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Initiatives to promote the responsible use of antibiotics and the development of new antimicrobial agents

Kezia Gyasi-Darko [1], Akosua Dufie Amofah [2], Doreen Ugwu [3], Jehu Narh Apaflo [4] and Edward Oware [5,*]

[1] *Department of Plant and Soil Science, Alabama A and M University, Huntsville, U.S.A.*
[2] *Department of Healthcare Marketing, East Tennessee State University, JC, USA.*
[3] *Jiann-Ping Hsu College of Public Health, Georgia Southern University, Georgia, USA.*
[4] *College of Nursing, The University of Texas at El Paso, TX, USA.*
[5] *Department of Physiology, School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Ghana.*

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Abstract

Antimicrobial resistance (AMR) is a serious threat to the nation's public health with over 2.8 million antibiotic-resistant infections in the United States annually. The focus of this study is on key initiatives to combat AMR via promoting responsible antibiotic use and antimicrobial development. As a result of wide implementation of antimicrobial stewardship programs (ASPs) in US healthcare settings, antibiotic misuse has been significantly reduced, and clinical outcomes have been improved. Further optimization of antibiotic prescribing practices is achieved by the expansion of ASPs to outpatient settings and the integration of advanced technologies. Funding and collaborations between the public and private sectors have been increased in efforts to stimulate antimicrobial innovation. The proposed legislation, PASTEUR Act, is to address economic challenges involved with the development of antibiotics, in addition to CARB-X and the AMR Action Fund supporting the manufacture of novel antibiotics. In the battle against AMR, the integration of stewardship and innovation efforts is essential, especially through inclusion of rapid diagnostics and stewardship-friendly antibiotics. Future work will focus on artificial intelligence in drug discovery and resistance prediction, alternative therapies, and global cooperation in AMR surveillance with increased global cooperation. These initiatives have the potential of making quite substantial strategic impacts for the US, including saving essential antibiotics in use, stimulating biomedical research for bolstering the economy and ultimately reducing the burden of resistant infections on the system of healthcare. A further continued commitment to these multifaceted approaches can continue to protect public health and maintain the efficacy of antimicrobial treatments in the United States.

Keywords: Antimicrobial resistance; Antibiotic stewardship; Drug innovation; Public health; United States

1. Introduction

Antimicrobial resistance (AMR) is one of the most important public health challenges facing the 21st century. Drug-resistant pathogens are becoming more common, threatening to erode decades of progress in managing infectious disease and could usher in a post-antibiotic era where basic infections that are easily cured, once again become life-threatening [1]. The gravity of such a situation is now becoming apparent to the United States, according to the Centers for Disease Control and Prevention (CDC), more than 2.8 million antibiotic-resistant infections occur each year and over 35,000 people die [2].

The roots of AMR are generally complex, such as the overuse and misuse of antibiotics in human and agricultural medicine, inadequate infection prevention and control practices, and a significant slowdown of the development of new

* Corresponding author: Edward Oware

antimicrobial agents [3]. Emergence and spread of resistant strains have been accelerated by the natural evolutionary process of bacteria, and selective pressure exerted by antimicrobial use. This phenomenon is of special concern in healthcare settings because of the high concentration of vulnerable patients and the frequent course of antibiotics which creates spatial and temporal factors that promote the spread of resistant organisms [4].

The threat of AMR is being recognized at the highest levels of government and health care administration in the United States. In 2015 and 2020, the White House released a National Action Plan in Response to Antibiotic-Resistant Bacteria which outlines a comprehensive, coordinated, multi-sector approach to address this crisis [5]. Even so, the AMR challenge continues to grow, and new and sustained efforts aimed at limiting inappropriate use of existing antibiotics and encouraging the development of new antimicrobial agents are needed [6].

Preserving the efficacy of our present-day arsenal of antimicrobials requires the responsible use of antibiotics, which may be encoded within the concept of antimicrobial stewardship. In healthcare settings, Antimicrobial Stewardship Programs (ASPs) have risen to prominence as an important strategy to optimize use of antibiotics, help patients, and reduce the pressure for selection of AMR [7]. Usually, these programs are run by multidisciplinary teams that deliver evidence-based interventions to ensure that antibiotics are prescribed as few as possible at the right dose for the right duration and the right route of administration. [7].

In efforts to encourage responsible antibiotic use, there is an immediate need to revive the pipeline of new antimicrobial agents. In the last few decades, however, the development of new antibiotics has slowed drastically, and most major pharmaceutical companies have abandoned that field because of scientific obstacles, regulatory hurdles, and unfavorable economic incentives [8]. This is very important because resistance is growing among pathogens, some of which are resistant to multiple or even all available antibiotics.

To address dual challenges of encouraging safe antibiotic use and supporting antimicrobial innovation, the changes will be multifaceted and require support from a broad range of healthcare ecosystem stakeholders. Participants in this include healthcare providers, researchers, pharmaceutical companies, policymakers, and patients. Successful stewardship programs, education of the public and healthcare professionals regarding the risks of antibiotic overuse, and an environment that encourages and supports development of new antimicrobial agents require collaboration.

This manuscript seeks to explore key initiatives that address these critical areas in the fight against AMR in the United States. Specifically, we will focus on two main pillars of action:

Antimicrobial Stewardship Programs: In this paper, we review strategies for the development and implementation of antibiotic stewardship programs in hospitals and clinics, with special attention to monitoring antibiotic use and promoting antibiotic prescribing responsibility. We will also look at educational efforts designed to help both healthcare providers and patients better understand the risks of overuse of antibiotics and the importance of following prescriptions for antibiotics.

Fostering Antimicrobial Innovation: We will explore strategies for promoting antimicrobial agent discovery through partnerships with research institutions and with pharmaceutical companies. Within this, an analysis of policies and incentives that promote antibiotic research and development, e.g., public-private partnerships and specific funding opportunities will be included.

This allows us to address these complementary aspects of AMR mitigation, providing a holistic understanding of what efforts are underway now, and what the future might look like to combat this growing public health threat. The initiatives discussed in this manuscript are important first steps toward maintaining the efficacy of currently available antibiotics while increasing the number of antibiotics in our antimicrobial arsenal for future generations. As we move through these initiatives, we need to understand that fighting AMR is not an overnight procedure, but an ongoing effort that needs continued effort, innovation, and collaboration among various sectors for a long time. The stakes are too high: modern medicine relies on the ability to properly treat bacterial infections, everything from routine surgeries to cancer treatment. Robust stewardship programs, and reinvigoration of antimicrobial innovation, are actions we can take to assist in working towards a future of diminished threat of untreatable bacterial infections and ensured access and use of antibiotics for generations to come.

2. Antimicrobial Stewardship Programs

Antimicrobial Stewardship Programs (ASPs) play a crucial role in the global fight against antimicrobial resistance (AMR). These programs aim to improve antimicrobial use by optimizing antimicrobial prescribing, minimizing adverse

drug reactions, and decreasing the spread of infection caused by multidrug-resistant organisms. With both regulatory requirements and importance of ASPs in preserving antibiotic efficacy, the implementation of ASPs has gained tremendous momentum in the United States.

2.1. Development and Implementation in Healthcare Settings

2.1.1. Hospital-based Programs

As part of their Conditions of Participation [9], the Centers for Disease Control and Prevention (CDC) mandated that all acute care hospitals implement antibiotic stewardship programs by March 30, 2020. There has been a huge regulatory push to adopt ASPs in U.S. hospitals. A study showed that the percentage of hospitals using established ASPs also grew from 64% in 2014 to 95% in 2020, a large amount of progress in implementing the ASP program [10].

ASP's typically based in hospitals are led by infectious disease physicians and pharmacists. Different strategies are used by these teams to optimize antibiotic use, including prospective audit and feedback, formulary restriction, and the development of clinical pathways for common infections. Use of these strategies has been associated with large reductions in antibiotic use and improvement in patient outcomes. For example, a meta-analysis on hospital ASPs found a 19% reduction in overall antibiotics use and a 12% reduction in the length of hospital stay [11].

2.1.2. Clinic-based Programs

Hospital-based ASPs have been widely implemented yet the uptake of ASPs into outpatient settings has been slower but is gaining steam. Prescribing for outpatient antibiotic use represents a substantial percentage of total antibiotic use and, therefore, is an important target for stewardship efforts. A study by King and co-workers [12] on introducing an outpatient ASP in primary care clinics showed a 12% reduction in total antibiotic prescribing and a 17% reduction in prescribing for acute respiratory infections [12].

New outpatient stewardship approaches emerged recently through telemedicine and electronic health record (EHR) interventions. For instance, Meeker and co-workers [13] have shown that incorporating clinical decision support tools in the EHR, enlisted along with provider education, will lead to 16% reduction in the use of inappropriate antibiotics in acute respiratory infections in the primary care setting [13].

2.2. Key Components of Effective Stewardship Programs

2.2.1. Monitoring Antibiotic Use

The success of ASPs depends on accurate measurement of antibiotic use. Hicks et al. [14] describe how the CDC's National Healthcare Safety Network (NHSN) Antimicrobial Use and Resistance (AUR) Module is a standardized method for hospitals to report and analyze antimicrobial use data. This is a system where we can benchmark and find opportunities for improvement.

Gradually, antibiotic use monitoring is being enabled by advanced analytics and machine learning algorithms. Luz and co-workers showed that machine learning could predict unnecessary antibiotic prescriptions with 85% accuracy, if applied, it could make more tailored interventions [15].

2.2.2. Promoting Responsible Prescribing Practices

ASPs employ various strategies to promote responsible prescribing, such as:

- Guidelines and Clinical Pathways: Guidelines for common infections based on evidence. A systematic review by Schweitzer suggests adherence to local antibiotic guidelines is associated with greater clinical outcomes and reduced antibiotic use [16].
- Rapid Diagnostic Tests: Guided by rapid diagnostic technologies to guide appropriate antibiotic therapy. In 2016, Timbrook [17] showed that use of rapid molecular diagnostic tests with ASP interventions resulted in a 24-hour reduction in time to optimal antibiotic therapy [17].
- Antibiotic Time-outs: Promotion of regular reevaluation of antibiotic therapy. A study found that a 72-hour antibiotic time-out protocol reduced antibiotic days of therapy by 17% [18].

2.3. Education Initiatives

2.3.1. Healthcare Provider Education

The success of ASPs needs continuing education for the healthcare providers. In a multi-center study, a comprehensive education program for primary care providers which includes online modules and in-person workshops led to a 20% reduction in inappropriate antibiotic prescribing for acute respiratory infections [19].

Antibiotic stewardship-focused curricula in medical and pharmacy schools have also been developed. A survey reported that 90% of pharmacy schools present at least some antibiotic stewardship education, but systematically, content and delivery varied significantly, emphasizing the need for standard curricula [20].

2.3.2. Patient Education

The prescription of inappropriate antibiotics remains a strong driver of patient demand. This pressure has been targeted for reduction by educational interventions aimed at patients. In 2020, Mortazhejri and co-workers showed in a cluster randomized trial that giving patients personalized antibiotic use reports and educational materials reduced antibiotic prescriptions for self-limiting respiratory tract infections by 15% [21].

Patient education has also been aided by the help of public awareness campaigns. In 2017, the CDC launched its 'Be Antibiotics Aware' campaign to increase awareness of antibiotic resistance and proper use [22].

2.4. Measuring the Impact of Stewardship Programs

2.4.1. Metrics for Success

To prove the value of ASPs as well as to identify potential improvements, it is important to evaluate the impact of ASPs. Common metrics include:

A measure of antibiotic use (DOT or DDD)

- Rates of Clostridioides difficile infection
- Rates of antibiotic-resistant infections
- Mortality and length of stay are clinical outcomes
- Antibiotic expenditures and costs for the entire healthcare system

A comprehensive review by Nathwani reveals that ASPs are associated with a 33.9% decrease in antibiotic inpatient costs and a 24% reduction in length of stay, neither of whom can be ignored, the latter in terms of patient, as well as economic consideration [23].

2.4.2. Case Studies of Successful Implementations

From numerous healthcare systems, successful outcomes from their ASP implementations have been reported. For example, the national stewardship program run by the Veterans Health Administration, implemented in 130 facilities, decreased antibiotic use by 12% and C. difficile infection rates by 3.1% over five years [24].

In this study, antimicrobial stewardship programs have been proven to be essential in the AMR fight. Initial work with their implementation in various healthcare settings has already resulted in significant reductions in antibiotic use and improved patient outcomes. Nevertheless, implementation of these programs is limited as they remain largely confined to a few healthcare settings and are not yet sustainable in the long run. We will need continued research, innovation, and policy and healthcare leadership support to fully realize the potential of ASPs in countering the threat of antimicrobial resistance.

3. Fostering Antimicrobial Innovation

The lack of new antimicrobial agents is a major problem in antimicrobial resistance (AMR). But for decades, the antibiotic pipeline has been drying up for scientific, regulatory, and economic reasons. To fill this critical gap, antimicrobial innovation efforts have been undertaken.

Driving antimicrobial innovation has been a key strategy of collaboration with research institutions. CARB-X is a global non-profit partnership that has been a critical partner in getting the ball rolling with early-stage antibiotic development.

Since 2016, CARB-X has supported 92 projects and 12 are underway in clinical trials [25]. The public-private partnership model has been proven to de-risk early-stage research and attract private investment in this model.

New antibiotics need to be brought to the market with the help of partnerships with pharmaceutical companies. In 2020, the AMR Action Fund launched with $1 billion from the world's 5 largest pharmaceutical companies as a pledge to develop 2-4 new antibiotics to market by 2030 [26]. This initiative closes the funding gap between early-stage research and clinical development, filling in the gap for smaller biotech companies.

Antibiotic development has been enabled by an environment of policy advocacy. The PASTEUR Act, recently introduced in the U.S. Congress, is a subscription model for the cost of novel antibiotics that could, potentially, predictably return investment to developers [27]. This legislation is a major step towards getting antibiotic development to a more broken economic model.

Antimicrobial research has been supported by funding opportunities. Funding for AMR research increased to $1.7 billion in fiscal year 2021 as the National Institute of Allergy and Infectious Diseases (NIAID) has stepped up investment in this area [28]. Barada, the Biomedical Advanced Research and Development Authority, has also provided large amounts of funding for the development of late-stage novel antibiotics, such as Achaogen and Tetraphase [8].

Nevertheless, challenges remain with antimicrobial innovation. Theuretzbacher analyzed WHO-priority pathogens and found that only 32 antibiotics addressed WHO-priority pathogens in clinical development in 2020, with only 5 being considered novel [29]. This suggests why antibiotics must continue to be developed.

4. Integration of Stewardship and Innovation Efforts

The successful mitigation of antimicrobial resistance (AMR) demands a synergistic, combined approach of antimicrobial stewardship programs (ASPs) and innovation. This integration guarantees that newly developed antibiotics are wisely used, and their effectiveness preserved, and at the same time will promote continued investment in research and development of antimicrobial therapeutics.

An area of integration is the integration of novel diagnostics into ASPs. Rapid diagnostic technologies offer the potential to greatly enhance antibiotic prescribing practices by permitting rapid identification of pathogens and their susceptibilities. Timbrook and co-workers found that the use of rapid diagnostics and ASP interventions resulted in shorter time to optimal therapy and reduced use of broad-spectrum antibiotics [17].

Secondly, stewardship-friendly antibiotics need to be developed. Indeed, some studies have suggested a framework for developing antibiotics that are inherently more amenable to stewardship, including narrow-spectrum agents and those with novel mechanisms of action [30, 31]. This is a way to link the goals of pharmaceutical innovation to sensible antibiotic use.

Data sharing between ASPs and research institutions can also aid in both stewardship practices and drug development priorities as data are shared between them. The ATLAS (Antimicrobial Testing Leadership and Surveillance) program is an example of how real-world resistance data can inform clinical decision-making, and spark research efforts [32].

5. Future Directions

Antimicrobial resistance (AMR) presents a continuing challenge that calls for steady innovation and adaptation. Different technologies are emerging, which are promising in improving antimicrobial stewardship and drug development techniques. As these anticipate antibiotic resistance patterns, optimize dosing regimens, and identify novel antimicrobial compounds, artificial intelligence (AI) and machine learning come into play. There are good reasons to believe that these technologies have the potential to significantly speed up drug discovery and to improve the precision of antibiotic prescription.

Alternative therapies, such as bacteriophages, immune modulators, and microbiome-based interventions, have great potential in the fight against AMR. These approaches could fill a gap in new methods to treat antibiotic-resistant infections and dramatically decrease the use of our traditional antibiotics. AMR surveillance and research need global cooperation. The Global Antimicrobial Resistance and Use Surveillance System (GLASS) has been developing initiatives to standardize and increase the number of countries that collect AMR data, making valuable information available for local, as well as global, AMR strategies.

For the future, AMR must be integrated into broader public health and environmental policies. It includes fighting antibiotic use in agriculture and improving water sanitation to slow the spread of resistant organisms as well as inserting AMR education into the training of healthcare professionals. Going forward, success in fighting AMR will hinge on governments, health systems, researchers, and the public to maintain sustained commitment to comprehensive, multifaceted measures to reduce inappropriate use of existing antibiotics as well as to develop new antimicrobial approaches.

6. Conclusion

The commitment to reducing antimicrobial resistance (AMR) and to promoting responsible antibiotic use as well as antimicrobial innovation is of paramount importance. Optimization of antibiotic use and improvement in patient outcomes are well-documented successes of antimicrobial stewardship programs. At the same time, the antibiotic pipeline is beginning to reinvigorate efforts to stimulate development of new antimicrobials. However, the fight against AMR will need ongoing commitment and sector collaboration. Working towards a future where effective antimicrobial treatments available means integrating stewardship and innovation efforts, leveraging emerging technologies, and in doing so fostering global cooperation. AMR is not a medical imperative; it is a societal imperative crucial to protect public health and ensure the efficacy of modern medicine.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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