A Critical Review of Dadgoster (2019) Antimicrobial Resistance: Implications and Costs

TABLE OF CONTENTS

1. INTRODUCTION

Antimicrobials are drugs that are used to prevent and treat infections in humans, animals, and plants (WHO, 2021). Antimicrobial resistance (AMR) develops when microorganisms evolve and cease to respond to medications, making infections more difficult to cure and raising the risk of disease spread, severe sickness, and death (WHO, 2021). As a result of microbial resistance to medication, antimicrobial therapies become ineffective and infections become increasingly difficult or impossible to treat (World Health Organization, 2021). Misuse and overuse of antibacterial agents in the healthcare and agriculture industries are the major reasons that contribute to the emergence of AMR (Dadgoster, 2019). AMR is caused by spontaneous evolution, bacterial mutation, and horizontal gene transfer of the resistant gene (Dadgoster 2019). There exists severe financial consequences of AMR including very high healthcare costs due to increased hospitalization and increased drug use. AMR would consequently have impacts on the patient, healthcare, and the quality of life. This review will analyze the epidemiology of causes linked to AMR, the global economic impacts of AMR, evaluation of surveillance data and statistics for AMR, and finally ethical issues associated with AMR and future research literature and actions to improve health outcomes for AMR. The review aims to critically analyze the design, result, accuracy, and validity of a study carried out by Dadgoster (2019), on the implication and costs of Antimicrobial Resistance, and using the knowledge and conclusions from this review to inform public health practice.

1.1. BACKGROUND

AMR is a serious challenge that has been constantly rising and spreading rapidly since the past decades (Mann *et al.,* 2021). AMR is the propensity of microorganisms to proliferate in the presence of antimicrobial medications that in time past were able to inhibit or destroy them (Founou et al., 2017). AMR is driven by evolutionary pressure through antimicrobial exposure in health care, agriculture, and the environment (Holmes, et al., 2016). Increase human consumption of antimicrobials whether clinically necessary or not as well as widespread prophylactic use of antimicrobials in agriculture has been associated with the proliferation of AMR (Shrestha, *et al.,* 2018). Other key drivers of AMR are in Figure 1 (Shrestha, et al., 2018).

All over the world, AMR has become a significant problem to public health, and it poses a more serious threat to the public health systems in developing countries. The future of healthcare is uncertain as regards infectious diseases because these diseases can no longer be treated by the available antimicrobials (Chokshi et al., 2019).

AMR infection has continuously led to a prolonged hospital stay, increased cost of alternative or second-line drugs, increased cost of healthcare, treatment failure, and consequently death (Prestinaci 2015). According to Center for Disease Control and Prevention (CDC), AMR adds a 20 billion dollar surplus cost annually, in the United States.

CDC also reported that AMR diseases result in a minimum of 26,000 deaths annually.

AMR complicates the conditions of patients that have diabetes, cancer, rheumatoid arthritis, and patients undergoing surgery and chemotherapy. To deal with AMR, physicians resort to carbapenems and polymyxins which are very expensive with numerous side effects and not readily available in developing countries (WHO, 2015). AMR continues to be a global menace that in decades to come can potentially cause serious catastrophe to the World if adequate measures are not put in place to curtail its prevalence.

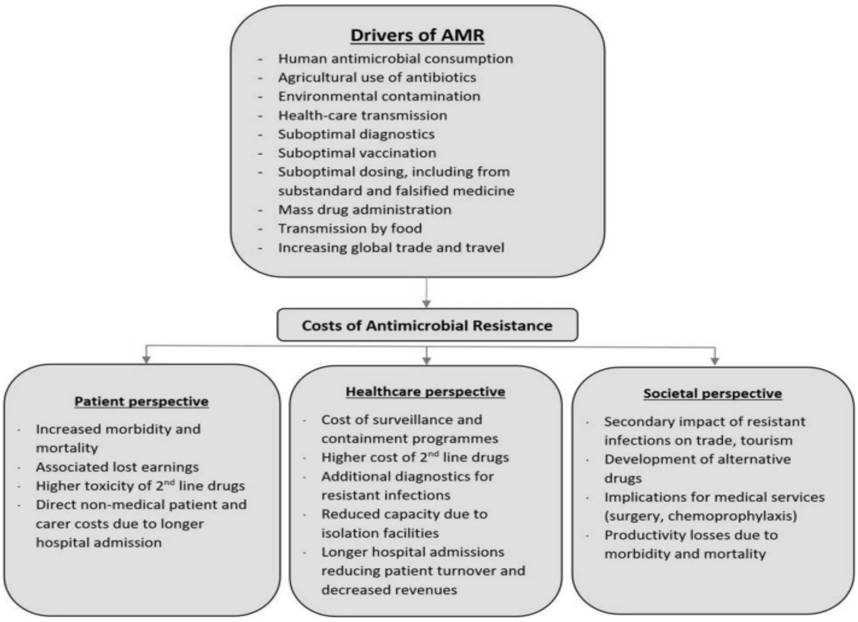


Fig. 1: Drivers and associated cost with AMR. Adapted: (Shrestha, et al., 2018).

1.2. AMR AS A PUBLIC HEALTH CONCERN

The ability of a disease-causing microbe to survive antimicrobial agents is a growing global public health concern (Booth & Wester, 2022). The Centers for Disease Control and Prevention (CDC) estimates that more than 35,000 people die each year from antibiotic-resistant illnesses in the United States (CDC, 2021). Research has shown that the probable causes of antibiotic resistance are the extreme use of antibiotics in animals and humans, antibiotics sold over-the-counter, increased international travel, poor hygiene, and antibiotics residues in manure and feces (Aslam et al., 2018).

Antibiotics consumption has increased significantly over the year. In 2000, the highest antibiotics consumption rate was in The United States, Hongkong, Spain, and new Zealand. However, in 2015, this rate was highest in low and middle-income countries such as Tunisia, Algeria, turkey, and Romania (Klein et al., 2018).

Antibiotics use in agriculture is a major factor contributing to AMR. Almost 80% of the antibiotics sold in the United States are applied to animal food (Bartlett et. al., 2013). Worldwide, in 2010, 63,200 tonnes of antibiotics were used in livestock production, a value higher than human consumption of antibiotics.

A recently published study by researchers from the Helsinki University Hospital (2019) showed that higher exposure to antibiotics that are commonly used are associated with an increased risk of Parkinson's disease. Antibiotic resistance has been recognized as a global public health issue by various organizations such as WHO, CDC, and Infectious Disease Society of America (IDSA) (Aslam et al., 2018). It would consequently be of great importance to emphasize the sales of antibiotics that are sold over the counter and gives access to its misuse without medical prescription, this is especially common in developing countries. O'Neil (2016), opined that for one reason or another, treating resistant illnesses is either difficult or prohibitively expensive, and as a result, many individuals die because there are no or too expensive alternatives. The British Review on AMR estimates that at least 700,000 people die each year from antibiotic-resistant diseases (O'Neil 2016) and that number is anticipated to rise dramatically in decades to come (O'Neil 2016).

2. SUMMARY OF STUDY

(Dadgoster*, 2019)* study unveils certain challenges caused by AMR which are associated with the misuse and overuse of antibiotics both in the healthcare and agricultural sector, these he attributed to laps in regulations and surveillance regarding their use, availability of the poor quality of antibiotics (especially in low-income countries), excessive use of antibiotics in food processing and animal rearing (Chokshi *et al., 2019*) increase in income level and easy travel routes, biological factors such as horizontal gene transfer (Chaw *et al.,* 2018) and gaps in knowledge (WHO, 2015).

3. CRITICAL REVIEW

This critical review will analyze the five key areas associated with AMR which include but not limited to the epidemiological causes, global economic impact, surveillance evaluation, associated ethical issues, and future research and actions to improve outcome. All these will be accessed below along with other observations of the research including the lapses in the study, especially as compared with other AMR-related studies.

3.1. EPIDEMIOLOGY OF CAUSES LINKED TO AMR

AMR is a leading cause of death in the world with the highest threat in low and medium-income societies. Bacterial AMR is a serious global health issue whose magnitude is as large as HIV and Malaria, and it has tendencies to even get larger. There are many causes of AMR which includes misuse or overuse of antimicrobials, use of antimicrobials in agriculture, sales of antibiotics over-the-counter which leads to self-medication by the patients, availability of financial incentives for physicians who prescribe more antibiotics, rise in the standard of living, insufficient regulatory policies on antibiotics use and spontaneous mutation by bacteria.

The misuse and overuse of antibiotics is a serious factor contributing to AMR. Studies have shown that many patients across the globe especially in developing countries believe that antibiotics would help to relieve cold and flu symptoms which are mostly viral in origin. This is further complicated by insufficient enforcement of regulatory policies (e.g in India and Vietnam) on antibiotics where antibiotics are sold over-the-counter without physician's prescription. Also, in developing countries, there are inadequate diagnostic tools, and patients are blindly prescribed antibiotics without relevant medical tests to ascertain the presence of a bacterial infection (Chaw et al., 2018). All of these factors contribute to the misuse and overuse of antibiotics that would potentially lead to AMR.

In 2019, various antimicrobial resistance collaborators carried out a study, which was purported by these authors to be the most comprehensive study on the estimate of AMR burden. This study estimated death and disability associated with bacterial AMR for 23 pathogens and 88 pathogen–drug combinations in 204 countries and territories. Based on the predictive statistical model used for this study it was estimated that 4·95 million (3·62–6·57) death was associated with bacterial AMR in 2019. Based on region, Western sub-Saharan Africa has the highest death rate associated with resistance to antimicrobials at 27·3 deaths per 100000 (20·9–35·3. Australasia has the lowest estimate at 6·5 deaths (4·3–9·4) per 100000. The six leading pathogens the deaths associated with bacterial resistance are *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii,* and *Pseudomonas aeruginosa.*

Agricultural use of antibiotics has also been a serious factor contributing to AMR in humans. In the United States, 80% of antibiotics are applied to animal food and the antibiotics consumption in livestock is higher than antibiotics consumption in humans. In 2010, livestock consumption of antibiotics was 63,200 tons. The use of antibiotics to treat livestock and also addition of antibiotics in animal drinking water as a means of prevention is also a problem. Colistin, a last resort antibiotic in humans has also been used abusively in promoting the growth of livestock, specifically pigs (United Nations, 2016). The use of farm animal waste, antimicrobial spraying on fields, and other actions to cure illnesses has resulted in increasing transmission levels of antibiotic resistance genes discovered at various levels of the environment (Mann et al., 2021). Fig. 2 depicts the route taken by antibiotics and antibiotic resistance genes as they pass through agriculture and livestock (Mann et al., 2021).

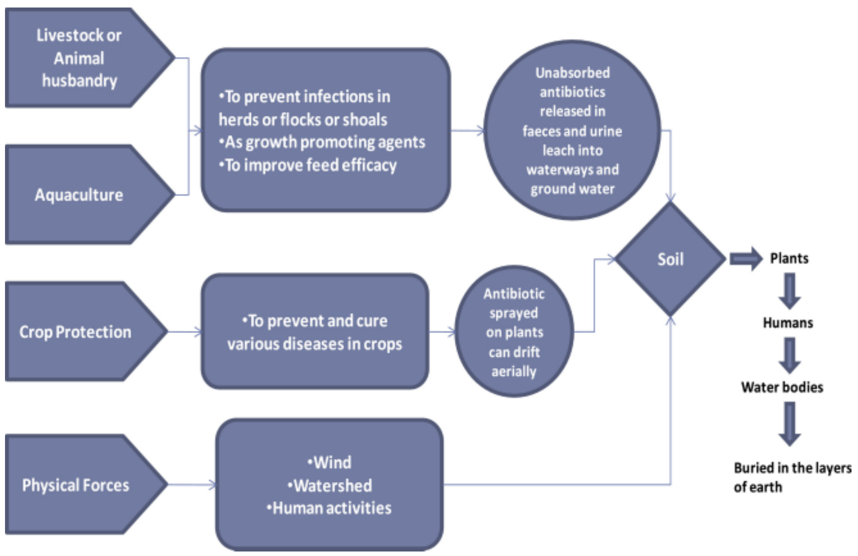


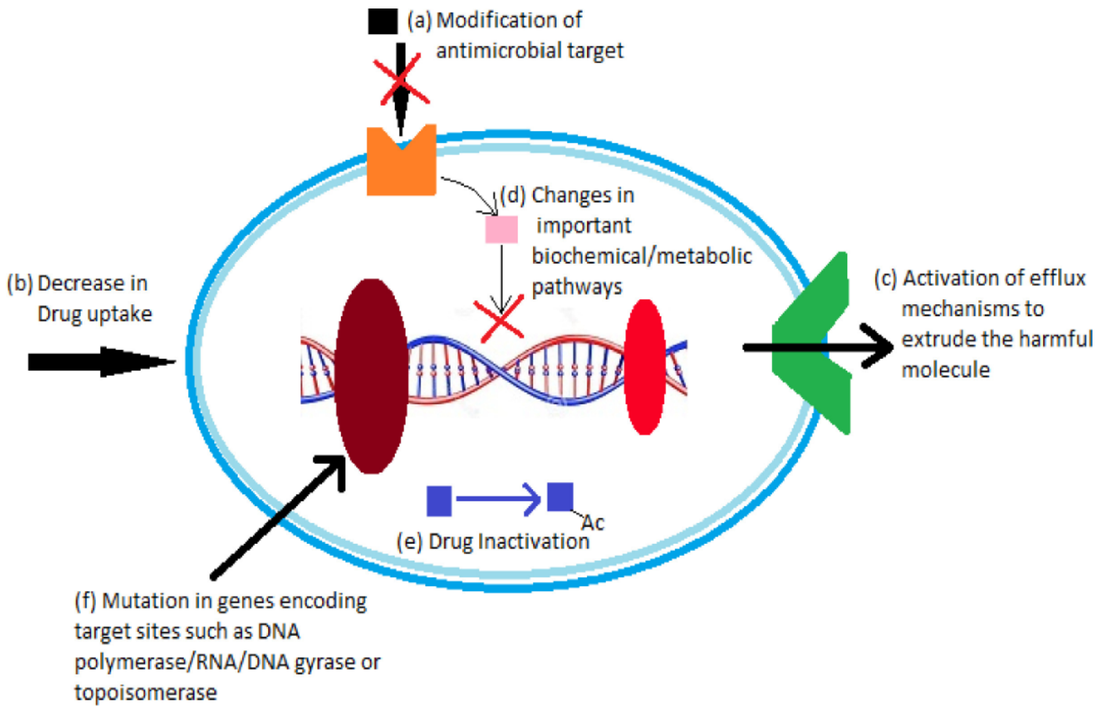
Fig. 2: Pathway of antibiotics and antibiotic resistant genes

Transgenic crops were meant to reduce antibiotic consumption and inhibit the spread of antibiotic resistance, but according to Mann et al., (2021), the opposite has happened, with the overuse of transgenic crops currently indirectly increasing antibiotic resistance (Mann et al., 2021). Aside from that, Mutina et al. (2016) showed that various bacteria use distinct strategies to fight antibiotic resistance, which may be classified as

(i) genetically based and

(ii) mechanistically based.

These strategies include (a) altering antimicrobial targets, (b) decreasing drug inactivation, (c) activating efflux mechanisms to expel hazardous compounds, (d) altering key metabolic pathways, (e) drug inactivation, and (f) altering target site genes (Mann et al., 2021) as shown in **Figure 3.**



According to the findings of the 2019 study by Collingnon and Beggs, the two major contributors to the rise in AMR are now better understood, in addition, the development of antibiotic-resistant organisms and/or genes coding for antibiotic resistance are significantly impacted by societal and economic variables such as the usage of antimicrobials and the dissemination of resistant microbes (Collingnon & Beggs 2019). According to Collingnon and Beggs (2019), the spread of resistant microbes happens mostly through direct contact with humans and animals, as well as through a variety of carriers such as water, direct contact with animals and food, insects and birds, agriculture, and aquaculture.

The development of AMR is exacerbated by multi-drug resistant bacteria, which result in longer-lasting illnesses in the body, which in turn increases the likelihood of transmission to other people (WHO, 2018). It has been shown that the prevalence of AMR is related to a variety of typical economic growth measures, including infrastructure, education, GDP, and public health expenditures (Collingnon & Beggs 2019). The study found that antimicrobial rates were connected with rising temperatures, lack of government administration, and the ratio of private to public health care costs (Collingnon and begs, 2019).

In other research, Manyi-Loh and colleagues 2018 discovered resistant bacterial strains that could be harmful to humans in animal-derived products, and they blamed this on the high demand for animal protein in developing countries, which prompted intensive farming that eventually led to antibiotic residues (Manyi-Loh et al., 2018).

Inadequate patient education, lack of diagnostic resources, and unskilled health professionals are all part of the medical impact of antibiotic resistance. However, inadequate drug regulating systems lead to insufficient administrative control, which is the root of AMR (Collingnon, 2019). According to Aslam et al. (2018), most countries lack the funds to enforce laws against poor medicine manufacturing and distribution. Katwyk et al. (2019), argues many countries have created antimicrobial action plans, but most are yet to develop policy intervention methods to decrease antimicrobial misuse. Using organised paperwork, the government can identify, characterize, and evaluate the relevant category of reviewed government laws to limit human antimicrobial usage (Katwyk et al., 2019).

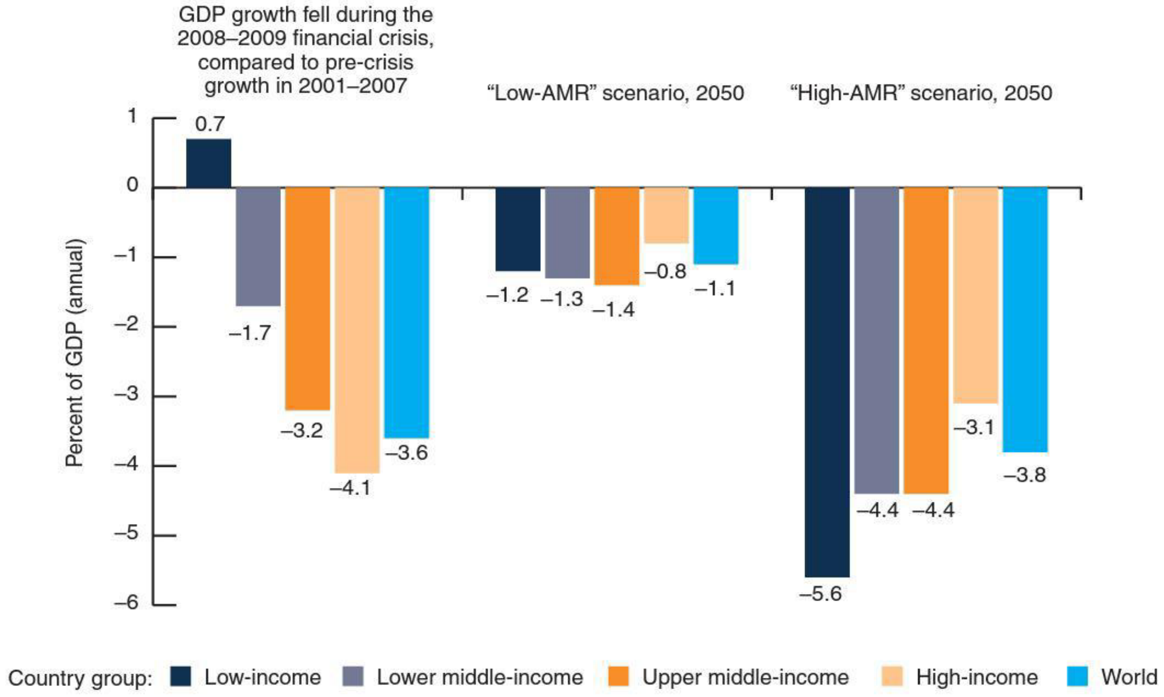
The “one health approach” to antibiotic surveillance has benefited AMR monitoring and management in some countries (Aslam et al., 2018). However, this study (Dadgoster, 2019) fails to provide any recommendations for improving antibiotic surveillance or implementing the “one health strategy” with evidence. A new systematic study and meta-analysis recommend reporting current AMR levels using laboratory-based AMR surveillance (Mouiche et al., 2019). To increase global AMR surveillance, governments must join the World Health Organization's Global AMR Surveillance System (GLASS), which now has 70 countries signed up. However, several nations lack efficient surveillance methods through laboratory and data management, which the UN calls for urgently (Schnall et al., 2019)

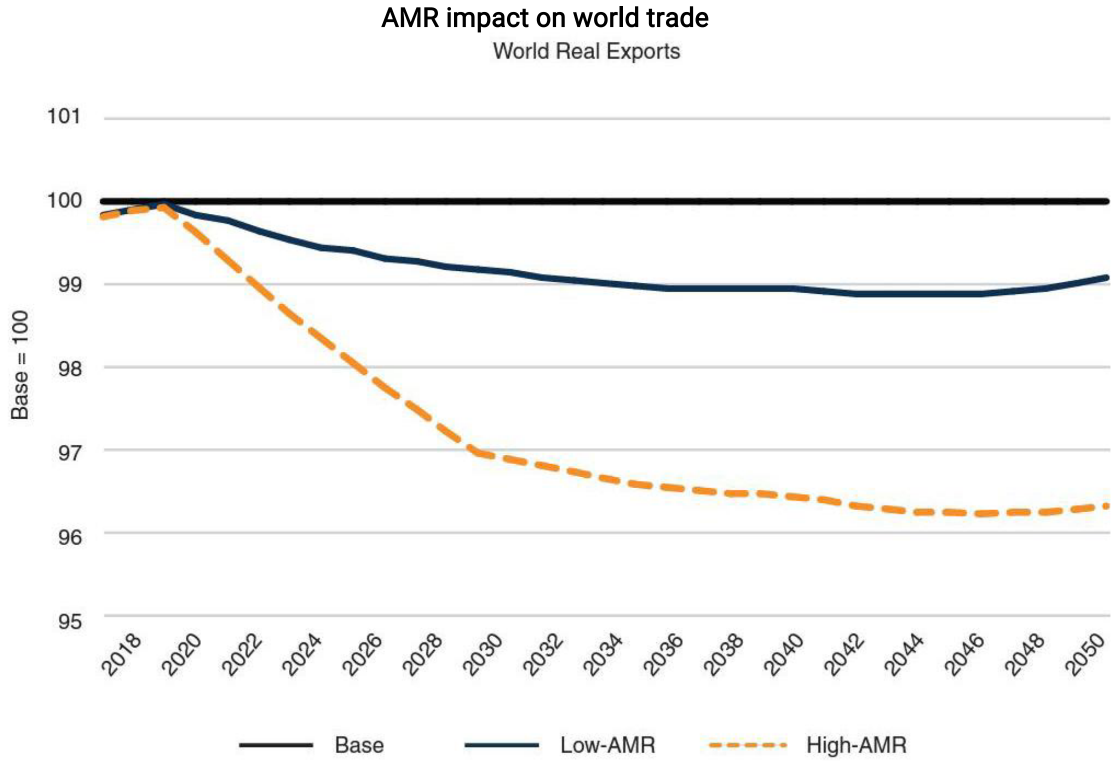
3.2. THE GLOBAL ECONOMIC IMPACTS OF AMR

The developing countries of the world are the most affected by AMR. Dadgoster (2019), showed in his research how AMR will severely damage the global economy, particularly those of underdeveloped nations (Dadgoster, 2019). According to a World Bank news release, AMR could cause economic damage worse than the 2008 financial crisis, with low -income nations being the hardest hit World Bank, (2016). AMR might also lead low-income nations to lose over 5% of their GDP and put up to 28 million people, largely in developing countries, into poverty by 2050. In contrast to the 2008 financial crisis, there was no medium-term recovery (World Bank, 2016). Real export volumes might decline by 1.1 percent in the low-AMR scenario and 3.8 percent in the high-AMR scenario by 2050 if AMR continues to expand uncontrolled (Bank, 2016). AMR might reduce livestock productivity by 11% in low-income nations by 2050. By 2050, annual spending in low- and middle-income countries might be 25% more than base-case levels, 15% higher in high-income countries, and 6% higher in low-income countries (Jonas, et al., 2017). Figures 4 and 5 show the Jonas and colleagues' estimates.

Economic Costs of AMR May Be as Severe as During the Financial Crisis

AMR could reduce GDP substantially—but unlike in the recent financial crisis, the damage could last longer and affect low-income countries the most (annual costs as % of GDP)




AMR impact on world trade
World Real Exports
Base = 100
101
100
99
98
97
96
95
2018
2020
2022
2024
2026
2028
2030
2032
2034
2036
2038
2040
2042
2044
2046
2048
2050
Base
Low-AMR
High-AMR

AMR has led to an increase in hospital length of stay, increased in healthcare, and increase in costs of antibiotics especially the last resort antibitiotics used to combat resistance cases. Dadgoster's research shows a link between income and antibiotic use with backing from several scholarly investigations. A different study (Shrestha et al., 2018) indicated that the economic costs of each antibiotic consumed exceeded their purchasing price. Shrestha et al. (2018) identified "the correlation coefficients between intake of antibiotics that induce resistance in S. aureus, E. coli, K. pneumoniae, A. baumanii, and P. aeruginosa were 0.37; 0.27; 0.35; 0.45; 0.52 respectively, they concluded. AMR-related economic losses in Thailand and the US totaled $0.5 billion and $2.9 billion. For macrolides, the AMR cost was $0.1, whereas quinolones, cephalosporins, and broad-spectrum penicillins were $0.7 each in Thailand. In the US a single unit of carbapenem cost $0.1, while quinolones, cephalosporins, and broad-spectrum penicillin cost $0.6. (Shrestha et al., 2018). In addition to these, AMR has impacted the workforce and human capital of nations due to death and sickness, These deaths reduce the population and reduce the labor force. In 2015, Taylor et. al opined that if there is no change in the current pattern of AMR, in 10 years the working population age of the world will reduce by 2 years.

3.3. EVALUATION OF SURVEILLANCE DATA AND STATISTICS FOR AMR

To effectively combat the Global AMR burden, reliable data estimates of the current and predicted future burden is essential (WHO 2019). Despite the global efforts of relevant bodies to bring about relevant data, our knowledge about the AMR burden is still limited (Jesse et al., 2019).

There have been many systems put in place for the surveillance of AMR Global Antimicrobial Resistance and Use Surveillance System (GLASS) was launched by WHO in 2015 to standardize the surveillance of AMR. Its purpose is to standardize the approach used in the collection, analysis, and interpretation of data related to AMR in different countries of the world. GLASS is limited in some ways because many nations especially developing nations lack the necessary tools needed to support effective surveillance (Cars 2019).

A national minimum data collection can assist build and implement an effective surveillance system (Safdari et al., 2018; Schnall et al., 2019). Our knowledge of the frequency of resistant illnesses is critically poor despite major worldwide efforts (Schnall et al., 2019). Legislators and healthcare professionals must be able to execute national AMR action plans and efficiently allocate resources to successfully tackle an apparent spike in resistant infections (Schnall et al., 2019). According to Aenishaenslin et al. (2019), scientists and international organizations have suggested one health surveillance for antibiotic resistance for over a decade. According to Aenishaenslin et al. (2019), countries adopting One Health surveillance systems require empirical evidence on how to integrate efficiently. The study of how different levels of integration affect the efficacy of One Health surveillance systems for AMR is critical for benchmarking and advocating optimal practices. Aenishaenslin et al., (2019). AMR surveillance systems can be integrated in different ways (Aenishaenslin et al., 2019)

To ensure integrated AMR surveillance programs are effective, they must be regularly evaluated (Nielsen et al., 2020). In the therapeutic setting, they will even be more valuable. Several evaluative instruments exist for different areas of AMR surveillance and One Health, according to Nielsen et al (2020). They discovered that AMR-PMP-The progressive management method went beyond AMR surveillance to include antibiotic residues in food. It also contained questions about national awareness efforts (Nielsen et al., 2020). As a result, using the tool necessitated familiarity with a bigger portion of the program.

AMR-PMP was viewed as user-friendly and meeting assessment goals, although it might benefit from further information on how to assess an initiative or activity's quantity and quality (Nielsen et al., 2020). In terms of country-level evaluation, the overall appearance was effective, but in terms of sector-specific evaluation, it was baffling (Nielsen et al., 2020). Stakeholders will be able to discuss actionable results thanks to the use of technology (Nielsen et al., 2020). Applying the Network for Evaluation of One Health (NEOH) approach, the result of the EU COST Action; for example, could provide an additional level of information for One Health components (Nielsen *et al.,*2020).

The World Health Organization's Global Antimicrobial Resistance Surveillance System (GLASS) will support the Global Action Plan on AMR (World Health Organization, 2015). Local, national, and regional action will be driven by AMR data collected, analyzed, and shared with countries utilizing GLASS. Global AMR Surveillance System (GLASS) combines patient, laboratory, and epidemiological data to assess AMR (WHO, 2015) It is recommended that countries implement the surveillance standards in stages based on their objectives and resources (WHO, 2015) The data on comprehensive population-based antibiotic resistance surveillance is lacking, say Iskandar et al., (2021). Obstacles include lack of laboratory capacity, poor health system governance, lack of health information systems, and money in LMIC (Iskandar et al., 2021). Developing countries face political and societal issues due to the high expenses of communicable diseases. Because accessible data is fragmented and non-representative, it is difficult to give relevant information to health policymakers (Iskandar et al., 2021).

3.4. ETHICAL ISSUES ASSOCIATED WITH AMR AND THEIR INFLUENCE ON POPULATION HEALTH

Antibiotic resistance raises a growing number of ethical issues. AMR is a multi-faceted challenge that affects the economy, human and animal health, agriculture, and the environment. Antibiotic resistance is a serious social issue because patients, farmers, and doctors misuse antibiotics, while doctors and veterinarians overprescribe them Littmann & Viens, 2015).

Ethics, as applied to AMR, raises several questions; who should have access to antibiotics? If access is restricted, should it be given to a few persons or everyone that needs it? Should the current use of antibiotics be restricted with the view to considering the potential AMR in the future generations?

To address the ethical issues of AMR, Abimbola et al. (2021) showed that restricting antibiotic delivery was the most popular solution. Antimicrobials have a large impact on human and environmental health, making this technique difficult to adopt. (Abimbola et al.,2021). If farmers are restricted, the quality and quantity of food produced may be compromised, with economic implications (Parsonage et al., 2017).

In a situation where a new antibiotic is introduced to the market, necessary actions need to be put in place, without which resistance to the new drug may arise within a few years. Stewardship measures would be effective in minimizing the incidence of AMR, thereby elongating the effective life span of antibiotics (Reactgroup, 2017).

It is critical that all stakeholders, including individuals, health care professionals, patients, society, and future generations, have access to information about the risks and make decisions about when and how antimicrobials are employed. We must take current actions to minimize future complications of AMR. By implication, it means that we should individually take responsibility to make sure that we minimize the unnecessary use of antibiotics. (Jasper and Viens, 2015).

Sadly, there may not be an absolute way of using antibiotics in the long run, this is because microorganisms possess the ability to continuously mutate and adapt to antibiotics. Thus, our efforts towards curbing the menace of AMR would be a continuous vicious cycle of obsolescence and resistance. So if this issue does not have an absolute fix, then our moral obligation would be to manage rather than fix the problem. One way to handle this reality is to see AMR as a slowly emerging or insidious problem that may get complicated in the future which thus emphasizes the need to build a resilient mindset that prepares us for a world where there are fewer effective antibiotics (Jasper and Viens, 2015).

3.5. FUTURE RESEARCH LITERATURE AND ACTIONS TO IMPROVE HEALTH OUTCOMES FOR AMR

Much research literature on AMR continues to emerge over the years because of the significant impacts of AMR on the global economy. Jane et al., 2021, conducted a study on publications on AMR-related issues. Bibliometric analysis of AMR research reveals that there has been significant growth in AMR publication for the past 10 years. After the release of WHO's Global Plan of Action on AMR in 2015, a steady increase in the yearly publication of AMR-related problems was observed, and the number of countries and the number of contributing authors increased threefolds and six folds respectively (Jane et al., 2021).

The emergence of inherited resistant genes and an increase in acquired resistance mechanisms by bacteria further poses threats to human health and wellbeing. The current Hospital-focused measures to fight AMR are no longer adequate. A new Proactive and realistic strategy to search for new sources of AMR in every situation in which antimicrobials are used is thus necessary. This new strategy will employ easy-to-use and cost-effective technology at the point of care to isolate and characterize phenotype bacteria and the result made readily accessible to inform treatment decisions (Jane et al., 2021).

Antimicrobial stewardship programs have been beneficial in managing the burden of AMR. However, many developing or low-income countries lack the necessary tools to implement this program effectively. In food producing-animal, antimicrobial resistance organisms(ARO) can cause disease in humans. Antimicrobial stewardship has been reported to decrease the rate of resistance in humans and animals (Patel et al., 2020). To prevent ARO from entering the food chain, improved stewardship, surveillance and advocacy are needed.

The use of digital technology and data across sectors in the economy and society can help to effectively mitigate the menace or burden of AMR. The integration of technology can bring about instant AMR diagnosis using readily available data and artificial intelligence.

There is a need for continuous research literature on AMR. as AMR continues to be a major problem to the Global economy and the society. Future literature should focus on the review of the effectiveness and output of the already established global action plans to attenuate and manage AMR. These literature should also suggests approaches that can be taken to further enhance the effectiveness of these plans and also suggest approaches that could be implemented to combat this insidious global problem. One major part to focus on is effective data surveillance systems, most especially for low and medium-income countries.

4. CONCLUSION

Dadgoster's study was thorough and showed with evidence, the causes of AMR as well as its implications on the patient, healthcare system, and the economy. Dadgoster suggested solutions that would help to manage AMR to attenuate the effects on the economy and society.

Dadgoster however did not comprehensively explain how these solutions would be structured and implemented towards mitigating the effects of AMR on the global society and economy. The study also did not emphasize the importance of effective collation and surveillance of AMR data towards achieving better management of AMR. All of these fallouts of the study are necessary for effective management of AMR burden as regards current trends and potential future trends in AMR.

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