Capstone Title: Antimicrobial Resistance in Black America: Unveiling a Looming Public Health Crisis

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INTRODUCTION

The emergence and spread of antimicrobial resistance (AMR) constitute an escalating global public health concern. Antimicrobial resistance occurs when microorganisms become more difficult to treat due to a change over time (World Health Organization, 2021). Since microorganisms have inherent resistance to some medications (i.e., not all medications work for all microorganisms), antimicrobial resistance specifically refers to germs becoming resistant to previously effective medicines (Munita & Arias, 2016). As resistance undermines the effectiveness of anti-infective treatments, once-treatable infections become challenging or even impossible to treat, complicating the course and cost of treatment and increasing mortality rates. Over 2.8 million drug-resistant infections and 35,000 deaths occur annually in the United States. The annual economic impact of antimicrobial resistance is a staggering $4.6 billion. (CDC, 2022). Globally, antimicrobial resistance is responsible for the loss of over 1.27 million people, and 5 million deaths are indirectly associated with AMR (CDC, 2022). This Capstone explores the development of antimicrobial agents, the emergence and dynamics of antimicrobial resistance, the intersections of health disparities and infectious diseases, consequences of AMR in Black America, current initiatives, and potential solutions to this critical issue.

ANTIMICROBIAL AGENTS: PIONEERING DISCOVERIES

Discovery and Development

Before the revolutionary era of antibiotics, comprehension and clinical treatment of pathogens were restricted. The *Yersinia pestis*–induced plague is responsible for various pandemics throughout history, including the Justinian plague (541-543 A.D.) with an estimated death toll of approximately 100 million people and the Black Death (1347-1351 A.D.) which claimed over 50 million lives in Europe (Uddin et al., 2021). Smallpox infections led to the death of an estimated 300-500 million individual. Additionally, the seven cholera pandemics, originating in 1817, resulted in 2.86 million fatalities, and the 1918 influenza pandemic caused approximately 50 million deaths (Liang et al., 2021; Sampath et al., 2021). Public health interventions proved effective in addressing the spread of infections but less effective in treatment measures. The use of natural medicine and antimicrobial herbs to mitigate infections predates the modern antibiotic era. Evidence from as early as 350-550 AD confirms antibiotic use in the skeletal remains found in ancient Sudanese Nubia, Egypt, Greece, and China (Aminov, 2010; Reygaert, 2018). German Nobel laureate Paul Ehrlich (the father of antibacterial therapy) proposed the magic bullet theory, suggesting that "bullets", like that of a gun, could selectively target microorganisms without harming the body (Aminov, 2010). By 1904, he developed **Atoxyl**[1] (marketed as Salvarsan) against a catastrophic *Treponema pallidum*[2] *(*syphilis) (Aminov, 2010).

In 1928, Sir Alexander Fleming's pivotal discovery of Penicillin marked the inception of modern antibiotics. While investigating Staphylococcus aureus bacteria, Fleming stumbled upon **Penicillin** in a petri dish contaminated with Penicillium mold (Gottfried, 2005). The term "antibiotic" was later coined by Selman Waksman, a distinguished soil microbiologist at Rutgers University, in 1941. Derived from the French word “antibiotic”[3] an antibiotic denotes a substance produced by one microorganism that can inhibit or destroy another (Gottfried, 2005). The significance of Penicillin became evident in 1941 when an Oxford police officer suffering from Staphylococcal septicemia became one of its first beneficiaries (Gottfried, 2005). Recognizing the potential, the United States government prioritized penicillin production for wounded soldiers, leading to widespread availability for the military by 1943 (Gottfried, 2005). The scientific breakthroughs with Atoxyl and Penicillin set the stage for discovering various antimicrobials, transforming patient care, and enhancing recovery and prognosis for bacterial infections, including those prevalent during World War II. More than a decade after Penicillin's discovery, Paul Ehrlich's theories led to the development of **Prontosil** for treating *Staphylococcal* and *Streptococcal* bacterial infections (Gottfried, 2005). Prontosil proved particularly effective against puerperal fever, a postpartum infection occurring several days after childbirth or miscarriage.

The discovery of **Streptomycin** in 1943 was a groundbreaking step in the management of the then-common "white plague", also known as tuberculosis, caused by *Mycobacterium tuberculosis* and the discovery of **Erythromycin** (macrolide antibiotic) and **Vancomycin** (Gottfried, 2005). The mid-20th century saw a surge in antibiotic development, effectively

treating a wide range of bacterial infections. The first official antifungal, **Nystatin**, was discovered in 1949, and shortly after, polyenes were developed. In the late 1960s, the landscape of antifungal treatment underwent a significant transformation with the arrival of newer border spectrum agents, including iodinated trichlorophenols and imidazoles (Smith, 1990). **Idoxuridine** was approved in 1963 as the first antiviral medication, creating the avenue for antiviral development (Kausar et al., 2021). In the 1990s, computer-based drug discovery aided the development of **Nelfinavir,** which was vital for the management of the human immunodeficiency virus (HIV) infection (Kausar et al., 2021). The discovery of **Ivermectin** resulted from screening microbial fermentation products for antiparasitic activity led by Professor Satoshi Omura (Campbell, 2016). Initially considered ineffective in standard antimicrobial tests, one of these isolates, when tested for antiparasitic activity in 1975, produced a potent anthelmintic compound known as ivermectin and its precursor (Abamectin), and subsequently gave rise to the macrocyclic lactone class of antiparasitic agents (Campbell, 2016). Anthelminthic development represented a significant advancement for both human and animal health. These innovations also had far-reaching impacts on agriculture and livestock care. Despite the challenges posed by antibiotic resistance, the production of novel antibiotics has eased the burden of infectious diseases and has been complemented by various public health initiatives.

Classes of Antimicrobials

Antimicrobials exhibit variations in their mechanism of action, the breadth of their activity, and their efficacy against specific microorganisms. Additionally, they may exert antimicrobial effects on one or more subgroups of microorganisms, including bacteria, viruses, fungi, or parasites. For instance, metronidazole (brand name Flagyl) is an antibacterial and antiprotozoal medication indicated for anerobic bacteria and parasitic infections like *Giardia lambda* and *Entamoeba histolytica*.

Antibacterial agents
Antibacterial agents are classified into five main classes: Beta-lactams, Aminoglycosides, Macrolides, Quinolones, and Tetracyclines. This classification depends on their chemical composition and mechanism of action and may be sub-grouped based on their antimicrobial coverage. Antibacterial agents work through various mechanisms to combat bacterial infections. One common mechanism is cell wall disruption, as seen in the action of antibiotics like penicillins and cephalosporins, which cause~~s~~ the bacterium to burst and die. Another mechanism involves inhibiting bacterial protein synthesis, preventing the bacterium from creating essential proteins for growth and reproduction. Some antibacterial agents interfere with bacterial DNA replication, hindering the bacterium's ability to reproduce and causing its eventual demise. Lastly, these antibiotics may target specific bacterial enzymes or metabolic pathways, disrupting crucial processes required for bacterial survival. Antibacterials are classified as either bacteriostatic, which inhibits the growth of bacteria, or bactericidal, which directly kills the bacteria. However, the clinical implications of this classification are

multifaceted and influenced by various factors such as the type of bacteria, bacterial load, site of infection, and the pharmacokinetic and clinical actions involved (Patel et al., 2023).

Antiviral agents

Antiviral agents target viruses directly (including viral attachment, entry, uncoating, or enzyme inhibition) or through the host cell factors. Classes of antiviral drugs based on their mechanism of action include viral RNA polymerase inhibitors, protein synthesis inhibitors, inhibitors of viral entry, and immunomodulators (Kausar et al., 2021). They have been proven effective in treating infections, managing chronic infections (e.g., HIV), and reducing the duration of diseases (e.g., influenza, herpes). Despite strides in antiviral drug development, many viruses remain without definitive treatment due to unique viral abilities to replicate using host cells, and it is very challenging to develop medicines that target viruses without affecting the host (Kausar et al., 2021).

Antifungal agents

Antifungal agents can be categorized according to their mechanism of action. Azoles (such as Ketoconazole) target the fungal cell membrane, Echinocandins (such as Caspofungin) target the fungal cell wall, Polyenes (such as Amphotericin B) target fungal membrane sterols, and 5-fluorocytosine inhibits nucleotide synthesis. (Ghannoum & Rice, 1999).

Antiparasitic agents

Antiparasitic agents target various parasites, including protozoa, helminths, and ectoparasites. These agents target parasites and vary in their mechanisms of action.

Clinical Indications and Importance of Antimocrobial Agents in Healthcare Systems

Public health measures predated the antibiotic era and were vital in controlling infectious diseases like cholera and typhoid fever. The discovery and use of antimicrobials significantly improved healthcare's capacity to manage and combat infectious diseases globally. The introduction of antimicrobials in medicine was critical in the epidemiologic transition from the "age of pestilence" described by infectious diseases, famine, and malnutrition to the "age of degenerative and manmade diseases" characterized by chronic diseases. The overall life expectancy also shifted from 20-40 years in the early 1900s to 66.8 years at the start of the 21st century (Omran, 2005; WHO, n.d.). Antibacterials alone save at least 200,000 lives per annum in the U.S. and extend life expectancy at birth by an additional 5-10 years (Gottfried, 2005). Antimicrobial agents have been vital in the treatment, control, prophylaxis, and suppressive therapy of diseases, along with symptom alleviation, supportive management, and aiding in the diagnosis of pathogens. The mortality rate from acute rheumatic fever, lung abscesses, septic abortion, and brain infections reduced drastically (11,866 in 1936 to 5,224 in 1952 to 4,854 in 1960). Overall mortality rate owing to bacterial infections reduced ~~(~~from 247.7 per 100,000 population in 1930 to 38.1 per 100,000 in 2002~~)~~ in the United States (Gottfried, 2005). Moreover, antimicrobial agents have been vital in treating and preventing the spread of low incidence, high-consequence pathogens like rabies, smallpox, and anthrax. These chemotherapeutic agents have helped eradicate deadly illnesses like smallpox and rinderpest globally. The local and regional elimination of endemic diseases has also been successful with antimicrobial agents.

EMERGENCE AND DYNAMICS OF ANTIMICROBIAL RESISTANCE

Historical Context

Antibacterial Resistance

The widespread use of antibiotics has serious consequences, as exposure to these drugs has profound effects on the bacterial ecosystem. Even before the discovery of antibiotics, scientists hypothesized that bacteria could break down anti-infectives using enzymes. Ernst Chain confirmed the hypothesis, and in the early 1940s, Fleming discovered Penicillin-resistant *Staphylococcal* strains. Both scientists theorized that more resistant strains would develop with penicillin use based on the principle of natural selection (Gottfried, 2005). The emergence of Methicillin-resistant *Staphylococcus Aureus* (MRSA), a strain of antibiotic-resistant Staphylococcus spp., was confirmed through reports from a London hospital in 1948 (Gottfried, 2005). This development has substantiated previously held theories regarding the potential for antibiotic resistance among bacterial strains.

The development of MRSA involves complex mechanisms, such as beta-lactamase enzyme production, altered penicillin-binding proteins, and acquisition of the mecA gene, leading to new penicillin-binding proteins with decreased affinity (Conly & Johnston, 2002). MRSA prevalence increased from 5% to 40% in the 1970s to 1980s. Vancomycin was clinically indicated for methicillin resistance in 1972, and reports of resistance emerged in 1996, with Vancomycin-

Resistant *Staphylococcus Aureus* (VRSA) reported in the U.S. in 2002 (Conly & Johnston, 2002).

In the mid-twentieth century, *Shigella* strains resistant to **Chloramphenicol**, Streptomycin, **Sulfonamides**, and Tetracyclines hinted at gene transfer through plasmids. Research confirmed plasmid-mediated gene transfer, indicating bacteria in the human gastrointestinal tract as potential reservoirs for resistance genes (Gottfried, 2005).

Discovered in 1943 from gram-negative *Streptomyces griseus* bacteria, Streptomycin revolutionized the treatment of tuberculosis caused by the once-isolating *Mycobacterium tuberculosis*. However, the acid-fast bacteria quickly developed resistance to Streptomycin-only treatment, prompting the adoption of combination therapy. This began with para-amino-salicylic acid (PAS) and later expanded to include **isoniazid, rifampin, ethambutol, and pyrazinamide**. (Gottfried, 2005).

Antiviral Resistance

As antiviral drugs, particularly nucleoside analogs, became crucial elements in medical interventions, concerns about the emergence of drug-resistant strains heightened. Nucleoside analogs have demonstrated reliability in treating herpes simplex virus (HSV) infections for over two decades. While cases of drug-resistant HSV are rare in patients with a healthy immune system—occurring at an incidence rate of only 0.1 to 0.7% — individuals with compromised immune systems face a higher risk, with a prevalence rate ranging from 4 to 7% (Bacon et al., 2003).

Resistance to most viruses, such as HIV, has rapidly emerged against antiretrovirals. Highly active antiretroviral therapy (HAART), introduced in the 1980s for HIV, increased patient lifespan but led to antiretroviral drug resistance (ARDR) (Paydary et al., 2013). ARDR cases, starting with **zidovudine** in 1992, revealed rapid resistance development within weeks to months, emphasizing the need for combination therapy (Paydary et al., 2013). Despite the effectiveness of combination antiretroviral therapy (ART), HIV continues to evolve, posing challenges to its management (Feder et al., 2021). The South African Hoffman study observed that viruses can spread and reach detectable levels even when they are not entirely resistant to all drugs in a particular combination therapy- this can lead to sequential drug resistance (Feder et al., 2021).

Viruses like influenza, hepatitis B and C also exhibit resistance to recent drugs. Amantadine, initially effective against flu viruses, faced resistance during the 1980 flu epidemic, reaching 90.6% for certain strains by 2006 (Smyk et al., 2022). Neuraminidase inhibitors like **oseltamivir** show concern for influenza strains developing resistance, though most strains become less resistant after treatment cessation (Smyk et al., 2022). In contrast, resistance persists after treatment in hepatitis B and C, limiting treatment options. For instance, **lamivudine** monotherapy in HBV and HIV coinfected patients showed 90% resistance to long-term use (Terrault et al., 2018).

Antifungal Resistance

Antifungal resistance was first reported in the 1990s, marked by the emergence of multi-drug resistant *Candida* species and azole-resistant fungi, including *Aspergillus* (Kontoyiannis, 2017). Historically, resistance to antifungal treatment was primarily observed in individuals with compromised immune systems or those undergoing prolonged antifungal therapy. However, this phenomenon has now expanded to affect immunocompetent individuals (Kontoyiannis, 2017). Notably, the rise of treatment-resistant *Candida auris* has become a significant concern in healthcare settings, where it is associated with mortality rates ranging from 30% to 60% in patients with compromised immune responses (Egger et al., 2022). Furthermore, the emergence of azole resistance in *Aspergillus fumigatus* presents a significant medical challenge, given the limited treatment alternatives available (Wiederhold, 2017).

Antiparasitic Resistance

In 1937, **Pentamidine** was first prescribed to treat sleeping sickness. However, it was not until 1949 that it was discovered to be effective against visceral *Leishmaniasis* (Capela et al., 2019). Similarly, **chloroquine** was once a widely used treatment for malaria (*Plasmodium* spp.) during the 1960s and 1970s, but it had to be discontinued because of the emergence of resistance. The current preferred treatment for malaria is **Artemisinin** and its derivatives, including dihydroartemisinin, artemether, artesunate, and arteether. Nevertheless, resistance to these drugs has been reported as early as 2008 in the context of Artemisinin-based Combination Therapies (ACTs) (Capela et al., 2019). Additionally, **atovaquone**, commonly used with proguanil to prevent and manage complicated and uncomplicated malaria, has demonstrated resistance when administered as a monotherapy (Capela et al., 2019).

MECHANISMS OF RESISTANCE AND CONTRIBUTORY FACTORS

Antimicrobial resistance is a phenomenon where microorganisms become resistant to previously effective drugs due to their inherent resistance or genetic mutations, horizontal gene transfer, biofilm formation, efflux pumps, enzymatic inactivation, and adaptive resistance (Munita & Arias, 2016). The rate of AMR development can be significantly impacted by factors like agricultural practices, household and personal care products, antibiotic prescribing and usage, globalization, and drug development.

Agriculture

The food industry is a major contributor to AMR. Many countries use up to 80% of medically important antibiotics in land cultivation, livestock production, and aquaculture (WHO, n.d.). AMR may arise from terrestrial bacteria (microorganisms from soil and freshwater, plant endophytes and lichens) and contamination from agricultural waste, water runoff, and wastewater systems (Watts et al., 2017). Even though closed aquaculture systems are isolated from the environment, they may still spread local AMR to open environments. This can happen, for example, through wastewater or aquaculture sludge, which is often used as fertilizer and can spread onto soil systems and produce (Watts et al., 2017). The transfer of AMR genes from environmental microbes to fish, human, and animal pathogens can have a significant negative impact on both aquatic and human health. A 2015 study unveiled a significant association

between the nasal carriage of livestock-associated Staphylococcus aureus (S. aureus) and the occurrence of skin and soft tissue infections (SSTIs) in individuals who had frequent and extensive exposure to industrial hog production (Nadimpalli et al., 2016). The research also found that there was a higher prevalence of SSTIs among children in households where adults had frequent and extensive exposure to industrial hog production (Nadimpalli et al., 2016). The link between aquatic and terrestrial resistomes (genes that resist infections) is particularly concerning because many antimicrobials used in farmed fish are essential for human use. For example, azole-resistant aspergillosis is suspected to be driven by the agricultural use of antifungals (Kontoyiannis, 2017). Cross-resistance may also occur even when antimicrobials are used in both humans and aquaculture (Watts et al., 2017).

Household and personal care products

Products like soaps, detergents, hand lotions, window cleaners, cleaning cloths, mouthwashes, toothpaste, surface sprays, garbage bags, plastic wraps, textiles, and carpet underlays may contain antibiotics to eliminate bacteria. However, there may be an insufficient amount of antimicrobial agents to fully eradicate microorganisms, leading to the survival, resistance, and multiplication of specific pathogens and the development of multi-drug-resistant organisms (MDR). In 2017, the FDA banned 19 antibacterial agents from soaps due to concerns about their effectiveness and AMR risk (Venter et al., 2017). While some household and personal care products have removed antibacterial agents from their formulations, there are still a considerable number of such products in the market that contain antimicrobial agents unnecessarily. For instance, studies have also shown that antibacterial dishwashing liquid may be effective in laboratory-based suspension tests but not in real household settings with used sponges, demonstrating that the efficacy of antibacterial products in real-life scenarios may be reduced (Allen et al., 2006). There is a growing concern that the excessive use of antimicrobial agents in personal care and household products contributes to the rise of allergic conditions such as asthma, eczema, and allergic rhinitis (CDC, 2022). Good bacteria are essential for supporting the immune system and maintaining gut, urinary, and vaginal health. However, using antimicrobial products may hinder the immune system's development by eliminating helpful microorganisms. When used in excess, products like mouthwash and toothpaste that contain antimicrobial agents may do more harm than good by disrupting the body's natural flora.

Antibiotic Use

Sir Alexander Fleming, who discovered penicillin, warned that the rise in demand for antibiotics could lead to their abuse (Ventola, 2015). Current studies have confirmed that antibiotic misuse is a significant factor contributing to the evolution of resistance worldwide. Overprescribing, incorrect prescriptions, and lack of adherence among patients are all contributing factors. In many countries,

antibiotics are unregulated and available over-the-counter (OTC) or online without a prescription, promoting access that enables misuse (Ventola, 2015). Within the United States, healthcare reimbursement models do not incentivize the conservation of antibiotics or the use of valuable new antimicrobials (Gotham et al., 2021). Hospitals and healthcare providers are often paid per prescription, which can lead to overuse, presenting negative consequences, including an increased risk of C. difficile infections, as well as the development of UTIs and yeast infections.

Globalization

Globalization has had positive effects on healthcare accessibility and global resource exchange. However, it has also played a role in the spread of infections and is expected to have a significant influence on AMR in the future. This impact stems from increased international travel and tourism, global supply chains for food and pharmaceuticals, and medical tourism. Globalization has promoted medical tourism, often driven by cost-saving or access to specialized care, along with international travel and tourism, and contributed to the spread of infections and the transmission of drug-resistant pathogens (Williams, 2001). This can be observed with the recent spread of COVID-19 infection and the cases of Ebola in Europe and North America. The Zaire Ebolavirus species spread to the United States from already infected individuals who were either medically evacuated into the U.S. for treatment or entered the country as regular airline passengers, and within the United States, infected two nurses who provided care to one of the patients (Bell, 2016). The global supply chains for food and pharmaceuticals facilitate swift transboundary movement of antibiotics, potentially contributing to the proliferation of antibiotic misuse, contaminants, and fake medications in developed countries (Williams, 2001). AMR could worsen if public health responses are inadequate and disease eradication efforts are suboptimal, thereby promoting the spread of infections and adverse effects of antibiotic misuse.

Pharmaceutical Research, Development, and Production

Several daunting challenges hindering discovery and novel antibiotic production beset the antibiotic research and development landscape. The escalating need for new antimicrobials to treat life-threatening infections caused by the worldwide spread of multidrug-resistant bacterial pathogens is at odds with the current investment levels in developing natural-product-derived and synthetic small molecules.

- <u>Profitability Challenges-</u> Researching and developing antibiotics is both expensive and time-consuming. Pharmaceutical companies incurred costs of almost $1 billion per new antibiotic in the early 2000s, and this figure has increased to about $1.5 billion in 2017 (Spellberg et al., 2004; Towse et al., 2017). Unfortunately, many drug

candidates fail during clinical trials, leading to significant financial losses. Even when successful, new medications are introduced to the market sparingly to prevent the development of antibiotic resistance. Furthermore, antibiotics typically have shorter treatment durations than chronic disease drugs, which generate long-term revenue. This creates a paradox where the more effective an antibiotic is, the less profitable it becomes, leading to a low return on investment. Consequently, only a limited number of companies have invested in antibiotic development due to this financial disincentive. In fact, seven out of the twelve pharmaceutical companies that effectively introduced a drug to the market in the past decade have become bankrupt or shut down their antibiotics business due to inadequate sales figures (Allen, 2022). Therefore, developing antibiotics that are both effective and economically sustainable is a delicate balance that requires significant investment and careful management.

- Scientific Challenges- Since the early 2000s, the production of antibiotics has drastically slowed down. The scientific challenge lies in finding effective novel antibiotics against drug-resistant bacteria. As potential targets have already been explored, it is difficult to identify new drug candidates. Innovation has not yet yielded promising clinical indications to increase the antibiotic pool or slow AMR progression.
- Regulatory Hurdles- The process that pharmaceutical companies have to go through in order to get their drugs approved can be an incredibly painstaking and protracted one. From the initial stages of testing and development to the clinical trials that are required to establish the drug's safety and efficacy, there are many hoops to jump through before a medication can be made available to the public. Additionally, regulatory agencies such as the FDA have strict standards that must be met, and the entire process can take several years and cost millions of dollars. Furthermore, after a novel antibiotic loses patent protection, generic versions become available, leading to reduced profitability due to price competition.
- Antibiotic Stewardship Programs- Antibiotic stewardship programs are designed to optimize antibiotic prescribing and use in various healthcare facilities. They aim to identify the most effective antibiotic regimens, improve patient outcomes, mitigate adverse effects such as Clostridium difficile infection (CDI), and curb rates of AMR (Centers for Disease Control and Prevention, 2023). These programs have been shown to have a direct impact in reducing MRSA infections by 21% and AMR-related deaths by 18% in 2019 as compared to 2013 (Centers for Disease Control and Prevention, 2023). To ensure the effectiveness of antibiotics, it is important that new antibiotics are only used to treat infections caused by multi-drug resistant bacteria, where no other effective treatment is available. However, pharmaceutical companies have expressed their dissatisfaction with antibiotic stewardship programs, claiming that they are too restrictive and could have negative implications for patients (Allen, 2022). This problem is further compounded by low Medicare reimbursements, which discourage hospitals from utilizing new antibiotics. For instance, despite 90% of US hospitals switching from using Polymyxin B (brand name colistin) to newer drugs like Avycaz for treating urinary tract infections, they are not investing enough in the new medication due to low Medicare reimbursement rates (Allen, 2022).

ANTIMICROBIAL RESISTANCE IN BLACK AMERICA

AMR has been a public health concern for more than a century, even before the discovery of the first antibiotic. With the occurrence and reappearance of infectious diseases, the issue has become even more significant, resembling a déjà vu of the initial epidemiologic transition. As a public health crisis, AMR undermines decades of advancements and innovation in medicine and the pharmaceutical industry, making infections and medical procedures riskier, leading to treatment delays and prolonged illness duration. Patients may become extended infection reservoirs, increasing the risk of spreading resistant microorganisms and jeopardizing the health of more individuals and healthcare professionals (Jindal et al., 2015). Moreover, protracted illness and treatment duration may escalate healthcare expenses and impose a heavier economic burden on families and societies, the impact of which is often underestimated. For instance, postoperative infection rates could increase by up to 50% and mortality rates by up to 30% if antibiotics are no longer employed for prophylaxis and treatment of hospital-acquired infections during total hip replacement surgeries (Smith & Coast, 2013). The global impact of AMR is enormous and has the potential to affect economies, international trade, travel, and security. The World Health Organization predicts that by 2050, there could be 10 million annual deaths worldwide, with 2.4 million occurring in high-income countries (IACG, 2019). Furthermore, there is an economic threat comparable to the global financial crisis of 2008-2009 due to increased healthcare utilization, impact on agriculture, trade, job loss, poverty, and inequalities (IACG, 2019).

For the Black community, antibiotic resistance poses a significant challenge~~,~~ mainly due to health inequities, limited healthcare access, and suboptimal infection control measures. Black Americans are also at a higher risk of developing conditions that require increased antibiotic usage. Out of the top ten states with the highest rates of STIs in 2021, six states (Mississippi, Louisiana, South Carolina, Alabama, Georgia, and North Carolina) were among the ten states with the highest Black American population (CDC, 2023). Black Americans had the highest rate of gonorrhea (653 per 100,000 compared to 79 per 100,000 in whites) and chlamydia (1,082 per 100,000 compared to 185 per 100,000 in whites), and the second highest rate of syphilis (42 per 100,000 compared to 9 per 100,000 in whites) (CDC, 2023). Between 2015 and 2019, non-Hispanic Blacks accounted for 68% of patients who presented with disseminated gonococcal infections caused by untreated gonorrheal infections that spread via the bloodstream to other parts of the body (Weston et al., 2022).

CDC's Active Bacterial Core Surveillance (ABCs) evaluates invasive bacterial infections of public health importance to monitor the emergence of AMR and promote adequate response to public health emergencies and other emerging infections. However, racial and ethnic data for minorities in the ABC report is inadequate, with up to 70% of data not including race. Nonetheless, the ABC report indicates that Black Americans are disproportionately affected by infectious diseases, and exhibit higher rates of Group B *Streptococcus* (10.3 per 100,000 population in Blacks vs 9.0 per 100,000 population in whites and 6.5 per 100,000 population in Hispanics in 2021), *Haemophilus influenzae* (1.3 per 100,000 population in 2021 vs 0.9 per 100,000 population in whites in 2021), *Neisseria meningitidis* (0.09 per 100,000 population vs

0.06 per 100,000 in 2021), and *Streptococcus pneumoniae* (8.9 per 100,000 vs 4.3 per 100,000 in whites in 2021) since at least 2017 (CDC Surveillance Reports, 2023). Limited access to healthcare services in predominantly Black neighborhoods further exacerbates this problem. For example, only 245 pharmacies are present in counties with the highest number of Black Americans compared to 3441 in counties with the lowest number of Black Americans (PolicyMap, n.d.). Furthermore, Black individuals had a higher rate of uninsurance than white individuals in at least 53% of counties that report uninsurance (PolicyMap, n.d.). The 2020 COVID risk index also revealed that the top 10 majority-Black counties faced greater rates of infections compared to counties with the least Black population (PolicyMap, n.d.).

Individuals of African descent have a higher likelihood of carrying the sickle cell trait. In cases where an individual inherits both copies of the trait, they develop sickle cell disease (SCD). Unfortunately, this predisposes many Black Americans to bacterial infections and an increased reliance on antibiotics. Prophylactic antibiotic regimens may be recommended to reduce the risk of invasive pneumococcal infections in SCD patients, which can be life-threatening. However, studies show that about three in four patients receiving prophylaxis still present with resistant strains of Streptococcus pneumoniae (Srisuwananukorn et al., 2020). Additionally, central venous catheter line placement, often used in pain management and exchange transfusion, is a significant risk factor for multidrug-resistant infections in all SCD patients. PPSV23 vaccination is recommended to reduce the risk of invasive pneumococcal infections by five-fold in SCD patients (Srisuwananukorn et al., 2020). However, this vaccine only covers a limited range of serotypes of S. pneumoniae, and SCD patients remain at high risk of contracting this disease and succumbing to its complications compared to the general population (Bryson, 2023). Invasive pneumococcal infections or their complications (e.g., meningitis) require antibiotic treatment, which may further fuel the spread of antibiotic resistance (Bryson, 2023). Furthermore, a study found that about 1 in 5 among sickle cell disease patients who had multidrug-resistant infections died within three years; this highlights that antibiotic resistance is a significant risk factor for mortality in these patients. (Srisuwananukorn et al., 2020).

RECOMMENDATIONS

To effectively tackle AMR, it is crucial to adopt a comprehensive and multifaceted approach that addresses the root causes of this growing problem. The potential death toll resulting from drug-resistant infections could be comparable to the worldwide mortality rate of COVID-19. Hence, it is imperative to explore global interventions aimed at preserving the efficacy of life-saving antimicrobials.

1. Build a healthy and vibrant antimicrobial pipeline: The global spread of drug-resistant bacterial pathogens has created a pressing need for new antimicrobials to treat life-threatening infections. However, the current investment in natural-product-derived and synthetic small molecules is inadequate to meet this need. To address this challenge, there is a critical need for strategic investment in novel options that prioritize efficacy, safety, cost-effectiveness, global accessibility, and low resistance potential (Paydary et al., 2013). The development of new antibiotics has heavily relied on natural sources and the modification of existing compounds since the discovery of penicillin. Moreover, the majority of antibiotics in clinical trials as of 2021 were ineffective against multiple

classes of microbes and consisted of less than 25% of all drugs in the drug development pipeline (Miethke et al., 2021). Despite advances in modern medicine, the research and development of antibiotics have resulted in only a handful of anti-infectives with unique mechanisms of action that differentiate them from existing antibiotics. This is particularly important since modifying existing classes does not eliminate the risk of cross-resistance. It is therefore crucial to invest heavily in new chemotypes and technologies to combat antimicrobial resistance. Direct Lytic Ams (DLAs) like exebacase, are one such chemotypes made up of purified proteins and peptides that have shown a low tendency for resistance. When administered with existing antibiotics, they can help suppress the development of resistance to other antibiotics (Schuch et al., 2022). Exploring polypharmacological compounds like combination therapies target multiple defined targets and have also been proven effective. These combinations can have additive or synergistic effects, especially when using distinct mechanisms of action, and are valuable in increasing the efficacy of existing antibiotics, preventing the emergence of multidrug-resistant organisms, and restoring the effectiveness of antibiotics made inefficient by resistance (Miethke et al., 2021).

2. Improve clinical and public health practices:
    a. Promote research in early diagnostic testing: Early and accurate diagnostic testing plays a pivotal role in facilitating prompt treatment with antibiotics that are specifically effective against the pathogen. This approach not only helps in refining an empirically selected regimen but also streamlines the process of de-escalating unnecessary antimicrobials. In particular, in settings where multi-drug resistant microorganisms are prevalent, a rapid turnaround time is of utmost importance.
    b. Expand vaccination and preventive therapy: An expanded pipeline for vaccination and the utilization of prophylactic monoclonal antibodies offer a promising solution for treating resistant pathogens such as C. difficile infections (Bassetti et al., 2017). Monoclonal antibodies are a viable option for treating patients with compromised immunity, who are often excluded from many vaccines and are particularly vulnerable to developing infections, many of which are resistant (Marston et al., 2016).
    c. Enhance measures for infection control and prevention of drug resistance in healthcare facilities: In May 2015, 196 countries made a commitment to the Global Action Plan to address antimicrobial resistance (Sneddon et al., 2022). The plan aims to increase awareness and understanding of AMR, strengthen knowledge through research and surveillance, reduce infection rates through sanitation and hygiene measures, optimize antimicrobial use in human and animal health, and promote sustainable investment for the development of new medicines, diagnostics, vaccines, and interventions across all countries. Although it is a welcome improvement and brings the much-needed level of awareness to world leaders, more global initiatives are needed to address the problem of AMR. Antibiotic stewardship and proper tracking are critical solutions in addressing AMR. Unfortunately, many countries lack tracking databases for emerging and resistant pathogens in their regions and cannot accurately report AMR data. The 2019 WHO's fourth Global Antimicrobial Resistance and Use Surveillance System (GLASS) report only included records from 70 countries, which is far

from enough (Dall, 2021). Despite reporting a sixfold increase in the number of infections compared to the 2017 data, these numbers may underestimate the prevalence and magnitude of AMR, and sufficient knowledge and surveillance are needed to control MDR on a global scale. Therefore, global reporting of emerging and resistant pathogens is essential to track pathogens, identify patterns, and create an action framework to address unique AMR endemic or epidemic cases before they spread globally, and is vital in the fight against AMR. Countries must also be encouraged to promote local antimicrobial stewardship programs and use resources such as the Global Antimicrobial Stewardship Partnership Hub (GASPH) for healthy partnerships to share best practices (Sneddon et al., 2022).

3. Legislative and regulatory solutions: While supporting current efforts to reduce the progression of AMR within the U.S., legislators must continue to provide funding to encourage ongoing research.
    a. Rebuilding the antibiotic market: Policymakers must explore ways to strengthen the antibiotic development pipeline and incentivize pharmaceutical companies through reimbursement reforms, market entry rewards or milestone payments, to stimulate antibiotic research and development.
        i. A nonprofit drug development model has been proposed to be vital in addressing AMR. The PASTEUR Act establishes a subscription model for antibiotic development, removing the burden of low return on investment and market challenges they face with novel antibiotic development and the financial incentive on pharmaceutical companies that often leads to low return on investment. This legislation ensures that pharmaceutical research progresses to address antibiotic development market failures and could potentially usher in a new era of antibiotic development (Sen. Bennet, 2023).
        ii. One potential strategy to support the development of antibiotics is through the implementation of pull and push incentive models. Pull incentives are market-driven mechanisms that reward successful antibiotic development, while push incentives involve direct investments in research and development (Årdal et al., 2017). Examples of pull strategies include patent extensions to prolong market entry of generic antibiotics, market-entry rewards to incentivize drug availability while unlinking compensation from sales volume, and tradable vouchers that are granted to pharmaceutical firms' post-regulatory approval of a high-priority drug (Dutescu & Hillier, 2021). On the other hand, push incentives include grants, subsidies, and tax incentives. For instance, CARB-X is an initiative that provided $360 million in funding for 92 projects in 12 countries over a five-year period (Dutescu & Hillier, 2021).
    b. Agriculture and aquaculture: By implementing strict guidelines and monitoring the use of antibiotics in the food production industry, legislators can help ensure that these drugs are used only when necessary. Additionally, promoting international trade agreements that discourage excessive use of antibiotics in food production can help reduce the prevalence of antimicrobial resistance. This could include measures such as limiting the amount of antibiotics that can be used in animal feed or requiring veterinary oversight for all antibiotic prescriptions.

c. Bolster national action plans: To combat the growing threat of antimicrobial resistance (AMR), lawmakers could collaborate with stakeholders and relevant agencies to create updated national action plans for AMR. Such plans could focus on measures to strengthen infection prevention and control practices, as well as to bolster pandemic preparedness efforts. By working together, these groups can address the complex challenges presented by AMR and ensure that our healthcare systems are prepared to respond to outbreaks and other emergencies.

4. Promote global AMR efforts: Global support will go a long way to addressing AMR in communities that abuse antimicrobial agents and in areas that lack proper health and drug distribution infrastructure.
   a. Transform drug distribution networks: Establishing a sustainable drug distribution, public health, and health systems network in developing countries is crucial for the judicious use of antibiotics, reduction of counterfeit antibiotics, effective public health surveillance and intervention, and proper management of infectious diseases, endemics/epidemics, thereby lowering the global rate of AMR. It is imperative to rigorously enforce infection control measures, maintain proper hygiene and sanitation standards, and appropriately dispose of or manage medical waste within healthcare facilities and communities. These measures are critical to combat AMR and maintain the efficacy of antibiotics.

   b. Educate the public: Engagement in public education campaigns will play a crucial role in raising awareness among the public about the significance of strictly adhering to accurate medical guidance for drug usage. These campaigns will specifically focus on educating the public about the importance of carefully following guidelines related to the correct indication, appropriate dosage, proper administration, and exact timing of drug intake. It is imperative that individuals are provided with accurate and up-to-date information about these aspects of drug usage to ensure optimal health outcomes and public awareness campaigns will serve as an effective means of achieving this objective.
   c. Utilize international partnerships and support: Global collaborations fortify the knowledge and expertise of the global health workforce, diminish health

disparities, tackle cross-border infectious disease risks, recognize the needs of countries and regions, and provide financial and moral support.

d. Strengthen local policies: Public health systems can collaborate with the government in setting new policies that prioritize antibiotic stewardship and address factors that exacerbate the problem. This includes regulating the sale of antibiotics, curbing the consumption of wildlife, and implementing restrictions on the excessive use of antimicrobials in agriculture, livestock, and aquaculture.
e. Promoting global Pandemic Preparedness and Response Strategies: A comprehensive global pandemic preparedness strategy not only mitigates the immediate risks associated with pandemics but also aligns with efforts to combat AMR. AMR represents an inherent pandemic risk in itself, which escalates when coupled with emerging public health threats. Therefore, it is crucial to implement coordinated and synchronized interventions to address both AMR and pandemic preparedness.

CONCLUSION

To effectively address the impending public health crisis posed by antimicrobial resistance (AMR), it is crucial to implement a comprehensive action plan that involves collaborative partnerships, legislative solutions, and pandemic preparedness strategies. A joint effort is strongly recommended to eradicate resistance reservoirs, disrupt transmission chains, and deploy effective prevention strategies worldwide. By implementing these measures, public and population health can be safeguarded collectively and strategically, while also addressing the unique challenges that Black communities face in the context of antimicrobial resistance.

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