Sustainable Development Goals (SDGs) and Antibiotic Resistance: The Need to Search Beyond

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons)

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

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Approval

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Ethics Statement

The study does not involve any human or animal trial.

Abstract

SDGs comprise 17 goals and 169 targets to tackle multiple and complex challenges of 21st century faced by the human race. The United Nations Organizations along with several organizations, NGOs have been working hard to achieve the goals through conferences, research, campaigns. In retrospect, it is alarming that the SDGs failed to control Antibiotic Resistance, threatening the global economy and health worldwide. As seen during COVID-19 pandemic, simple hygiene measures, e.g., washing hands frequently, wearing masks, using sanitizers, can play an important role in battling infectious microorganisms. One must grow awareness to stop illogical antibiotic prescription, to reduce overall infections and to educate people about the possible disastrous impact of ABR. This review aims to draw the attention of healthcare workers and policymakers, healthcare agencies to recognize the importance of targeted hygiene and preventing and controlling the ABR to achieve the SDGs.

Keywords: Bacteria; Sustainable Development; SDGs; Resistance; Partnerships.

Dedication

I dedicate my work to Md. Saif Mahmud and my family.

Acknowledgement

I would like to express my gratefulness to the almighty Allah for his kindness to me and giving me this life. It is a matter of immense pleasure that I acknowledge the help and guidance I have received from Brac University. My respected supervisor Dr. Md. Abul Kalam Azad**,** Assistant Professor, Department of Pharmacy of Brac University provided me with energy, enthusiasm and valuable counseling to work on this project. I am very much thankful to him for his priceless guidance and support during my Thesis. Besides, I would like to express my sincere gratitude to everyone for pushing me beyond my limits.

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List of Acronyms

ABR	Antibiotic Resistance
AGP	Antimicrobial Growth Promoter
ARGs	Antibiotic Resistance Genes
DEA	Drug Enforcement Administration
DNA	Deoxyribonucleic acid
DSDG	Division for Property Development Goals
DNDi	Drugs for Neglected Diseases Initiative
FDA	Food and Drug Administration
FAO	Food and Agriculture Organization of the United Nations
GARDP	Global Antibiotic Research and Development Partnership
GDP	Gross Domestic Product
GLASS	Global Antimicrobial Resistance and Use Surveillance System
HEDL	Hygiene in home and everyday life
HGT	Horizontal Gene Transfer
IACG	Low Interagency Coordination Group
LMIC	Low and middle-income country
MDG	Millennium Development Goal
NGO	Non-Governmental Organization
OIE	World Organization for Animal Health Organization

RNA	Ribonucleic Acid
SDG	Sustainable Development Goal
UNDESA	Department of Economics and Social Affairs
UNICEF	United Nations Children's Fund
VIPPS	Verified Internet Pharmacy Practice Sites
WAAW	World Antimicrobial Awareness Week
WEF	World Economic Forum
WHO	World Health Organization

Glossary

Antimicrobial Resistance	:	Disease-causing microbes that have acquired the ability to antimicrobial drugs that would kill sensitive organisms of the same strain; therefore, any pathogen that is less susceptible than its counterparts to a specific antimicrobial compound or a combination of compounds.
Antimicrobials	:	A term that involve both antibiotics and microbicides
Antibiotics	:	A generic drug used to treat infectious diseases
AIDS	:	Acquired immune deficiency syndrome is a disease of theuman immune system caused by the human immunodeficiency virus HIV).
Acinetobacter baumannii	:	A species of Gram-positive bacteria which maybe terrestrial or aquatic.
Adhesins	:	Specific proteins that promote adherence to host-cell membranes in bacterial cells.
β-Lactam Antibiotics	:	A generic class of widely used antibiotics including penicillin derivatives such as cephalosporins, monobactams, and carbapenems.
β-Lactamase	:	A specific kind of enzyme produced by some bacteria leading to resistance against β-lactam antibiotics.
Bacteria	:	Microscopic, single-celled organisms with biochemical and structural characteristics different from other living organisms.
Bacteriophange	:	A virus that infects bacteria.
Biofilms	:	Closely existing bacterial communities
Cephalosporins	:	A type of β-lactam antibiotics originally derived from Acremonium
Conjugation	:	The process by which two cells join and exchange genetic material
Genome	:	The entire genetic composition of any living organism

Gram-Negative Bacteria	:	A classification of bacteria with different the cell wall composition that leads to the inability of the microorganism to accept a certain stain.
Gram-Positive Bacteria	:	A classification of bacteria with different the cell wall composition that leads to the ability of the microorganism to accept a certain stain.
Horizontal Gene Transfer	:	An asexual process of exchanging genetic material from another organism.
Immunoglobulins	:	A class of proteins produced in lymph tissue that function as antibodies in the immune response.
Intrinsic Resistance Gene	:	A gene that code that reduce an organism's response to antibiotics.
Klebsiella pneumonia	:	A species of Gram-negative bacteria that cause pneumonia found in soil, water, humans and other animals.
Metabolism	:	The internal processes in an organism that are necessary for living.
Methicillin-resistant Staphylococcus aureus (MRSA)	:	A type of bacteria that is resistant to β-lactams antibiotics such as oxacillin, penicillin, and amoxicillin.
Microbe	:	A microorganism that can replicate in humans including bacteria, viruses, protozoa, and fungi.
Mutation	:	A spontaneous genetic change that occur through exposure to radiation mutagens leading to change in structure of the protein.

Narrow-Spectrum Antibiotic	:	Antibiotics which are effective against a limited number of microorganisms.
Pathogen	:	A disease-causing organism.
Penicillin	:	Antibiotics derived from Penicillium fungi.
Plasmid	:	A cellular ring of DNA that is capable of replication.
Pseudomonas aeruginosa	:	A type of disease-causing bacteria that can cause inflammation and sepsis in humans and animals.
Recombination	:	A combination of genes.
Staphylococcus aureus	:	A Gram-positive bacteria that is a part of the skin flora on skin.
Sulfonamides	:	A group of antibiotics containing sulfonamide group.
Tetracyclines	:	A group of antibiotics that hamper protein synthesis.
Virulence	:	Ability of an infectious bacteria to cause infection

Chapter 1

Introduction

1.1 SDGs as a Context of Study

The 2030 agenda is based on the Sustainable Development Goals (SDGs), which aim to alter the world by addressing a variety of issues. Despite the fact that Goal 3 encourages people of all ages to live healthy lifestyles, ABR was not given significant emphasis in the Sustainable Development Goals. Antibacterial resistance is responsible for roughly 800,000 fatalities per year (Littmann, Zorzet, and Cars 2016). As a result, it is a significant worldwide issue. ABR is considered by the WHO to be one of the worst worldwide public health concerns in human history. The misuse and abuse of antibiotics has expedited the process, posing a worldwide health and development hazard. Antibiotic resistance is highlighted in the SDGs as a threat to global health and the economy that requires undivided attention from all stakeholders. Several essential SDG initiatives, according to some experts, will be impossible to fulfill without an effective solution of ABR, antimicrobials, and especially antibiotics. This hot topic is connected to maternal death rates, children's mortality rates, infectious illness outbreaks, and so on (P. Howden-chapman & E. Chisholm, 2018). As a result, the major methods are antimicrobial resistance control and prevention through rational antibiotic use, antibiotic regulation, and improved cleanliness.

Because ABR is a worldwide malignancy, it is critical to comprehend the dynamics of the situation in order to manage it. In many countries, bacterial cause a large number of deaths each year (Cars and Jasovsky 2015). The World Health Organization has classified them as dangerous bacterial infections in need of new medicines as they develop ARGs. Nonetheless, the WHO has emphasized the need of maintaining a close eye on this worldwide issue (WHO, 2014).

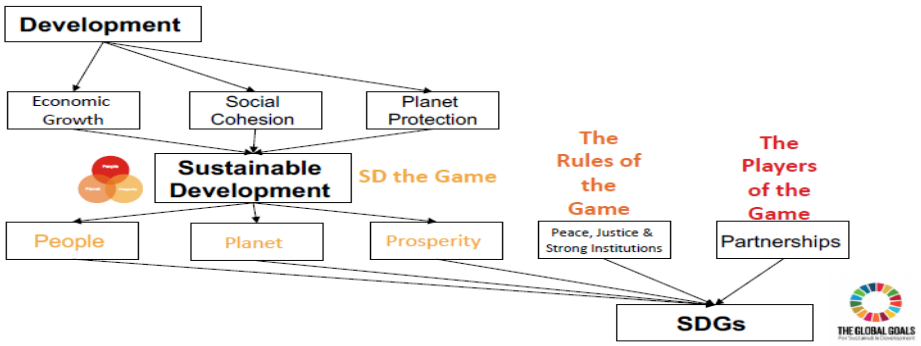

Fig 1: The WHO's Agenda is a comprehensive plan for the benefit of people, the environment, and economic success. It aims to take the big and transformational measures that are immediately required to shift the globe into a path that is sustainable that drives us forward. The economic, social, and environmental elements of sustainable development are all important considerations (adapted from Mateus 2020).

1.2 Historical Perspective

In learning the history of evolution, ancient human civilization had been profoundly influenced by infectious diseases. As we flip the pages of history, the plague of Athens with the downfall of Balkan state and later of ancient Rome Empire, the human populations were exposed to virulent infections from time to time. However, there was no genuine scientific evidence of the existence of these germs. People thought any illnesses were caused by magic or spirits. Then, wanderers, explorers and conquerors and armies carried these virulent microorganisms around the world. This led to the development of a complicated interactions between the microorganism and hosts leading to the emergence of various illnesses (Katzung 2011).

1.3 Current Perspective

Thankfully, as time passes, healthcare practitioners are becoming more aware of the importance of these infamous microorganisms. It is self-evident that reducing infection cannot be accomplished

without first controlling the microorganisms. As witnessed in today's pandemic, it entails complete avoidance of pathogens and antibiotic-resistant strains in the environment. Furthermore, combating antibiotic resistance has become a global concern. As ABR continues to inflict carnage in hospitals and institutions, the state government and international leaders must make significant investments. Indeed, healthcare organizations realize the tremendous influence of infectious illness on population health (Chokshi et al. 2019). As a result, in May 2014, the United Nations General Assembly adopted a global action plan with the goal of ensuring the achievement of infectious therapeutic applications using safe and efficacious techniques for as long as possible. This entails high-quality drugs being used properly and in a timely way, as well as being available to people who need them. Every country will develop its own antibiotic resistance national action plan with international and domestic support, in accordance with the global policy. The worldwide action plan lays out the measures needed to achieve five strategic goals:

(1) Increase public awareness

(2) Increase awareness of antibiotic resistance

(3) Gain information via surveillance and inquiry

(4) Decrease the frequency of infection and antimicrobial agents

(5) Ensure the long-term viability investment in antibiotic resistance prevention (WHO 2017).

1.4 The Purpose of the Study

The purposes of the study are the following:

i. To understand the importance of SDGs
ii. To investigate the effect of antibiotics resistance worldwide and understanding the importance of hygiene at home and everywhere
iii. To provide a feasible yet effective approach to tackle resistance starting from our own community.

Chapter 2

Methodology

For recent and relevant data, several renowned journals were carefully selected from The MEDLINE, PubMed, Research Gate, and EMBASE databases. Other data were collected from secondary sources, such as online articles, textbooks, documentaries, year projects, etc., to conclude the current situation. The data extraction was carried out independently from original articles that included the eligible author, date, sample data, design, and information related to the topic to explore perceptions and concerns about SGDs targets and means to combat antimicrobial resistance. This review paper is a reflection of these articles.

Chapter 3

Getting to Know SDGs

3.1 The Theme

The Sustainable Development Objectives, also known as the Global Goals, are a collection of 17 interconnected goals established by the United Nations General Assembly in 2015 with the purpose of achieving a better and more sustainable future for all by 2030 (Buhendwa 2020). These objectives are a series of measures aimed at forging a strong collaboration that will enhance people's lives while also protecting the environment. These targets include eliminating poverty, improving healthcare, and attaining gender equality, as well as reducing inequality and increasing economic development. The Millennium Declaration, which was officially announced during the Millennium Summit in September 2000, is also included in the goals. The Johannesburg Declaration on Sustainable Development and the Plan of Application were issued in 2002 as a result of this. At the United Nations Conference in Rio de Janeiro later that year, member states approved "The Future We Want." The General Assembly established an Open Working Group in 2013 to further explore a proposal. At the UN Sustainable Development Summit in 2015, the entire process culminated in the adoption of the 2030 Sustainable development Agenda, which includes 17 SDGs.

Fig 2: UN's Sustainable Development Goals (SDGs) set of 17 goals with 169 targets (adapted from Totten 2018).

This was a pioneering moment as it lead to the adaption of several others programs, such as:

- Sendai Framework for Disaster Risk Reduction (March 2015)
- Addis Ababa Action Agenda on Financing for Development (July 2015)
- Annual High-level Political Forum on Sustainable Development

Today, the DSDG which is a part of the Department of Economic and Social Affairs provides support for the implementation of SDGs and other associated programs. DSDG plays a key role with the United Nations system to support the 2030 Agenda (Hoffman and Behdinan 2016). This includes:

- Reduction of maternal mortality to below than 70 per 100,000 live births globally. According to studies, 40 percent of all nations have fewer than 10 physicians per 10,000 people and fewer than 40 nursing and midwifery workers per 10,000 people than the global average. Maternal death rates are highest in Eastern Asia, Northern Africa, and Southern Asia due to pregnancy and delivery. In low and lower middle-income nations, the rates are substantially greater, with young teenagers being the most vulnerable. The maternal mortality ratio is 14 times greater than in industrialized regions, as can be shown. The committee's goal is to reduce the number of infants and children under the age of five who die to less than 25 per 1,000 live births (Guclu et al. 2021).
- AIDS, TB, malaria, and other tropical illnesses, hepatitis, water-borne disorders, urinary tract infections, and communicable diseases (Islam et al. 2019).
- Promote mental health and well-being, and keep narcotic drug and alcohol misuse under control.
- Reduction in the number of people killed in car accidents.

- In developing nations, family planning, information, and sex education methods and programs are required. This means availability of sexual and reproductive health goods and services has improved.
- Reduce pollution and contamination through providing worldwide healthcare facilities and the availability of high-quality, cheap medications and vaccinations.
- Tobacco control must be implemented in all countries.
- Invest in vaccine and medication research and development in underdeveloped nations to combat communicable and non-communicable illnesses.
- In underdeveloped nations, improve healthcare facilities through recruiting, developing, training, and retaining health workers.
- Develop early warning systems, risk reduction strategies, and risk management strategies for health hazards.

Many of the Millennium Development Goals are impossible to be implemented due to corruption. Corruption is at the core of most of the problems that emerging countries are experiencing. Some have experienced a longer time of peace than the Scandinavian countries have as there has been less internal unrest on a national scale in this country. The issue of racial discrimination is a topic that frequently causes internal strife in the United States. Many South American countries are still battling drug, and instability, etc (Buhendwa 2020).

Rank	Country	Score	Performance by SDG
1	Sweden	84.72	
2	Denmark	84.56	
3	Finland	83.77	
4	France	81.13	
5	Germany	80.77	
6	Norway	80.76	
7	Austria	80.70	
8	Czech Republic	80.58	

Fig 3: The UN SDG Index. Five years have already gone, it would be dishonest not to acknowledge all of the significant progress made toward the achievement of these objectives. Many diverse rural places all around the world are now able to get clean drinking water. Furthermore, more political accountability has been accepted (adapted from Buhendwa 2020).

3.2 SDG and Health

As previously discussed in Chapter 1, WHO believed that several crucial targets related to SDG 3 are impossible to establish without effective antibiotics (Pradhan et al. 2017). The prominent The Every Woman Every Child initiative also believed that antibiotics to be the life-saving essential commodity in the Millennium Development Goals in LMICs. Another alarming factor is the emergence of communicable diseases, which cause an estimated 600 million new infections. There have been 214,000 reports of sepsis deaths annually due to drug-resistant pathogens. Which hampers the initiatives to reduce mortality SDG target 3. For instance, gonorrhea is one of the most common STI along with HIV transmission, tuberculosis, and malaria (P. Howden-chapman & E Chisholm, 2018). According to a recent report published in 2018 an estimated 6.2 million children died from various diseases where 5.3 million deaths occurred in the first 5 years, particularly in Sub-Saharan Africa and Southern Asia. Besides, children suffering from severe acute malnutrition are at a higher

risk of death from common illness such as diarrhea, pneumonia, and malaria. Alarmingly, most of the developing countries have less than 10 medical doctors per 10,000 people.

Also, some key finding show that:

- In 2019, an estimated 38 million individuals are infected with HIV around the world.
- In 2019, an estimated 1.8 million individuals will become HIV-positive for the first time worldwide.
- In 2019, about 690 000 individuals died as a result of AIDS-related causes.
- More than 32.7 million individuals have died as a result of AIDS-related diseases since the beginning of the pandemic.
- Adolescent girls and young women throughout the world are subjected to gender-based inequities, exclusion, discrimination, and violence, which puts them at a higher risk of contracting HIV.
- Women all across the world are at risk of contracting HIV.

3.3 SDG Interaction: SDG 1 and SDG 3

The Health and wellbeing of an individual are closely related to poverty as the reduction in poverty leads to improved health. For a nation to have progressive economic growth, poverty reduction is a contributing factor. With rising income, an individual ensures some benefits, like a nutritious diet plan, improved health care facilities, better health awareness, and medicines, leading to a positive outcome for the society. Many health issues are associated with poverty, including aids, diarrhea, tuberculosis, and malaria, etc. Lastly, the implementation of SDG 1 involves good governance, awareness, investment, and an improved healthcare system. The poor face the highest risk as treatment of these deadly infections is costly and involves time-consuming processes (Brødsgaard and Kleinet 2019). As a result, ABR negatively influences national economic performance.

3.4 SDG Interaction: SDG 2 and SDG 3

Health and nutrition are intertwined linked. Malnutrition puts the body vulnerable to various disease conditions generally. It makes an individual unable to carry out daily work—similarly, nutrients and energy from food help maintain fundamental body functions. The rise in hunger will result in immediate deterioration in health, difficulty in carrying out normal biological, physical, metabolic, psychological, and neurological development. On the other hand, a reduction in hunger results in better immunity, improved food security, a healthy environment, and reduced transmission of infectious disease transmission (P. Howden-chapman & E Chisholm, 2018).

3.5 SDG Interaction: SDG 4 and SDG 3

Better education correlates with increased awareness, knowledge, and health. Formal education has an impact on making smart judgments, maintaining good health, and embracing new ideas (Pradhan et al. 2017). As a result, without adequate educational qualifications, it is impossible to live a healthy lifestyle. SDG 3 aspires to reduce illness and death among young mothers, infants, the elders, and small children, especially in low-income countries. Surprisingly, this includes infectious and non-communicable illnesses, cigarette and drug addiction, road traffic accidents, and sound and polluted air all over the world. Other SDGs intersect with the constitution, such as the significance of social issues, decreasing inequalities between and within nations (SDG 10), workplace conditions, food security, and agricultural output (SDG 2), employment, energy supplies (SDG 7), education (SDG 4), and accommodation, among others. The magnitude of the problem, on the other hand, is enormous. Economic development (SDG 8) is interwoven with resistance to antibiotics in numerous ways and is closely tied to the fulfillment of several of the SDGs (Pradhan et al. 2017). As a result, long-term income prosperity with adequate and productive employment for everyone, as well as good work for

all. Microbes are thought to be responsible for 700,000 fatalities per year. As a result, developing antibiotics for the detection and treatment of infectious illnesses adds to the community's health-care costs, potentially lowering production, total income, and tax revenues in LICs. Economists think it decreases GDP, making AMR a major worldwide stumbling block.

3.6 SDG Interaction: SDG 6 and SDG 3

SDG 6 emphasis on ensuring pure water and sanitation. It is proven that the lack of clean water and proper sanitation facilitates the spread of deadly pathogens which afterwards cause diseases and leads to increased morbidity and mortality. Besides, huge amount of waste generated by humans from hospitals and clinics, drug manufacturing plants, as well as animal and plant agriculture release antibiotic residues with drug resistant bacteria in our ecosystems. These antibiotic residues deposit in water through sediments and soil (Bartram 2009).

3.7 SDG Interaction: SDG 12 and SDG 3

It is reported that 5.7 million people die each year from common infectious diseases. Therefore, antibiotics can be regarded as a valuable global resource. An estimation shows that that the sustainable supply of antibiotics could stop 445,000 cases of deaths in children globally. Hence, antibiotics is regarded as an essential part of the human privilege to healthcare. To fulfil the requirement, stakeholders must put special care on antibiotic distribution and consumption to reduce the need for antibiotics in the long run. The Government could employ international framework that includes new antimicrobials and diagnostics for public healthcare needs.

Chapter 4

Microbes and Antibiotics

4.1 What are Antibiotics?

Antibiotics are examples of antimicrobials that are used to treat infections in living organisms. Antibiotic Resistance (ABR) occurs when bacteria do not react to antibiotics, making illnesses more difficult to treat and spreading diseases and mortality. As a result, rapid action is required to meet the Sustainable Development Goals. ABR has been one of the top ten worldwide public health risks, according to the WHO. The misuse and abuse of antimicrobials has expedited the process, resulting in a worldwide health crisis (Neill 2014). Furthermore, factors such as a lack of clean water and sanitation promote the spread of microorganisms, resulting in mortality and disability, disease that need costly treatments, and difficulties (Hoffman and Behdinan 2016).

4.2 A Brief History of the Development of Antibiotics

Long before discovering antibiotics, bacterial infections were treated using ancient folk medicines, which proved to be quite hazardous for many conditions. As, these techniques were insufficient against the destruction of microbes, the mortality rates were high (Wright 2007). In the 19th century, Louis Pasteur and Robert Koch confirmed that the microbes were responsible for diseases like cholera (Madigan et al. 2006). This moment revolutionized the correct approach identifies the core disease, and select the therapy. Moreover, Paul Ehrlich, the founder of chemotherapy, recognized the antimicrobial ability of sulphonamides. Again, in 1928, Alexander Fleming discovered and developed Penicillin for medical purposes. This led to the golden age of antibiotics, where most of the antibiotics we use today were discovered (Katzung 2011). Later, several novel antibacterial agents are represented by the most recent registered representatives, such as linezolid, daptomycin, and the topical drug retapamulin are

examples of antibiotic classes. In fact, they were first presented in 2000, 2003, and 2007 consecutively (Silver 2011).

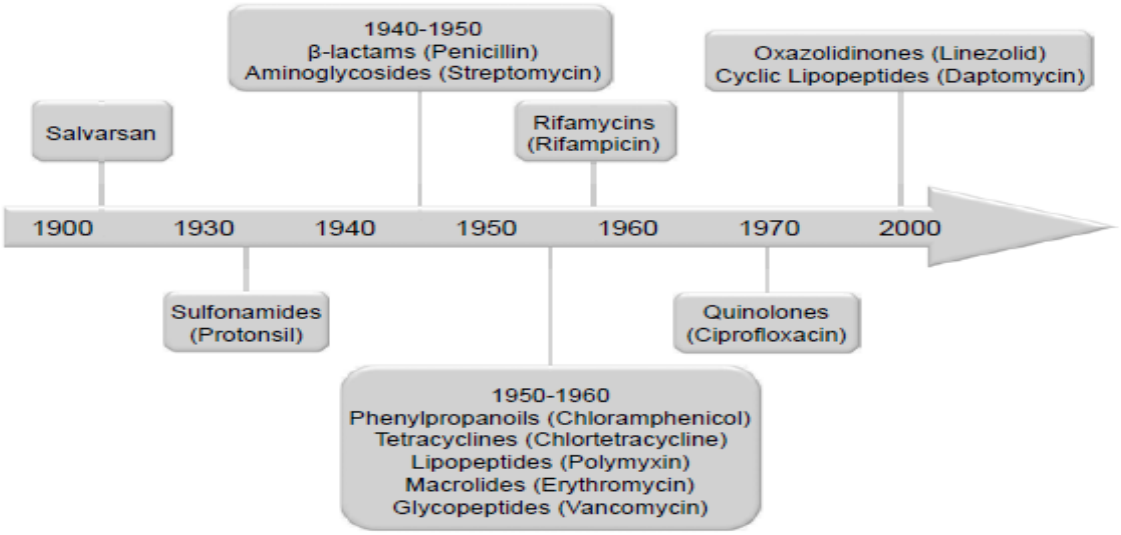

Fig 4: Timeline of Antibiotics discovery (adapted from Pietsch 2015).

4.3 Clinical Classification of Antibiotics

Antibiotics are strictly classified into two groups: natural origin and synthetic origin. In any case, the mode of action is somewhat similar as both work by inhibiting bacterial cell walls, disrupting the cell wall, stopping serious processes within the cell, or destroying critical cellular structures making the internal structures vulnerable. Secondly, antibiotics can also be divided based on their ability to destroy bacteria: bacteriostatic and bactericidal. Bactericidal bacteria affect the spectrum of activity, including killing the bacteria, whereas bacteriostatic chemicals inhibit the growth of the bacterial cells (Wall et al. 2016). Overall, these antibiotics work either by inhibiting cell wall synthesis, cell membrane arrangement, folic acid metabolism, protein synthesis, and DNA replication or as combination of these mechanism.

4.4 Mode of action

Antibiotics can have totally different modes of action to inhibit the synthesis of important cellular structures like the plasma membrane, macromolecule synthesis, replication of deoxyribonucleic acid replication, and other pathways of metabolism (Awad et al., 2012). If the internal structure of a bacterium is taken in consideration, both Gram-positive and Gram-negative bacteria contain an outer rigid membrane structure referred to as peptidoglycan layer. Nevertheless, Gram-positive bacteria have an intense thick rigid peptidoglycan layer intertwined with tough peptide bridges. On the contrary, Gram-negative bacteria have a thin peptidoglycan layer. Various antimicrobials essentially ought to penetrate the cell by diffusion to reach the target. The presence of lipopolysaccharide-lipoprotein structures within the plasma membrane of gram-negative microorganisms makes the process quite challenging. As a result, some antibiotics use liquid transmembrane channels called porins. These tiny porins are found within the bacterial outer membrane as a port of entry. Antibiotics, such as Penicillin, bacitracin, cephalosporins, inhibit peptidoglycan layer production (Awad et al., 2012). In comparison, others like puromycin, aminoglycosides, tetracyclines, mupirocin, and oxazolidinones hamper the method of protein synthesis. Some, including quinolones, rifampicin, and sulfonamides, stop desoxyribonucleic acid synthesis by interfering with desoxyribonucleic acid coiling (Adegboye, Babalola, and Akinpelu 2012).

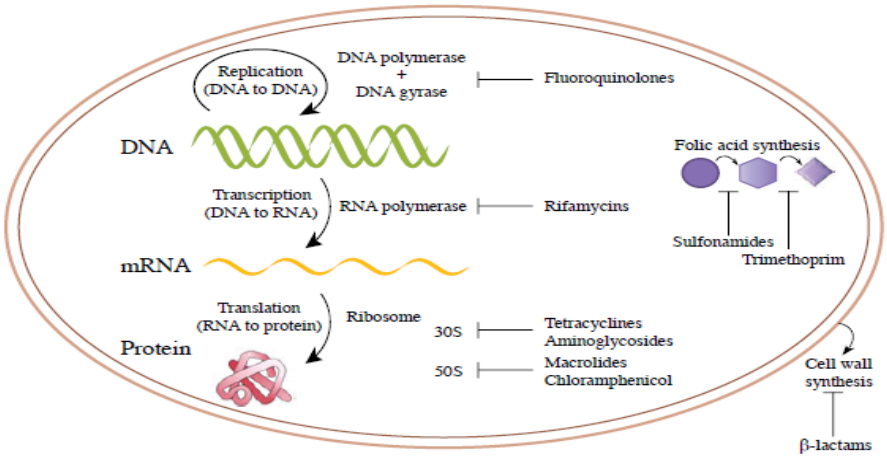

Fig 5: Major antibiotics and their targets (adapted from Pietsch 2015).

4.5 Defining Resistance

Antibiotics are agents which show significant growth inhibition of particular microorganism strains. Waksman screening platform detected a zone of bacterial growth inhibition around a paper disk containing a cellular extract (Strebhardt & Ullrich 2008). This brings a new concept of Minimum Inhibitory Concentration, which is the concentration of drug that stops visible microorganism growth under vitro conditions (Kahlmeter 2013). MIC values for different species can be used to predict the clinical outcome of various diseases. Besides, MIC values can help medical studies evaluate the therapeutic outcome, clinical factors, including the pharmacokinetics and pharmacodynamics properties of the antibiotic and drug toxicity (Murray et al. 2005). Additionally, considering these mathematical and empirical data, manufacturers can determine the failure and success of antibiotic treatment in medical care. Thus, the medical studies consider MIC values as a tremendous breakpoint in combating resistance development (Gajdács et al. 2021).

4.6 Resistance Mechanisms

The alarming acceleration of antimicrobial resistance puts an enormous socio-economic hindrance on the healthcare system. Bacteria, along with other microorganisms, possess a unique capability to adapt, evolve, and survive by developing a resistance phenomenon (Seiffert et al., 2013). The process of antibiotics resistance can be through an intrinsic mechanism, along with other processes like mutation, gene transfer from different species or strains, or changes in metabolic pathways (Hegstad et al., 2010; golf player et al., 2010). In addition to intrinsic antibiotic resistance, there are spontaneous DE Novo mutations within their body and uptake of external genetic material via horizontal sequence transfer (HGT). It has been found that body mutations will arise without any external influences. The transfer of external genetic material occurs through the processes of transformation, transduction, or conjugation. Therefore, link between the infectious agent and deoxyribonucleic acid can supply the resistance genes (Martinez 2009). As a result, these genetic alterations increase the MIC of microorganism strain resulting in increased drug resistance by three classes: (i) altering the drug target, resulting in reduced target status, (ii) modifying the drug, resulting in a decrease drug-target affinity; (iii) reducing the effective drug concentration that reaches the target (Brown and Wright 2016).

All three mechanisms reduce the ability of the drugs to slow growth, and drug targets will be less vulnerable to drug inhibition by the incidence. Mutations in the genes for Deoxyribonucleic acid gyrase or Deoxyribonucleic acid topoisomerase increase resistance to quinolones, rifampicin, and other antibiotic drugs. Secondly, changes in genetic code by homologous recombination of deoxyribonucleic acid sequences from organisms become proof against antibiotics by the acquisition of deoxyribonucleic acid from related species. The recombination creates genes, along with mutations, changes in the binding site of the target,

and target sequence amplification can even cause phenotypic resistance. Also, there are cases where the drug target is substituted by another drug-resistant target leading to a loss of antibiotic activity (Marcusson et al., 2009).

4.7 Mutation Rates

Beneficial mutations are selected to aid adaptation to evolve conditions, and they are a key driving factor of evolution. According to experts, such spontaneous mutations occur at deficient levels through point mutations, deletions, insertions, amplification, gene transmission events. The incidence of a mutation during its lifespan is termed the mutation rate (Hershberg 2015).

Random mutations will frequently be beneficial or neutral in terms of their impact on the microorganism. However, some mutations become quick depending on the fitness value of a de novo mutation and the potential competitive advantage in a specific environment. The mutation rate is different in different species and between chromosome regions within a single species (Luria & Delbrück 1943). DNA regions coding for heavily transcribed genes are more variable and vulnerable to mutations than intergenic or non-coding regions.

Today, with improved technologies such as next-generation sequencing, more precise and accurate estimates of mutational rates can be made.

4.8 Beta-Lactamase Production

Like previously said, bacteria possess an outer complex cell wall structure containing protein channels called porins. Minor positively charged hydrophilic antibiotic drug molecules pass through them quickly. On the contrary, gram-negative bacteria develop resistance by reducing the permeability of these channels (Seiffert et al., 2013).

4.9 Carbapenemase Production

Carbapenemase is the enzyme that is capable of hydrolyzing carbapenem antibiotics such as doripenem. The bacterium that turns out carbapenemase have a restricted treatment choice as they offer resistance to cephamycins. Carbapenemase genes mutate and offer various resistance which spread through organism by horizontal gene transfer to a different bacteria. Nowadays, infections are rising because of carbapenem manufacturing bacterium is increasing and becoming related to mortality, commonly seen among gram-negative bacterium, notably among the family Enterobacteriaceae (Nordmann & Poirel, 2014).

4.10 Methicillin Resistance

Methicillin-resistant since its discovery in 1996, Staphylococcus aureus (MRSA) has been regarded as the primary threat associated with the emergence of antibiotic resistance (AMR). MRSA strains have recently been discovered to have multidrug resistance patterns as a result of conjugative insertion of extra resistance genes (Ohlsen et al., 2013). One year after putting this second-generation beta-lactam antibiotic into clinical observation, methicillin-resistant Staphylococcus aureus (MRSA) was shown to fight against the effects of antibiotics. Infections produced by penicillin-resistant S. aureus strains have a greater death rate than infection caused by susceptible penicillin strains, which is an established fact. The carrying of a mobile container of genes known as the cocci container body, which contains mecAcistron, which is resistent to beta-lactam antibiotics as well as penicillin, is linked to the genetic foundation of penicillin resistance in S. aureus (Katayama et al., 2010).

Table 1: Resistance rates of Gram-Negative Rods. The antibiotic resistance rates of non-fermenter Gram-negative rods are given. 6.5% of S.maltophilia and 4.4% of B.cepacia isolates are resistant to trimethoprim/sulfamethoxazole which is the first choice of use against such isolates (adapted from Guclu et al. 2021).

%R					
	A.baumannii	P.aeruginosa	Others	S.maltophilia	B.cepacia
Piperacillin	96.2	37.7	35.7		
Cefepime	95.1	29.5	44.1		
Ceftazidime	94.2	31.5	26.7	79.7	29.9
Imipenem	92.8	39.8	25.8		
Meropenem	93.1	34.3	24.9		20.3
Ciprofloxacin	93.4	32.8	26.7		
Levofloxacin	91	36.4	20.6	7.1	7
Amikacin	77.6	19.9	34.3		
Gentamicin	78.9	29.6	35.6		
Tobramycin	60.8	14.7	32.8		
Netilmicin	75.7	33.2	34.3		
Trimethoprim /sulfamethoxazole.	75.6			6.5	4.4
Colistin	12.8	7.5	23.2		
Tigecycline	18.6	85.2	16		

4.11 Vancomycin Resistance

Vancomycin is the most widely used antimicrobial for the management of penicillin-resistant bacteria. It was found among enterococci bacteria in 1980 and is particularly effective against penicillin-resistant strains like MRSA. However, recently, bacterial strains with full antibiotic resistance have evolved, and they are now seen in S. aureus and Enterococcus species all over the world (Hidayat et al., 2006). Resistance is developed by plasmid transfer via conjugation mechanisms, according to some studies.

4.12 The cycle

MRSA resistance typically occurs once a mecAcistron capable of encryption penicillin resistance can be horizontally transferred to a different penicillin-sensitive strain of S. aureus. Insufficient infection control measures along with continuous exposure of susceptible humans to antibiotics have made the situation considerably difficult to prevent the spreading of MRSA that successively prohibit the selective treatment of MRSA infections globally. Sadly, numerous studies have reported that MRSA developed resistance to the most common antibiotics used to treat its infections.

The incidence of infectious diseases have increased in the past century. These diseases challenge the freedom of public to carry out their regular activity, especially LICS across the globe. Infections spread through organisms in a community through a sequence of events termed as “chain”. There are several interconnected steps. Therefore if these steps are interrupted, it can stop a microorganism from spreading (Infection 2020).

The steps include: i. Invasion by Infectious agent (pathogen)

ii. Reservoir

iii. Exit pathway from the reservoir

iv. Mode of transmission

v. Portal of entry into a host

Pathogens, including bacteria, viruses, fungi, and parasites enter the host where it lives and multiplies. Animate reservoirs involve living organisms such as humans, animals and birds, whereas inanimate reservoirs include water, soil, food, feces, external fluid, and other non-living objects. These vicious organisms exit the host via blood, water droplets, secretions, and urine. Once the microorganism has exited the reservoir, it attacks another host through a portal

of entry via direct contact, indirect contact, or air (Klompas et al., 2020). Exactly the same situation is seen in COVID-19 infection where the virus-filled fluid particles exit respiratory tract of an infected person via the mouth and nose throughout respiration. In the end, these droplets are available to infect another person. As seen with most contagious infections, such as COVID-19, transmission happens mainly when particles that are expelled from the mouth, nose, or conjunctiva (WHO, 2020, Jun 9). Secondly, the new recipient comes in physical contact with drops deposited from any surface, followed by subsequent transfer to the recipient's metabolic process.

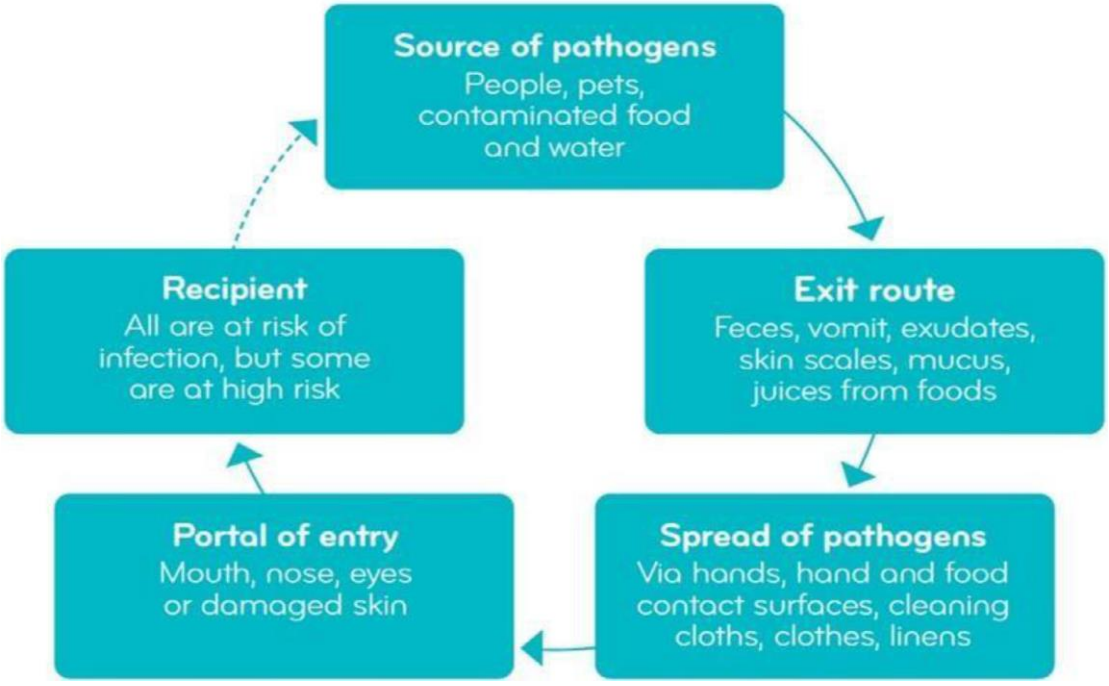

Fig 6: The infection cycle (adapted from Maillard et al. 2020).

4.13 More about transmission: The COVID-19 Crisis

According to WHO and other healthcare authorities, the potentially malicious coronavirus disease along with SARS and MERS has proven to have airborne transmission. Airborne transmission occurs when fluids from an infected individual remain suspended in the air to be transmitted to the respiratory tract of another susceptible host (Santarpia, et al., 2020, July 29).

The situation become worse in poorly ventilated, congested spaces such as homes, offices, shopping malls, and public transports, as the infectious droplets remain suspended in air for a long time (WHO, 2020).

4.14 The Current Update

According to the 1948 agenda, SDG 3 involves ensuring good health and wellbeing for everyone in every sphere of life. WHO defined health as a state of complete physical, mental, and social wellbeing and not merely the absence of disease or infirmity. If the situation is not dealt with, the consequences can be devastating due to increased treatment costs and morbidity and mortality, leading to decreased productivity. Therefore, in current times, it is encountered that the increased costs of treatment and loss of income put a terrible burden on household economies. This, it reduces tax revenues while creating an additional need for social services. It is reported that antimicrobial resistance could reduce GDP between a 1.1% and 3.8% decrease of global GDP by 2050, according to World Bank. Antibiotic resistance undermines antibiotic use in human health or animals and food production on a wide scale. The global spread of resistant bacteria is a slow pandemic. Antibiotic resistance is complicating the situation of multiple bacterial infections across the world. Besides, the effects of antibiotic resistance on poverty and economic growth are devastating. As we flip the pages of history, the pandemic of the Spanish flu killed 40-50 million people worldwide in 1918 by bacterial infection; the Swine flu killed 77 fatal cases by bacterial infection. Also seen in Covid-19, antibiotics no longer work to control the adverse effects of epidemics globally effectively.

4.15 The Need for Awareness

WHO and other Healthcare agencies admit the perilous impact of infectious diseases on health sector across the border (Doremalen et al., 2020). Similarly, they agree that strict prevention

measures must be taken immediately to fight infection. HEDL is a potential driver in tackling antibiotic resistance in the community. Therefore, HEDL must be must be everyone's responsibility.

Indeed, it is a strong responsibility of the public to take great care for their health to save everyone in the community and the entire mankind against infection. However, it is also the duty of the heath care agencies to promote hygiene as a principal part of public healthcare system.

Since the situation needs coordinated action, various nations have taken coordinated actions.

- GAP

In 2015, the World Health Assembly approved the Global Action Plan1, which was backed by the Regulatory Agencies of FAO and the OIE. The concept was created in 2001 with the goal of spreading a worldwide strategy for combating antimicrobial resistance and developing treatments to limit and reduce its development.

- Tripartite Joint Secretariat on Antimicrobial Resistance

The UN High Level Meeting on AMR, convened by Heads of Government at the UN General Assembly in New York in September 2016, collaborates closely with FAO and OIE to lower AMR levels and halt its progression through a "One Health" strategy. The UN Secretary-General convened the IACG to bring together international organizations to develop a plan to address the spread of antimicrobial resistance.

- WAAW

WAAW was formally established, and the name was later modified to the World Antimicrobial Awareness Week. In a larger sense, WAAW is a global campaign to raise public awareness of AMR's global impact and to encourage people to practice good hygiene. Starting with WAAW

2020, the Tripartite Executive Committee agreed to move all future WAAW dates to November 18–24, with the theme “Antibiotics: Handle with Care.”

- GLASS

WHO established the Global Antimicrobial Resistance and Use Surveillance System (GLASS) in 2015 to develop techniques for surveillance of AMR in people and the use of antimicrobial medications. GLASS facilitates the acquisition, analysis, interpretation, and exchange of data by nations, as well as the provision of technical help to LICs and the facilitation of their participation in GLASS.

- Global Research and Development priority setting for AMR

Since 2017, the WHO has seriously emphasized the creation and research of innovative antimicrobial medicines, vaccines, and detection technologies in order to spur innovation capabilities in operational activities in the health sector. Every year, WHO conducts an analysis of which was before and clinical antibacterial investigations in connection to the WHO prioritized pathogens list.

- Global Antibiotic Research and Development Partnership (GARDP)

GARDP was established by the WHO and DNDi with the goal of developing novel therapies that target a drug-resistant bacteria that has been identified by the WHO by 2025.

Chapter 5

Causes of Antibiotic Resistance

5.1 Unregulated Animal Industry

Along with human bodies, antibiotics are also administered in animal bodies to mitigate and cure diseases in animals, as well as act to promote growth and wellbeing in animals. Besides, news has it, antibiotics are used as preservatives in plant agriculture and industrial procedures. The perilous use of antimicrobial additives in animals and plants lead to terrible consequence of development of resistance in bacteria. These resistant bacteria which in turn can be can be transferred to human bodies as they consume animal, plant products, and environmental spread. Additionally, disposal of human sewage and wastewater from agricultural and industrial locations put a selection pressure; hence, the resistant types gain a competitive advantage over the susceptible types which can favor the survival of antibiotic resistant genes within the microbial community. Alarmingly, experts believe the use of antibiotics continues to stand as a strong association between agricultural use of antimicrobials and the development of multidrug resistant bacteria. Strangely, it has been suggested that the majority of antimicrobials used worldwide are given to animals for the purposes of producing food. To cut the long story short, these findings prove that animals act as a major reservoir of drug resistant bacteria, and in return, act as strong contributors of transmission of multidrug resistant bacteria in across the borders. Researchers have found strong link between the spread of bacteria, such as S. aureus, from pigs to farmers leading to infections as further transmission occurs animals to farmers (Manyi-Loh et al. 2018). Sadly, due to the extreme lack of proper healthcare system, the a large number of population are at risk in developing countries as they live in close contact with animals; therefore,

increasing the chances of transfer and breed of resistant microorganisms from animals to humans. To show how such continuous exposure acts as a hazard, some research studies have been performed at the University of Lowa where the researchers performed a study to identify staphylococcal infections in pig farmers. The researcher began by asking farm workers whether they had been previously contracted and diagnosed with specific bacterial infections. This study involved the medical information as such infections can take weeks to months to manifest. Also, researchers collaborated with physician groups, medical staffs and a large groups of patients. Results show that livestock-associated S. aureus may be prevalent in living in areas with high animal density. Besides, antimicrobial growth promoters enhances the development of bacteria. AGPs at sub therapeutic concentrations are expected to have a significant impact on microorganisms. The usage of AGPs as feed additives in intensively farmed animals has drastically increased. It has been discovered that resistance is transferred as the gut microbiome of animals encourage them to consume more through a long periods of time in order to boost growth rates (Wall et al. 2016).

5.2 Poor Monitoring in Patients

As seen in regular cases, poor compliance plays a role in the development of resistance. Patients often show no interest to continue a full dose as previously prescribed by a physician, miss doses in a day intentionally or unintentionally, or there is a fear that antibiotics will interact with outer medicines. Also, as seen in some developing countries, lack of proper nutrition and knowledge reduce the effectiveness for the treatment (Clift 2019).

5.3 Antibiotics in Soil and Water

Pathogenic microorganisms from humans and animals are continually discharged into water bodies. These creatures possess antibiotic-resistance genes. Water is not just a source of antibiotic-resistant bacteria, but also spread and introduce resistance genes into the ecosystem. Moreover, the introduction of antimicrobial agents, detergents, disinfectants, and industrial discharge, heavy metal pollution aids evolution and resistance organisms in water environment. Antibiotic overuse in aquaculture is rampant where the environmental bacteria operate as a source of resistance genes.As previously discussed, animals rare given antibiotics due to a variety of reasons. Therefore, soil and water are important carriers of the spread and persistence resistance. Substances in soil can quickly enter water where the drainage systems are insufficient. Consequently, antibiotics remain in soil and surrounding water bodies around animal and plant agriculture, so the water is taken by plants and crops. The rate of uptake is typically low, but with high antibiotic concentrations the reverse is true. As a result, antibiotics can accumulate on plant surfaces. Besides, these crops and plants receive manure application containing more antibiotics pose a greater danger of health danger. A research study conducted on soil samples in Denmark showed a significantly higher levels of spectrum β-lactamase antibiotic showing the link and consequences of the complex issue of AMR.This is a concerning matter as industrial antibiotics that are linked to environmental matrices are dissolved by water. Binding to soil particles retards biodegradation and accounts for the medications' long-term persistence in the environment. Antimicrobial agents persist in soil due to their interaction with soil components. Sulfonamides, macrolides, trimethoprim, cephalosporins, and fluoroquinolones are antimicrobial agents that can be detected at potentially active quantities in in water bodies. This information clearly correlates with yearly consumption of antibiotics by human. Interestingly, heavy metals also bind with humic acids, suggesting

that multiple antimicrobial actions may exist simultaneously in the water film associated with soil organic particles. Indeed, it appears as though the presence of humic compounds, both dissolved and mineral-bound, increases antibiotics' environmental mobility. Aluminum and iron oxides have the potential to modify these interactions by altering their surface charge. For example, sorption of ciprofloxacin on such oxides results in a variety of ciprofloxacin-surface complexes. As a result, mobility into the subsurface is restricted which leads to high amounts sulfonamides (20 103 ng/ml) have been detected (Baquero, Martínez, and Cantón 2008). Besides, in recent times, a large variety of antibiotic agents, such as trimethoprim may be found in urban waterways. Besides, the discharge of pharmaceuticals into rivers and lakes as a result of sewage effluent treatment is a rising source of worry. Medications are commonly found in effluents at concentrations ranging from less than 1 ng/L to more than 100 ng/L, including propranolol, diclofenac, gemfibrozil, ibuprofen, and acetaminophen. The releases have an impact on aquatic creatures in or around ecologically sensitive areas (Larsson, de Pedro, and Paxeus 2007).

5.4 Unskillful Prescribers

Although healthcare experts help to treat infections, but some may maximize the rate at which infections develop. As seen in poor and rural communities, lack of proper evidence-based information may worsen the situation. As they is lack of high quality testing in rural areas, they fail to choose the correct antimicrobials. As a result, due to absence of strict surveillance and limited laboratory antimicrobial testing, they issue prescriptions that based on a syndromic approach everywhere leading to the development of resistance (Maillard et al. 2020). Besides, medications that are no longer effective lose their worth in the pharmaceutical industry, therefore market leaders must encourage safe and responsible use of medicines. In this way, they can maintain their efficacy, and through discovery and

development of new medications. They can so help fight against multidrug resistance with brand-new ideas, innovation and creativity by fostering collaboration between policymakers and academics. The pharmaceutical sector, to guarantee that innovative drugs are developed. Globally, the pharma giants can use technology to prevent, diagnose, and treat disease through partnerships between the public and private sectors (WHO 2017).

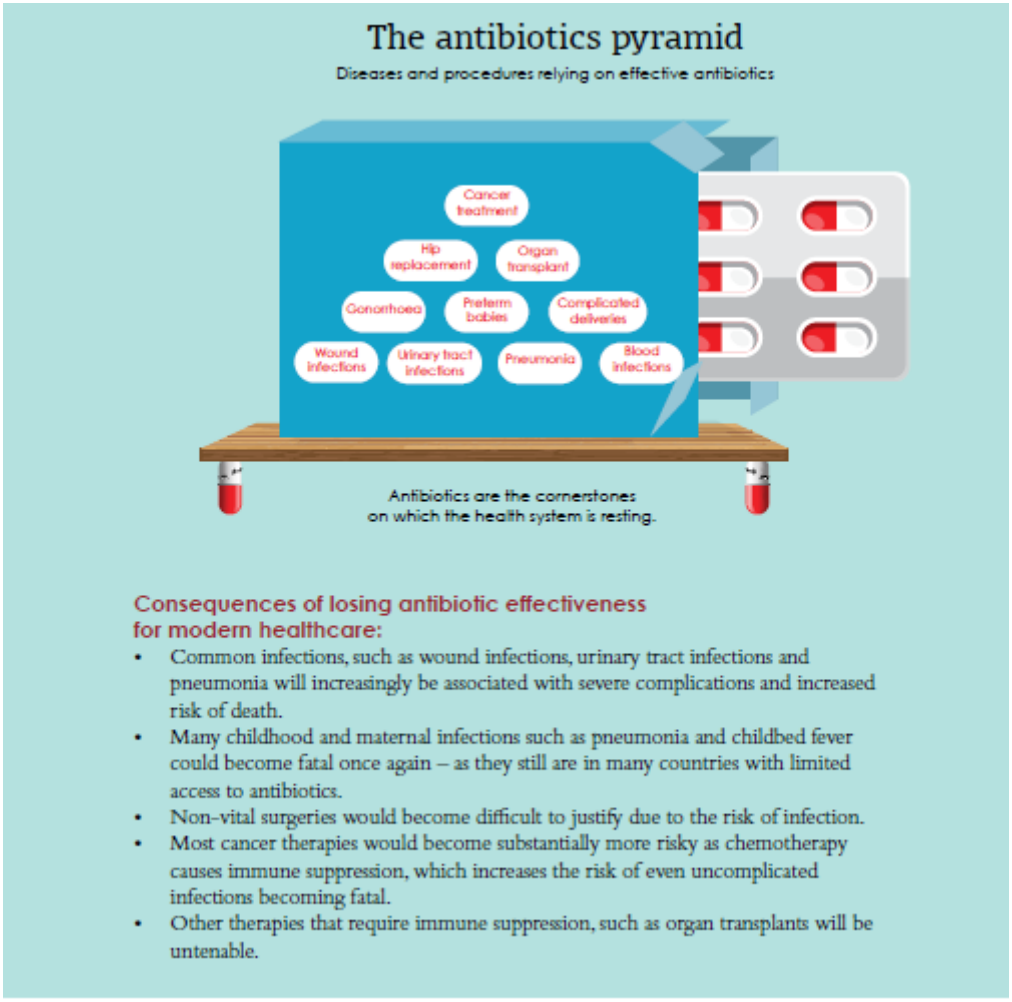

Fig 7: Access, overuse and sustainable consumption of antibiotics (adapted from van der Heijden et al. 2019).

5.5 Direct Fecal Releases

It is predominantly seen that AMR exposures occur in farm animal agriculture where the local sanitation is insufficient. In some parts of the world like Asia, with heavy use of antibiotics, ABR might arise from animal feces. According to the WHO and UNICEF, in 2015 2.3 billion

people lacked basic sanitation and many millions practice open defecation. Therefore, animal fecal matter contribute to antibiotic resistance in areas with inadequate sanitation.

5.6 Livestock Fecal Matter

Growing crops requires good soil, which provides important components for healthy soil, such as organic matter and microorganisms, such as bacteria and fungus, among other things. These vital organic materials not only offer food and shelter for microorganisms, but they also help to maintain soil structures and enhance soil fertility as well. For thousands of years, farmers have applied large amounts of manure to their fields to supplement the soil's organic matter content. The unfortunate reality is that manure from animals includes germs that can contaminate food and water, resulting in infections and contributing to the development of ABR in humans.

5.7 Degrading Drug Quality

The lack of sufficient testing capacity together with of low quality antimicrobials is a burning factor in the misuse of available useful antibiotics. As seen in most LICs, antibiotics can be directly purchased without a proper paperwork or medical prescription or doctor’s recommendation. It is often seen that drugs are dispensed by untrained personnel who are willing to sale medication to anyone. Even there are extreme cases where pharmacies operate without legal license, plus the absence of proper consultation, diagnosis and proof-reading prescriptions are a bonus. Some lack the proper storage facilities need to ensure optimum pharmacological performance of medicines. Emergence of counterfeit drugs, adulterated and sub-standard antimicrobials into the pharmaceutical markets needs strict monitoring since it itself is a major issue. Eventually, these preparations help in pathogens being exposed to

therapeutic concentrations of the drug which could otherwise be avoided (Farha and Brown 2019).

5.8 Wastewater

Wastewater is another route for spreading antibiotic-resistant organisms, particularly resistant strains, such as the carbapenem-resistant Enterobacteriaceae . However, the cleaning processes do not sufficiently remove all resistant bacteria. Eventually, it potentially impacts water users, such as water in household uses, irrigation systems, and consumption by livestock or humans (Brødsgaard and Kleinet 2019).

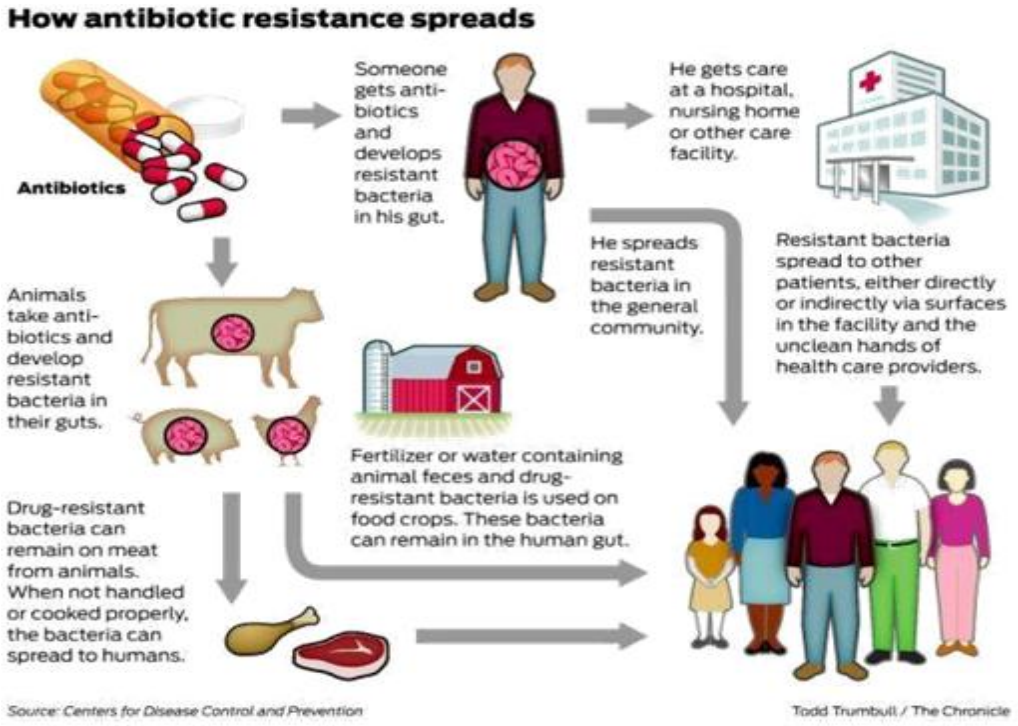

Figure 8: *How Antibiotic Resistance spreads to the community (adapted from Rajendran 2018).*

5.9 Innovation Crisis in Antibiotic Discovery and Development

In recent years, a number of interventions have been initiated to address the antibiotic scarcity. The need of innovative incentives for antimicrobial research has been highlighted by the

Swedish EU presidency. Following publication of the EU Action Plan on Antimicrobial Resistance, the Innovative Medicines Initiative launched a new program named "New Drugs for Bad Bugs". The partnership between the Singaporean Agency for Science, Technology, and Research and AstraZeneca to produce antibiotics for Gram-negative infections is another example of a public-private partnership in this field. DNDi which works with the University of Dundee's Drug Discovery Unit3, and the Medicines for Malaria Venture, which combines with Genzyme Corporation and the Broad Institute, are two more examples. Other recent reforms include the Joint Programming on Antimicrobial Resistance, which has made the discovery of new antibiotics and antibiotic alternatives a top priority on its strategic research agenda. However, many people, even those in the business, have criticized the approach's success in fostering Research and Development. The antibiotics issue isn't unique, and many observers have underlined the necessity of revitalizing the pharmaceutical industry's overall innovation potential. The movement away from physiology-based drug development and more towards target-based drug discovery might be one cause. In order to speed and enhance medicine development, a complete scientific study was perhaps neglected by focusing on processes rather than ailments.

Chapter 6

Strategies to Combat Antibiotic Resistance and Facilitate SDGs Achievement

6.1 Strengthening of Infection Prevention Practices

As seen in present COVID-19 situation around the world, regular hygiene practices have a profound impact on infectious disease. To cut the long story short, prevention is central to battle infections. . Secondly, the rise of new microorganisms as well as existing strains are creating havoc in the society, many of which were unknown in the past. Thirdly, changes in lifestyle and recent climate change will facilitate the transmission of infectious diseases in near future. Lastly, great care must be given to handle patients with reduced immunity which is linked with other health conditions like high blood pressure, diabetes, etc. This vulnerable group includes elderly patients, patients discharged from hospital, patients with serious health conditions, and patients undertaking drug or therapies, such as cancer, organ transplants etc.

Healthcare agencies should recognise the threats imposed by these emerging pathogens. HEDL must be promoted by the state as a part of public health. As it involves the intervention of the state, the tactics of implementing this intervention depends on differentiated health systems of various states/cities. Besides, the availability of necessary resources further amplifies the potential harmful effects. As a result, healthcare workers recognize the need for strict guidelines should probably be enforced in tackling antibiotic resistance. Therefore, national and state level policy makers must come out with effective measure to address the spread of infection through their policymaking process and healthcare infrastructure. Fortunately, some strong strategies are currently being designed

to develop and modernise hygiene behaviour in our everyday life by the state in some countries.

(i) Hygiene education in all institutions aim to ensure that all students at every levels have a minimal knowledge of antibiotics, their usages and proper hygiene practice.

(ii) There has been initiatives to train school nurses to promote infection control. For instance, the Local Community Infection Prevention and Control teams in the United Kingdom have been ordered vocational training.

(iii) Since 2016 great approaches has been taken for public engagement on antibiotic resistance. Also, an official website of the National Health Service was launched for everyone to provide solid information for the public on hygiene practices in the United Kingdom.

(iv) Germany undertook “Framework Hygiene Plan for Outpatient Service 2013” for taking adequate care of old patients at home through Technical Regulations and Accident Insurance and Occupational Safety Guidelines Availability. The control policies are evaluated by regularly.

(v) European Union founded a food hygiene promotion project to prevent the transmission of foodborne illnesses. This project aims to change consumer behaviour and eradicate reduce infections risk through food safety policy.

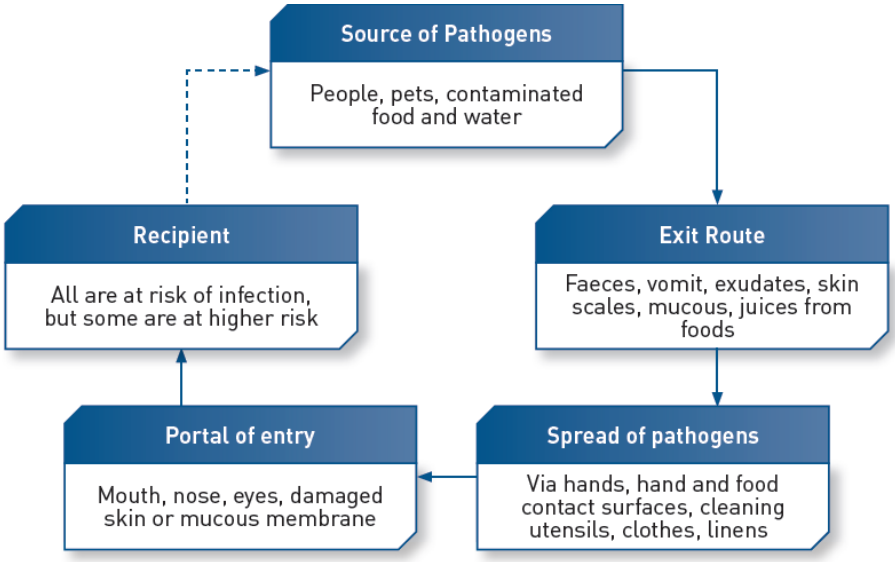

Figure 9*: The chain of infection transmission (adapted from Bloomfield et al. 2018).*

6.2 Prevention of Prescription Medication Overdose

In several parts of the world, for instance, the United States, there has been a sharp rise in mortality from an irrational prescription medication overdose. Therefore, the state policymakers needs to make legislative and regulatory recommendations.

(i) Prescription of antibiotics usage must be combated through educational measures through physical and mental examinations, doctor shopping, and tamper-proofing prescription forms, and regular clinic regulation.

(ii) There must be strict antibiotic monitoring and emergency response unit.

(iii) Prescribers of health care, as well as the general public, must be educated. This can be done through the safe storage, usage, and disposal of potent antibiotics could be the focus of community education campaigns. Besides, prescribers must be trained on the subject including alternative modalities, antibiotic overdose screening (Schroeck et al. 2015).

(iv) Reports say the antibiotic overdose is higher among children and people in their 50s than the overall population. Additionally, the elderly may be more inclined to take many medications at the same time to treat or manage multiple diseases, a practice known as polypharmacy. Polypharmacy is linked to worse health outcomes in the elderly, according to a systematic literature review published in 2005. The increased risk of drug interactions between many drugs, as well as the complexity of treating and managing various bacteria, are largely to blame for these negative results. As a result, successful care coordination and reductions in polypharmacy instances may be necessary for improved health outcomes in this population (Statements, Statements, and Database 2015).

6.3 Evidence-Based Approaches to Eradicate the Problem

Forming a group combining doctors, cops, and public health officials, the best promising policies and strategies for resistance is proper diagnosis strategy actions which are now judged to be the most promising to combat prescription antibiotic overdose. This includes:

(i) Legislation mandating a practitioner to examine or assess the physical health of a patient. Before prescribing or distributing potent drugs, a practitioner must examine the patient. Physicians, dentists, pharmacists, physician assistants, and nurses are all included in this category (kelsey 2015).

(ii) Legislation to prevent patients from acquiring antibiotics by going to a different doctor. Therefore, the prescribers can benefit from online database systems to keep the records of the patients and access to information. They can verify this information both before and after the initial prescription is written (Byrne et al. 2019).

(iii) Hospitals and clinics must registered with the state to receive a certificate or license. Owners may also need to be licensed prescribers. Unannounced inspections can be undertaken if the company is in good standing in the state. And to verify documentation.

6.4 Prohibiting Self Medication Practices

The WHO has issued many therapeutic recommendations including prevention strategies to inhibit self-medication practices. The WHO also recommends limiting the unnecessary use of antibiotics. Surprisingly in a study, 21.9% of those polled said they have used antibiotics in the past because of personal experience. Antibiotic use was also reported by 5.7% based on a friend's or relative's recommendation. Approximately 20% of participants stated that the reason for their absence was due to their belief that self-medication with antibiotics was the answer, hence it is not required to see a doctor because of their particular circumstances, along with their previous knowledge of the medicine. Other factors include cost-cutting, time-wasting, and visiting the doctor on a regular basis is inconvenient (Abduelkarem et al. 2019).

Self-medicating participants were asked to submit information regarding how they obtained their antibiotics, and it was discovered that a striking 69.3% acquired their antibiotics from a community pharmacy, while 20.8 percent utilized leftover medications from their homes. Furthermore, participants were asked what they would do if they experienced any side effects while taking antibiotics, and 47.6 percent said they would stop taking antibiotics, 4.4 percent said they would switch to another type, 5.4 percent said they would keep taking antibiotics, and 56.4 percent said they would continue taking antibiotics. Hopefully, the results of this study revealed that the participants relied heavily on their physicians and pharmacists as the most readily available sources of information for appropriate antibiotic use. Sadly, it also revealed that a portion of the participants consulted the drug leaflet, sought advice from family or

friends, and searched the internet. Relevant state entities to improve regulations and enforcement of existing state laws, such as

(i) Require physical examinations before prescribing any medicine and those that require patient identification before dispensing an antibiotic—can help to limit the irrational use of antibiotics.

(ii) The concerning authority have to educate customers by issuing guidelines for those who purchase health products (U.S. Department of Justice 2000).

6.5 Unlawful Internet Pharmacies

In recent years, the Internet has pervaded every area of people's life, including their health. This has made it easier to purchase medicines, especially antibiotics online. The majority of illegal Internet pharmacies have their own websites. These could be drug-advertising portals that direct customers to other websites where they can place orders and pay for them. Unfortunately, some Internet pharmacies operate without licenses or registration and administer pharmaceutical preparations comprising potent pharmaceuticals and psychotropic substances without requiring a prescription, and dosage regimen which is totally prohibited (Ghodse 2010). Some patients revealed that they took antibiotics for 4–7 days. However, 20% said they only used the antibiotic for one to three days, and just 14.3% said they used it for more than seven days. Surprisingly, when asked when they stopped taking antibiotics, over three-quarters of participants said they stopped taking them at the end of the course. 22.2 percent, on the other hand, said they would quit taking antibiotics as soon as they felt better. In addition, strategic steps are required where authorities must ensure that legislation and the application of laws and sanctions by courts are stricter with regard to the illegal operation of internet pharmacies in particular, such as

(i) The Royal Pharmaceutical Society of Great Britain has developed a project that will provide people ordering from internet pharmacies with direct access to the Society's website, allowing the pharmacy is properly registered with the Society (Ghodse 2010).

(ii) Visitors to the website can check the pharmacy and pharmacist's registration information, ensuring that they are obtaining medicines from a legitimate pharmacist. Furthermore, public awareness efforts should inform the public about the dangers of unlawfully running internet pharmacies (kelsey 2015).

(iii) Involvement of national professionals, relevant international organizations, broadband providers, financial sectors, and pharmaceutical associations. These guidelines are anticipated to serve as a beginning stage for global cooperation, leading to internationally adopted controls on this relatively new supply of antibiotics (kelsey 2015).

(iv) State medical boards must regulate medical practices in each state, including the issuance of licenses and the ability of practitioners to write prescriptions. State boards of pharmacy must be responsible for regulating, licensing, inspecting, investigating, and enforcing pharmacy regulations in their area.

(v) States enact legislation to regulate Internet pharmacies expressly. However, much of this legislation focuses on making sure that online pharmacies follow current rules and establishing consequences for illicit sales. Some states have taken more targeted measures (Kelsey et al. 2009).

(vi) There should be law mandating all pharmacies to receive VIPPS certification .For instance, the must pass legislation that defines and/or regulates Internet pharmacies (Kelsey et al. 2009).

(vii) Further prevent access to banned substances via internet transactions (Kelsey et al. 2009).

6.6 Prohibiting the Use of Antibiotic in Animals

While Antibiotics are also used in livestock farming where antibiotics are employed for disease mitigation and prevention of animals, growth promotion, and feed efficiency. So, the overuse of antimicrobials in agricultural sector contribute to the progress and development of resistance (FDA 2018). Interestingly, the soil has a connection between the air, water, and organisms, and serves as a reservoir of antibiotic-resistant microbes. According to a recent report, animal husbandry consumes 75% of all antibiotic use globally, and is expected to increase to 67% worldwide by 2030. Moreover, many countries do not have adequate control to monitor the misuse of antibiotics in the first place. In agricultural sector, immediate measures must be taken to discourage antimicrobial use. Thus, improved animal nutrition, improved living circumstances with optimized waste management, biosecurity management, plus natural immunity can result in infection prevention and control, and state policymakers must impose concerted effort to reduce the unjustified use of antibiotics. Moreover, prescribing prebiotics, probiotics, bacteriocins, vaccination, and anthelminthic therapy limit antibiotic consumption. These strategies hope to diminish the need of antibiotic needed for treatment. Furthermore, the use of antibiotics without prescription and supervision animal farming should be forbidden. The state should hire veterinary inspectors and pharmacists to enforce the regulations and guarantee that farmers have access to consultations on antibiotic dose, strength, and administration (FDA 2018). Prior to prescribing antibiotics, the goal and causative agent of the condition must be verified.

The marketing and sale of prescription pharmaceuticals is regulated by federal agencies such as US FDA which regulate the sale and administration of medications at both the federal and state levels. The FDA oversees the safety and efficacy of medications and medical equipment, as well as determining which drugs are permitted to sell.

The Federal Trade Commission and the FDA oversee drug vendors' lawful claims and regulate marketing tactics on a national level.

Besides, the DEA is in charge of regulating the prescription and dispensation of restricted substances in the United States. The DEA is authorized to enforce the lawful administration of prohibited substances, and all prescribers and dispensers of controlled substances must register with the agency.

It's worth noting that certain states allow pharmacists to sell naloxone without a prescription.

According to federal law, pharmacies must:

(i) Place information about their physical location on the bulletin board with the name of the pharmacy and its address and telephone number.
(ii) Post the pharmacist in charge's credentials, such as the license number.
(iii) After receiving certification of registration for its physical location,
(iv) Display the DEA's seal of approval.
(v) The National Association of Boards of Pharmacy must renew the licenses of pharmacies assessed were in conformity with US laws and practice standards
(vi) The sale of prescription medications to anybody without a valid prescription must be declared illegal under federal law (FDA, 2011).

6.7 Monitoring of Antibiotic Prescription and Availability

Undoubtedly, health conditions such as respiratory tract infection, urinary tract infection, and fever has become a major threat to people across the globe. The diagnosis and treatment need frequent use of antibiotics as other conventional drugs are not routinely available for use. Nonetheless, for this purpose, the awareness program is mandatory. In many cases, antibiotics are being dispensed in the case of viral infections as well as fevers with no known cause (Nathan and Cars 2014). In many areas, there is numerous evidence indicating that the over-prescription and lack of regulation contribute to the development of ABR (Superbugs article.pdf n.d.). Therefore, the solution requires private and public incentives, guidelines from regulating authorities and involvement of more and more pharmacists in clinical surroundings. Also, the overuse of antibiotics has resulted from private benefit private benefit and lack of health infrastructure. Also, the presence of low quality substandard medicines at incorrect doses quicken the rate of resistance. Therefore, it the core duty of the policy makers to put more focus on this matter allocate resources for collective implementation in different states (UNESCO 2016). Besides, other awareness campaigns can be carried out, for instance, public awareness campaigns, marketing campaigns, and pharmacist training to avoid unintended consequences. According to a recent study conducted in Bangladesh, young children are frequently the genuine victims of antibiotic overuse. According to the inquiry, antibiotics for children aged 0-4 years were purchased in 26% of cases, while antibiotics in quantities smaller than a single day's dosage were purchased in 48% of cases. Pneumonia and diarrhea are the two most frequent infectious diseases among children, with diarrhea killing over 230 000 children each year. However, according to one study, the percentages of adequate antibiotic treatment for pneumonia and diarrhea were 57.1 percent and 67.8 percent, respectively. Misuse of medications in the treatment of acute diarrhea in children under the age of five is common, with WHO-recommended therapies seen in just 26.7 percent of cases and metronidazole

administered in all 38.6 percent. The most prevalent therapeutic mistake in dysentery is the use of many and inappropriate antimicrobial medicines (UNESCO 2016). Patients' photo identity is checked at the pharmacist. Because antibiotic resistance is on the rise, pharmacists may ask patients to show photo identification when picking up their medications at the pharmacy. This could be accomplished by demanding that a patient's identity be verified prior to the acceptance of a prescription drug claim. In some places, such as Virginia, legislation is being proposed that would require people to show photo identification when picking up restricted narcotic prescriptions. The Government Accountability Office suggested that insurers remove deceased patients and physicians from their systems to avoid paying claims for fraudulent prescriptions. This problems can be solved by:

(i) There must be Federal Law to inhibit pharmacist sell antibiotics without proper prescriptions. In that case, information about their physical location must be placed on the bulletin board (kelsey 2015).

(ii) After receiving certification of registration for its physical location, the pharmacist in charges must display credentials (license number) along with seal (Kelsey et al. 2009).

(iii)The sale of prescription medications to anybody without a valid prescription must be made illegal under the federal law (FDA, 2011).

6.8 Banning the Unethical Marketing and Promotion of Antibiotics

The reduction of transmission of infectious diseases involves a variety of miscellaneous factors; however, banning the unethical marketing and promotion of antibiotics seems the most significant. Prominent companies are using supreme irrational marketing strategies to promote innovation. Undoubtedly, this appears a lucrative idea to solve the challenges facing the global antimicrobial regime. This recent trend demands exclusive policy that involves the imposition of worldwide marketing bans on antimicrobial which includes renovations in marketing

strategies, price, packaging, and all online/offline advertisements. Again, there needs to be a strict regulations on cross-border effects implemented by certain countries (Ayukekbong, Ntemgwa, and Atabe 2017). A variety of restorative materials focusing on new targets and perhaps other strategies should be investigated to at least partially successful in the battle against bacterial infections. Although some of the ones that have previously gotten scientific attention, there is a need for further investigations. Experts suggest that the marketing and sale of prescription pharmaceuticals is regulated by a number of federal agencies (US Food and Drug Administration, 2011).

(i) The role to ensure the safety and efficacy of medications and medical equipment, as well as determining which drugs are permitted to sell must be controlled by the regulating authority (Kelsey et al. 2009).

(ii) The regulatory authority, for instance the FDA in the USA, oversee drug vendors' lawful claims and regulate marketing tactics on a national level. DEA is in charge of regulating the prescription and dispensation of restricted substances in the United States (kelsey 2015).

6.9 Targeting with the Stability

Virulence characteristics are currently being studied by scientists. Additional methods that can be used in conjunction with the use of antibiotics targeting virulence characteristics rather than synthesis or growth routes. The goal of this strategy is to lower their virulence feature, and it ensures targeting genes concerned in microorganism motility or clogging the arrangement of the proteins within the organelles which lead to a considerable hinder the spread of the infection.

There is a way of inhibition of secretion systems. There are some microorganism genes which take part in secretion of macromolecules, particularly those taking part in pathologic process. The looks a good approach to influence virulence that will advantage more elaborate analysis.

6.10 Improving Hygiene and Sanitation

The recent Covid-19 situation made a great impact on improving living condition around the globe and sanitation practices to diminish the circulating environmental microbes around us. Scientists widely believe that transmission of pathogens is made through human contact, unhygienic food and water, and vectors. Therefore, equally priority must be given to the hygiene processes needed to remove pathogens from hands, arms, body and other surfaces. It is widely assumed that contaminated surfaces can increase the rate of infection, therefore, some steps can be followed, such as:

(i) Incorporating appropriate antimicrobial product, such as disinfectants or sanitizer that kill pathogens.

(ii) Using antimicrobial products as well as physical processes, such as heat (Rajendran 2018).

(iii) Health agencies and professionals must put special emphasis on cleansing of hands, food, water, clothes, fabrics, cooking utensils, toilets, baths, floors, washbasins, walls, furniture etc (Bloomfield et al. 2018).

It is also the exclusive responsibility of healthcare professionals and policymakers to investigate common misunderstandings about health and cleanliness and focus on producing positive outcomes for standard of living (Faiz and Ariful 2011).

6.11 Vaccination

As seen in recent COVID-19 situation, vaccines are a crucial mode of protection against infectious diseases around us. However, several prominent drugs from numerous companies available in the market, but these have proved to be insufficient to control the mass destruction. In such delirious situation, vaccines seem to be a ray of hope, and researchers are working laboriously to bring the best innovation. As seen in previous pandemics, only an effective vaccine can stop the deadly outbreak as in 2020. Developing an effective vaccine within a short period of time can be quite challenging, but some renowned giants, such as Pfizer/Biontech, Moderna, AstraZeneca, have made major breakthroughs in the market. Others are in the clinical trial stage ready to hit the market soon. Both nation and international approaches have been made to fasten the elaborate progress and greater emphasis have been put on good manufacturing practices and logistical facilities. Besides, vaccines provide herd immunity susceptible population, such as, measles, infectious disease measles, diphtheria, hepatitis etc. Hopefully, vaccines serve the best treatment choice by many professionals, but this approach much be strengthened by strict hygiene practices.

6.12 Role of Stakeholders

With the new deadly variants of microbes, the issue concerning the development of AMR needs the attention of stakeholders and government agencies locally and globally. Sadly, there has been in lack of new plans and action development in economically poor developing countries. Therefore, the World Health Assembly puts great emphasis on surveillance, equal coverage, responsible usage, and infection are all important considerations among these countries (Årdal et al. 2016). To guarantee long-term viability, coordination is one of the characteristics that is frequently mentioned which needs to be successfully carried out by UN organizations and exemplified by the United Nations and the WHO's resolutions on antibiotic resistance. Higher

degrees of collaboration, on the other hand, are required for various other aims. This involves the exchanging of information transfer of information and data between countries—for example, information distribution and instructional materials on illness management and therapy. Thus, coordination is required for effective global governance as well as the adoption of appropriate measures. Other aims, for example, encouraging universal access, ethical usage, and other initiatives which will be even more important in the future of innovation.

The first and foremost task is providing education to health care providers about rational prescription writing and the significance of evidence-based prescription practices through training. Plus, the whole needs to be educated about the continuously evolving microbes through media professionals and scientific information delivered in multiple pathways to inform the general public. Luckily, WHO has assigned a strict roadmap to tackle ABR. Also a number of new initiatives have been taken by regulatory agencies which includes the US government assigning a 'National Strategy for Combating Antibiotic-Resistant Bacteria' in September 2019. Likewise, the Canadian Government issued the Federal Action Plan while some African countries have launched the GARP as a medium for developing laws on antibiotic resistance.There are some steps that international and national stakeholders must do in order to achieve the global plan's purpose and goals.

(i) A basic component of combating antimicrobial resistance must be education, training, examination, professional registration, or certification for professional organizations' professional development.

(ii) The professionals must promote antimicrobial resistance awareness and excellent hygiene practices.

(iii) National State members should involve organizations, such as the FAO, the OIE, and the World Bank to promote antimicrobial resistance knowledge. Together they

can develop and implement global communication programs, such as an annual global antibiotic awareness campaign.

(iv) Other stakeholders, such as civil society organizations, trade and industry organizations, employee organizations, scientific education foundations, and the media, should work together to improve public awareness and understanding of infection prevention and antimicrobial medication use across all sectors.

(v) Incorporate the rational use of antimicrobials curriculum to encourage a deeper knowledge and raise public awareness, and supply public media with accurate information timely.

(vi) Recognize antimicrobial resistance's indications and symptoms as a top priority for action across the board, with government departments included. Make veterinary medicine and agricultural practice a strong role in an annual international events (WHO 2017).

6.13 Alternative Advances

Due to rise in microbial resistance, completive market and the advancement in research and development by pharmaceutical companies, great advances have been made in this field. There are currently few other alternatives approaches which are mentioned below:

6.13.1 Stem Cell Therapy

The SARS-CoV-2, also known as COVID-19, because great damage to an individual's immunity as COVID-19 patients generates significant inflammatory response. In recent situation, researches have claimed stem cell therapy to be a blessing to treat COVID-19 patients. As previously discovered, stem Cells have the eligibility to cure any internal organ damage by inhibiting the release of cytokines in the internal environment system. Thus,

they support the repair of internal organs. Interestingly, the concept is made into practice through clinical trials for the treatment for COVID-19 (Golchin et al., 2020) patients, cancer patients, and patients suffering from genetic disorder.

6.13.2 Probiotics

Probiotics therapy, such as Bacillus, Lactobacillus, Lactococcus, and Streptococcus, is a treatment option which destroy disease-causing microorganisms by producing antimicrobial substances such as bacteriocins to improve the internal flora. They stick to inner intestinal mucosa. As a result, external deadly microorganisms cannot survive as these friendly bacteria compete with pathogens for nutrients and space. Probiotics also improve the intestinal immune response along with the better digestion and absorption food to provide nutrition (Ayukekbong, Ntemgwa, and Atabe 2017).

6.13.3 Bacteriophage

The use of bacteriophage is a promising substitute for emerging infections. Many researchers and scientist support bacteriophage therapy to conventional antibiotics. Bacteriophages have the ability to invade bacterial cells and stimulate the cell death.
At present when the world is facing the worst global health crisis and economic catastrophe, the pharmaceutical companies and other healthcare organizations must explore the eligibility of phage therapy (Ayukekbong, Ntemgwa, and Atabe 2017).

6.13.4 Plasma Transfusion

There are now miscellaneous pharmaceutical companies and research institutes which are conducting intense research endeavors in plasma transfusion. It has been suggested that cold plasma jets might be a safe and effective alternative to antibiotics in the treatment of multi-

drug resistant diseases, according to a research published in the Journal of Medical Microbiology in January. According to the findings of the team of Russian and German researchers, a ten-minute treatment with low-temperature plasma was not only effective in killing drug-resistant bacteria that cause wound infections in rats, but it also enhanced the rate at which the wounds healed. The findings imply that cold plasmas may be a potential treatment option for persistent wound infections in situations when other methods have been ineffective (Ermolaeva et al. 2011).

6.13.5 Quorum Sensing

While vaccine development is a time consuming process, an important alternative approach may be provided by quorum sensing. Quorum sensing prevents and treats infectious diseases. Gram-negative microorganism utilize N-acyl Lhomoserine lactones (AHLs) which possess lactone rings and carboxylic acid incorporated to the chain. Quorum sensing inhibitors attenuate microorganism virulence. A recent study carried out in pathogens like Pseudomonas aeruginosa, Vibrio, and eubacterium, Cholera, etc. showed that the Sensing system is a potential treatment of microorganism infections. Since a few vaccines had a successful clinical trials, many believe that the Sensing system will be beneficial over typical antibiotics (Ayukekbong, Ntemgwa, and Atabe 2017).

6.13.6 Nano-Antibiotics: New Novel Strategy

Recent advancements in Nano-antibiotics systems paved the pathway to enhance the therapeutic efficiency of nanoparticles to combat antibiotic resistance globally. The concept has been practice in other areas of science where the magnetic nanoparticles are made to accelerate by the external magnetic field. Due to their unique, sophisticated properties are gaining high acceptability from the scientific community, and they are claimed to be

beneficial for cancer treatment. They have low toxicity and improved bioavailability in the area of nanomedicine than traditional antibiotics (Saravanan et al. 2021).

6.14 Hindrance

Undoubtedly, there are numerous challenges to finding permanent solutions to the global problem of antibiotic resistance. First is the irresponsible prescribing of antibiotics on the part of the doctors and healthcare practitioners. This gives rise to the ineffective treatment of many common infections such as pneumonia, common cold, urinary tract infections, cancer treatment, wound infections, organ transplants, etc. The global impact of antimicrobial resistance is rising as clearly demonstrated in COVID-19 situation. Therefore, increased morbidity and mortality in clinical and community settings is rising too. Secondly, worldwide food trade accelerates the spread of different bacterial species, and from bacteria in animals to humans. Legal regulation of antibiotic sales is strict in certain parts of the world, but it is challenging to implement in practice in others. Thirdly, the abuse or overuse of antibiotics is enough to deteriorate the situation (Maillard et al. 2020).

6.15 Final Words and Suggestions

AMR does not have a proper cure at this moment. One can consider it a silent killer that diminishes the effectiveness of treating many common diseases and surgical procedures. Undoubtedly, the topic deserves public attention. Else, it can affect countless victims of drug-resistant infections as seen in previous years. The issue requires a collective approach locally and globally.

Research and assessments at the national level should be conducted to better understand the specific needs of LMICs in terms of access to effective antibiotics, and a greater emphasis should be placed on the availability of vaccines.

Efforts to improve worldwide access to antibiotics must incorporate and improve appropriate use, such strengthening health systems through technical and financial support, increasing access to diagnostics, along with increasing primary prevention measures, among other initiatives.

Furthermore, nations' laboratory capacity and surveillance operations will need to be strengthened in order for them to be able to monitor their access to potent antibiotics and quickly switch to other medicines if resistance develops. It is suggested by experts that the use of surveillance data must become normal protocol for governments to monitor a usage and execute any required remedial steps if they are not already doing so (Mendelson et al. 2016).

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