture, gene reassortment, inactivation, capsular polysaccharide, protein-based vaccines, and genetic engineering (Stanley, 2014). Genetic engineering and the use of animal models are highly impacted in vaccine development today.

The vaccine usually mimics the body's immune system in responding to infections and external agents. Before dwelling on vaccines, let's discuss briefly the immune system. An immune system is an approach or strategy that has been developed to protect against infection. It's broadly made up of two components, innate (natural) and acquired immunity. The immune system uses cellular and humoral mechanisms in providing immunity.

Innate immunity is the first line of defence against infection. The mechanisms of innate immunity comprise physical barriers which are made up of the skin, mucus membranes, normal flora, and another antimicrobial peptide. Phagocytic cells, lysozymes, cytokines, and other proteins kill pathogens.

Acquired immunity confers immunity following previous exposure to a particular infectious agent. It's usually brought about by lymphocytes which proliferate and mount an immune response. These lymphocytes produce comprise of B cells and T cells which, the B cells produce antibodies that are bound to pathogens and help in removing them from the body while T cells assist in eliminating the infectious agents.

Vaccines are biological substances that prepare the body's immune system against a particular disease by stimulating the immune system to produce antibodies specific to that particular agent that causes the disease. Vaccines are used before infection set in, to prevent disease occurrence and also used in disease eradication in a population. Despite vaccine development, there exists a wide gap in understanding the mechanisms by which vaccines protect inoculation (Bali, and Rafi, 2012). Therefore the immune system developed different strategies in conferring immunity from pathogens by the action of immune cells (Zhu *et al*., 2010). The T-helper cells that produce interleukin 21, differentiate B cells and generate memory cells (Shane, 2011).

T cell-based vaccines usually induce antigen that's specific to a particular memory T-cell that is usually long-lasting and can protect against further infection. However, the quality, magnitude, and persistence of vaccines that produce an immune response are regulated by the innate immune system (Bali and Rafi, 2012). Vaccines are categorized broadly into two categories; the live attenuated vaccine which contains the weak variant of the infectious microorganism, mount a strong immune response, and provide immunity that lasts for several years, i.e. long-lasting immunity. The other category is the subunit vaccine which contains adjuvants. The adjuvant may be starch oil, lecithin, alum, etc. subunit vaccines include inactivated toxins, conjugated and carbohydrates vaccines (Stanley *et al.*, 2007). Vaccines are formulated and designed in different forms and are also delivered to the various site of administration to achieve the desired effect. The most common site of vaccine delivery is subcutaneous and intramuscular routes, others are nasal mucosa and the gastrointestinal tract

and they show an effective result. Each route of delivery depends on the presence of dendritic cells. Following vaccine delivery, these dendritic cells are responsible for absorbing, processing, and presenting the antigens to T-lymphocytes where a robust immune response is mounted on them (Ryan, 2017).

Vaccines are thought to confer immunity against infection via neutralizing antibodies, and antigens that are specific to a particular antibody response following vaccine inoculation are usually quantified using serological tests. Vaccines and vaccination come with several complications ranging from their efficacy, side effects, the virulence of the infectious agents and strains, as a result of these problems scientists develop different approaches and strategies of vaccine technologies which include isolated proteins, subunits, split products, peptide, marker vaccines, live vector and nucleic acid technologies (Michael, 2018).

Considering the increase and rapid spread of antimicrobial resistance worldwide, scientists believed that developing a vaccine against antimicrobial resistance should be part of the solution. However, many challenges may be encountered in developing this vaccine ranging from the host, infectious agents, and also the environment. The vaccine can reduce the prevalence of antimicrobial resistance by depopulating the number of infectious agents for a particular infection in a population (Marc and George, 2016). The world health organization evaluated antibiotics resistance bacteria suitability for vaccine development and also compared based its health impacts, vaccine uptake probability, and its success in the context of research and development.

However, vaccines against several infectious agents are in the preclinical and clinical stage of development which includes Staphylococcus aureus, Clostridioides difficile, extraintestinal pathogenic Escherichia coli, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Klebsiella pneumonia, and Mycobacterium tuberculosis, etc. with many challenges involved (Francesca *et al*., 2021). Vaccines against antimicrobial resistance will prevent resistance to known and unknown infectious diseases.

5. WHAT ARE THE PROS AND CONS FOR USING THE VACCINE ON AMR?

5. 1. The Pros

Some of the pros for using vaccine as a remedy on AMR include;

The use of vaccines against Antimicrobial resistance will reduce the irrational use of antimicrobials drugs, especially in humans and animals. When vaccines against antimicrobial resistance are used, animals and humans will be vaccinated against a particular infection. Therefore, there will be no blind treatment or diagnosis. For example, people use antibiotics to treat viral infections or otherwise. But when vaccines are available, there'll be specificity in treatment.

Furthermore, one of the most important advantages of using vaccines against antimicrobial resistance is it'll confer herd immunity, whereby unvaccinated individuals in a population will also be prevented. There are certain individuals and places especially in developing countries that do not receive vaccines, but when it's available and a certain percentage of people receive it, they'll serve as a way of preventing the entire population.

Moreover, using vaccine against antimicrobial resistance will reduce the economic burden of buying antimicrobial drugs to individuals, especially in low-income countries because most vaccines are given free of charge in prevention and disease eradication programs.

Antimicrobial resistance causes economic challenges due to spending on drugs and long hospital stay as a result of persistent diseases but when vaccine is available, such burden will be reduced.

5. 2. The Cons

Some cons associated with using vaccine in AMR include:

Firstly, when vaccine against antimicrobial resistance is available, especially in developing countries where there's no rules and regulations governing drugs usage, many individuals will overuse this vaccine due to fear of contracting infectious diseases and this might lead to another problem or even loss of lives.

However, some individuals especially in developing countries find it difficult to accept vaccines due to their adverse effects and other cultural, or religious reasons.

There may also be vaccine resistance as a result of improper vaccine use, changes in the host, environment, and infectious diseases. The vaccine may be misuse by other people both in humans and animals and as a result of that, another resistance may develop. Moreover, it's a natural phenomenon for microorganisms to defend itself from attack by, with time the microorganisms may also become resistance to the vaccine.

There may be set back in antimicrobials research and development because of vaccine availability against variable infectious agents. Availability of vaccine will lead to slow down in drugs research, some researchers may focus on another field while drugs discovery aspect might be abandoned.

Moreover, infectious agents are evolving so also the vaccine approach. Therefore, the development of vaccines takes a longer duration than expected. Infectious agent might develop new strains and the vaccine would not work.

Furthermore, when a vaccine against antimicrobial resistance is produced, there'll be challenges in its supply and delivery, especially in low-income and developing countries. In vaccination programme, it's not all community receive the vaccine as a result of transport facilities to urban areas and there's no available storage facilities to prolong it shelf-life.

More so, in developing countries, improper disease diagnosis and lack of diagnostic tools is one of the major causes of antimicrobial resistance, therefore, availability of vaccines against antimicrobial resistance will make the scientists to focus less in diagnosis of a particular disease. As we know that, vaccine mount an immune response on a pathogen, which lead to production of antibodies specific to that pathogen, but with time this antibodies may gradually decline or wane.

6. CONCLUSION

Considering the negative impact and the danger of antimicrobial resistance globally with the wide knowledge gap combat it, development of new antimicrobial drugs, and the obstacles in vaccines approach and strategies, there's a need to avert its occurrence through employing the strategies needed. Government and other nongovernmental agencies should provide the necessary fund and assistance to drug development pharmaceutical industries, and research institutes. Rules and regulations governing the use of antimicrobials in humans, animals, and agriculture should be implemented. Public awareness and enlightening on the effects of antimicrobial resistance should be increased among individuals. Diagnostic tools and facilities

should be increased in every health sector because improper diagnosis also instigates antimicrobial resistance. Workshop and training should be programmed among health care professionals on how to diagnose and prescribe drugs based on disease conditions. Improved hygiene and sanitation in the community, use of probiotics in animals is most preferable than using antibiotics drugs, increased routine monitoring and surveillance of antimicrobials resistance at all levels.

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