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The Impact of Antimicrobial Resistance on Co-INFECTIONS: Management Strategies for HIV, TB and Malaria

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Antimicrobial resistance is a growing global health problem, especially in the management of co-infections such as HIV, TB, and malaria. AMR occurs when a pathogen develops resistance against antimicrobial agents, which results in less effective treatments and contributes to increased morbidity and mortality. Co-infections further worsen this condition by introducing complex interactions among pathogens that complicate disease progression and treatment protocols. This review discusses the impact of AMR on co-infection from a multifaceted perspective, considering cases of HIV-TB, HIV-malaria, and TB-malaria. It considers the main factors contributing to the emergence and dissemination of resistant varieties: interactions between pathogens, horizontal gene transfer, and inappropriate antibiotic use.

The study has highlighted that comprehensive management strategies, including antimicrobial stewardship, better diagnostics, vaccination, and addressing the basic underlying risks, such as poor sanitation and comorbid conditions, are urgently needed. Advanced diagnostic testing and strong infection control are crucial in lessening the burden of AMR. From a wider perspective, the paper calls for global collaboration in developing new antimicrobials and raising public awareness about using antibiotics judiciously.

It concludes by stressing once more the need for integrating global health to address AMR and improve treatment outcomes to protect public health from the compounded threats of antimicrobial resistance and co-infections.

Keywords: Antimicrobial Resistance (AMR); co-infections; Human Immunodeficiency Virus (HIV); malaria; management strategies; Tuberculosis (TB).

1. INTRODUCTION

Antimicrobial resistance is the ability of an organism be it virus, bacteria, fungi or parasite to confer resistance to the actions of antimicrobial drugs initially meant to eradicate their survival. [1]. This ability of organisms to form resistance to potential drugs makes treating infections a dilemma for physicians and scientists. Over the years led to a rise in mortality all over the nations. [1] Co-infection is a condition that goes hand in hand with antimicrobial resistance and it is simply the presence of two or more diseases causing microorganisms in a person at the exact time, these microbes tend to form a more complicated infection that is more difficult to treat thereby resulting more fatality [2].

WHO has explained further that AMR happens due to natural selection, although the role of humans in exacerbating its process cannot be estimated for example, the abuse of antimicrobial drugs in both animals and agriculture which is more common in low and middle-income countries like Nigeria is one major cause if the rise in the burden of AMR because people living in this region have little or no access to professional consultation so majority who fall among this class tend to self-medicate.[1] The convergence of AMR and co-infection especially in HIV, TB, and Malaria must be addressed for the sake of the well-being of public health because it strengthens the fact that resistant organisms can spread and persist, co-infection can worsen results and limit available treatment options, AMR and co-infection in HIV, TB and Malaria cause a higher death rate [3]. Addressing AMR and co-infection needs a diverse approach which includes more efforts in developing new treatment options, putting infection prevention and control measures in place, promoting antimicrobial stewardship and its appropriate use, more research and support collaboration set in place, sustainable development and global

security be promoted, making health care affordable for the financial constraints' individuals [4].

1.1 Study Objective

The primary objective of this study is to investigate the implications of antimicrobial resistance on co-infections. We focused on HIV, tuberculosis (TB), and malaria.

The specific aims of the study include:

1. Assessing the Prevalence of Antimicrobial Resistance: To evaluate the prevalence and patterns of antimicrobial resistance among pathogens associated with HIV, TB, and malaria in various geographical regions.
2. Understanding Clinical Outcomes: To analyze the impact of AMR on clinical outcomes in patients suffering from co-infections, including treatment efficacy, duration of hospitalization, and mortality rates.
3. Identifying Risk Factors: To identify and characterize the risk factors contributing to the development and spread of AMR in populations affected by co-infections.
4. Evaluating Treatment Strategies: To review current treatment strategies for managing co-infections in the presence of AMR and to propose evidence-based recommendations for optimizing patient care.
5. Exploring Public Health Implications: To explore the broader public health implications of AMR in co-infections, including its effects on healthcare systems, economic burden, and strategies for prevention and control.
6. Promoting Awareness and Education: To promote awareness and education regarding AMR and its consequences among healthcare providers, policymakers, and the general public to foster collaborative efforts in combating this global health threat.

2. CO-INFECTIONS AND ANTIMICROBIAL RESISTANCE (AMR)

2.1 Antimicrobial Resistance in HIV-TB Co-Infections

HIV and tuberculosis (TB) co-infection remains a significant global health threat. Despite TB being curable, it continues to be a leading cause of death, especially among those with HIV. Antiretroviral therapy (ART) has improved HIV treatment but still poses a risk for active TB onset. Treating HIV and TB co-infection involves multiple medications over an extended period, presenting challenges for all age groups [5]. Antibiotic susceptibility testing (AST) is the primary method for identifying bacterial resistance and guiding appropriate treatment [6]. Surveillance studies rely on AST results to produce epidemiological data on bacterial pathogens and antimicrobial resistance (AMR), which are crucial for national, regional, and international efforts to combat AMR [7]. The disk diffusion test remains the recommended technique for determining antibiotic susceptibility, based on measuring and reporting the bacterial inhibition zone.

2.2 Antimicrobial Resistance in HIV-malaria Co-infections

Antimicrobial resistance (AMR) is now widely acknowledged as a hazard to public health, and efforts have been made to lessen its impact everywhere in the world in recent years. Nigeria faces the same difficulties as many other nations when it comes to AMR [8]. The rise in mortality and cost burden resulting from the advent of microbes resistant to several drugs has been nearly exponential. Therefore, there has never been a better time to emphasize the responsible use of antimicrobial medications. Nigeria must lead the way in combating antibiotic resistance because it is the most populous nation in West Africa. All pathogens, whether bacterial, fungal, parasitic, or otherwise, can develop resistance. Nevertheless, conversations about antimicrobial resistance (AMR) typically centre on bacterial resistance. There are two main resistance stories in malaria, only one of which is relevant to antimicrobial resistance (AMR) [9].

2.3 Antimicrobial Resistance in TB-malaria Co-infection

Antimicrobials are drugs that prevent and cure infectious diseases in humans, animals, and plants. They include antibiotics, antivirals, antifungals, and anti-parasitic.

When bacteria, viruses, fungi, and parasites stop responding to antimicrobial medications, it's known as antimicrobial resistance (AMR) [10]. Drug resistance increases the risk of disease transmission, serious sickness, disability, and death by making antibiotics and other

antimicrobial medications ineffective and making it harder or impossible to treat infections [10]. AMR is a normal mechanism that develops over time as a result of pathogen genetic alterations. Human activities hastened its origin and spread, mostly through the improper and excessive use of antibiotics for the treatment, prevention or management of illnesses in people, animals, and plants. Bacteria can develop acquired antibiotic resistance as a result of phage, plasmid, or transposon-mediated horizontal gene transfer, or mutations [11]. There is little evidence of drug resistance genes horizontally transferred in *M. tuberculosis*; instead, resistance primarily emerges from chromosomal alterations under the selection pressure of antibiotic use.

3. FACTORS CONTRIBUTING TO AMR IN CO-INFECTIONS

AMR can make treatment plans extremely difficult in certain situations [12]. Some of the factors associated with antimicrobial resistance in co-infections include:

3.1 Pathogen Interactions

In many cases of co-infections, different pathogens may interact synergistically and antagonistically, which affects their growth and resistance patterns [13] The competition among microbial pathogens in the host for resources and space builds up survival instincts in these pathogens which further increases the emergence of resistance strains [14]. Due to this synergistic relationship, when one pathogen is overpowered by an antibiotic, other pathogens may survive, proliferate, and lead to the dominance of the resistance stains [15]. For example, in certain respiratory infections, bacteria like *Streptococcus pneumonia* and viruses like influenza can synergistically enhance each other's pathogenicity, thus leading to severe disease progression, and eventual antimicrobial resistance [16].

3.2 Horizontal Gene Transfer

For single pathogenic infections, pathogens can develop antibiotic resistance through spontaneous mutation, although this would take a long time if it depended solely on self-adaptive mutations [6]. However, in the events of co-infections, these create an ideal platform and environment for horizontal gene transfer (HGT) [17]. Horizontal gene transfer involves a process where genetic material, such as antibiotic-resistance genes, is exchanged between different microorganisms, thus greatly fostering collaboration among bacterial populations in antimicrobial development [18]. Mechanisms such as transformation, transduction, and conjugation enhance the spread of resistance genes among multiple microbial species, which can facilitate the spread of resistance [19]. Recent studies have shown the emergence of "superbugs" which are said to possess antibiotic-resistance genes on their plasmids that were transferred through HGT, thus granting them tolerance to almost all antibiotics [20].

3.3 Inappropriate and Overuse of Antibiotics

The consistent overuse of antibiotics, especially when they are not appropriately indicated at the time of use, has contributed significantly to antibiotic resistance [21]. According to the Centers for Disease Control and Prevention, approximately one-third of antibiotic use in the population is either not needed or appropriate at the time [22]. Clinicians frequently prescribe broad-spectrum antibiotics due to diagnostic uncertainty, aiming to cover all potential pathogens. However, this approach can inadvertently promote the selection of resistant strains among the pathogens [23]. The use of broad-spectrum not only kills the susceptible bacteria, it also exerts selective pressure on resistant strains, thus enhancing their proliferation [24]. Another important problem is the concept of self-medication with antibiotics [SMA], this has been linked with an increased possibility of inappropriate drug usage which further puts patients at increased risk of developing adverse drug reactions, and the eventual development of antimicrobial resistance [25].

Therefore, both the clinicians and the patients must understand and follow the concept of antibiotic stewardship, which refers to concerted efforts made by healthcare workers in healthcare settings to ensure that antibiotics are used only when necessary and appropriate, thus prescribing the right drug at the right dose at the right time for the right duration.

3.4 Delayed or Inaccurate Diagnosis

In the absence or deficiency of appropriate diagnostic tests, it can be difficult to ascertain what nature of the pathogen is causing an infection [26]. This can lead to delayed

treatments and inappropriate use of antibiotics, which further prolongs the disease progression and leads to antimicrobial resistance. Furthermore, co-infections pose more diagnostic challenges, leading to delayed or inaccurate identification of causative pathogens [26]. Therefore, advanced diagnostic tools, such as multiplex PCR and next-generation sequencing, are needed to accurately identify pathogens in co-infections and guide targeted therapy [27]. Furthermore, point-of-care tests that can differentiate between viral and bacterial infections must be made readily available to help reduce unnecessary antibiotic use and promote antibiotic stewardship [28].

3.5 Host Immune Responses (Immunological Factors)

Co-infectio28ns can alter the host immune responses, this can invariably affect the outcome of antimicrobial treatment [29]. Various viral and bacterial infections can also suppress the immune response. Particularly vital infections, they can potentiate the pathogenic properties of bacteria that would naturally not cause any damage to the host [opportunistic infections], creating a thriving environment for these pathogens despite antibiotic therapy [30]. Furthermore, this immune modulation can lead to treatment failure and the persistence of resistant strains.

3.6 Environmental Factors

Resilient infections are known to spread rapidly in healthcare settings, especially within hospitals. The proximity of patients with different infections facilitates the transmission of resistant organisms [30]. A community's environment can facilitate the transmission of illnesses and the emergence of resistance due to elements including overcrowding, poor sanitation, and limited access to healthcare [31] Studies have shown that organisms that are resistant to antimicrobial agents are often spread from patient to patients in health care facilities, typically via the contaminated hands of health care workers, contaminated surgical equipment, or generally from hospital environmental fomites [32]. This type of spread typically, involves the transmission of a single strain of the antibiotic-resistant organism. Some common antibiotic-resistant organisms seen in hospitals include methicillin-resistant staphylococcus aureus MRSA, Vancomycin-resistant enterococcus, Multidrug-resistant gram-negative bacilli, and clostridium difficile [33].

3.7 Agricultural Practices

One major factor contributing to antimicrobial resistance is the use of antibiotics in agriculture for livestock illness control and growth enhancement [growth supplements and growth promoters] [34]. Humans can contract resistant bacteria by eating infected food items or by coming into close contact with them. Animal excrement routinely circulates antibiotic-resistant bacteria throughout the ecosystem, which can be harmful to people and easily transmitted through food chains [35]. This can cause complicated, incurable, and chronic infections in people. Antibiotics released into the environment by agricultural runoff also favour resistant microorganisms, which can be converted into diseases that affect humans [36].

4. EFFECT OF AMR IN CO-INFECTIONS

When one or more of the pathogens involved are resistant to treatment, co-infections have the potential to greatly worsen the severity of diseases [27]. Longer sickness durations, higher rates of transmission, and higher death rates can all be caused by antimicrobial resistance. For example, multidrug-resistant TB (MDR-TB) complicates treatment protocols, and people with HIV frequently co-infect with TB. When HIV patients are exposed to MDR-TB, their immune systems are already weakened, which increases treatment failure and fatality rates [37].

The presence of resistant pathogens in co-infections can result in serious health consequences, such as extended hospital stays, increased medical interventions, and, in some instances, death [38].

4.1 Transmission of Resistant Strains

AMR can proliferate more easily in healthcare settings and communities when resistant organisms co-infect. Resistant strains can find a home in infected people, where they can spread to others by direct contact or environmental contamination. Because of the ongoing cycle of infection and resistance created by this transmission, it is difficult to contain outbreaks and safeguard susceptible groups. This rise in antimicrobial resistance (AMR) presents a serious threat to public health in areas like sub-

Saharan Africa where co-infection rates are high [39].

Furthermore, through horizontal gene transfer, co-infections with pathogens that are resistant to an organism can aid in the spread of resistance genes. Multi-resistant strains may evolve as a result of this happening inside the host or in the community [40]. For instance, if a patient is simultaneously infected with many resistant germs, this could result in the exchange of resistant genes and the emergence of new, even more difficult-to-treat multi-resistant strains.

4.2 Complicated Diagnosis and Treatment Regimens

The diagnosis procedure is often complicated by antimicrobial resistance in co-infections since it is more difficult to pinpoint the precise bacteria causing the infection and ascertain their resistance profiles. The inability of conventional diagnostic techniques to discriminate between resistant strains and those that are not could result in the wrong or delayed course of treatment. As a default treatment approach, the use of broad-spectrum antibiotics can aggravate resistance further by applying selective pressure to microbial populations, which promotes the survival and spread of resistant strains [41].

Similarly, AMR in co-infections makes treatment plans more difficult because medical professionals have to take drug interactions and the possibility of pathogen cross-resistance into account. Multiple medications with distinct mechanisms of action may be needed by patients, which could raise the risk of side effects and decrease adherence to prescribed treatment plans [42]. Patients and healthcare professionals may find it difficult to manage co-infections with resistant strains since it requires constant monitoring and modifications to treatment regimens.

5. MANAGEMENT STRATEGIES FOR REDUCING ANTIMICROBIAL RESISTANCE AND CO-INFECTIONS

Antimicrobial resistance (AMR) greatly threatens global health [43]. It may lead to common treatments that become ineffective, causing illnesses to be prolonged, hence more deaths and treatment costs increasing [44]. The problem is further compounded by the co-infections of diseases like HIV, tuberculosis (TB), and malaria, which often require sophisticated drugs, hence an increased risk of resistance. Better infection control is indispensable in fighting these issues. Hand hygiene is a simple but extremely effective basic measure for infection control. Healthcare workers, patients, and caregivers are to follow stringent hand hygiene procedures in the form of alcohol-based rubs and handwashing with soap and water to intercept transmission routes of infectious agents [45]. It prevents both the spread of pathogens and the occurrences of infections that otherwise would need to be treated with antibiotics, thus helping to reduce the development of AMR.

Another crucial principle of infection control is the application of standard and transmission-based precautions. Standard precautions in health care mostly rely on infection prevention—the use of PPE, safe handling of sharp objects, and proper sterilization of medical devices. In cases of some specific infections, additional transmission-based precautions, including contact, droplet, and airborne precautions, should be taken [46]. Such measures can help to contain the spread of drug-resistant organisms and pathogens associated with co-infections such as TB and HIV, which could increase the burden of disease and complicate treatment strategies. Strict cleaning protocols, along with effective disinfectants, limit the survival of such pathogens on these various surfaces. This has been found to greatly reduce cases of Healthcare-Associated Infections (HAIs) [47,48].

Vaccination prevents infections that would need to be treated with antimicrobials and therefore eventually create resistance [49]. Vaccines for pathogens like the influenza virus, pneumococcus, and Haemophilus influenza type B (HIB) have significantly reduced the incidence of infections likely to need antibiotic treatment [50] second, vaccines against diseases such as TB and malaria directly reduce the burden of co-infections, reducing the need for complicated drug regimens that fuel resistance [51,52].

5.1 Enhanced Antibiotic Stewardship

Antibiotic stewardship refers to a set of coordinated strategies designed to optimize the use of antimicrobial medications, enhance patient outcomes, reduce microbial resistance, and limit the spread of infections caused by multidrug-resistant organisms [52,53]. Enhanced antibiotic stewardship improves patient outcomes

by ensuring that individuals receive the right antibiotic, at the right dose, for the right duration. This targeted approach minimizes potential harm, such as adverse drug reactions and secondary infections, leading to better clinical outcomes. Furthermore, responsible antibiotic use reduces healthcare costs by decreasing unnecessary antibiotic prescriptions, thereby minimizing the occurrence of drug-resistant infections and lowering overall treatment costs associated with these complex cases [54,55]. Enhanced antibiotic stewardship is also crucial in managing co-infections, such as those involving HIV, tuberculosis (TB), and malaria. Effective stewardship ensures that antibiotic use does not exacerbate resistance issues in co-infecting pathogens, thereby supporting more successful treatment outcomes [56-58].

5.2 Addressing Underlying Risk Factors and Comorbidities in AMR and Co-Infections

Multiple comorbid illnesses such as diabetes, chronic lung disease, and malnutrition can aggravate the risk of co-infections and AMR [59]. For instance, malnutrition weakens the immune system, making individuals more susceptible to infections and lowering their ability to react effectively to antimicrobial treatment [60, 61]. In diabetes, the malfunction of the immune system and the poor healing of wounds can trigger chronic infections, usually requiring extensive use of antibiotics, which fulfils the premise of resistance. The treatment of this comorbidity utilizing integrating healthcare measures can not only involve infections but also decrease the need for antibiotic therapy, therefore, minimizing AMR [62, 63].

An impaired immune system represents a considerable risk for the combined acquisition of coinfections and the development of AMR. The nature of the virus, which is immunosuppressive, renders HIV patients more vulnerable to developing TB. The coexistence of a dual infection will alter the treatment protocol and may result in the utilization of several antimicrobial agents, hence, the possibility for resistance development will increase [64]. By treating immune depression caused by HIV with antiretroviral therapy (ART), the incidence of TB and other opportunistic infections could be decreased and antibiotics could be used to a lesser extent, therefore decreasing the chances of emergence of AMR through the reduction of the dependency on antibiotics. Socioeconomic factors have a major influence on AMR and co-infection transmission. Poor living circumstances, overcrowding, and the lack of healthcare facilities all influence infectious diseases such as TB and malaria to spread very rapidly among humans. These habitats are usually at the forefront of dangerous exploits, in that individuals free from infection may take antibiotics without ever being directed. Bolstering healthcare systems, facilitating access to clean water, and sanitation, and educating the community about the safe use of antibiotics can all greatly reduce the chances of these risk factors [65].

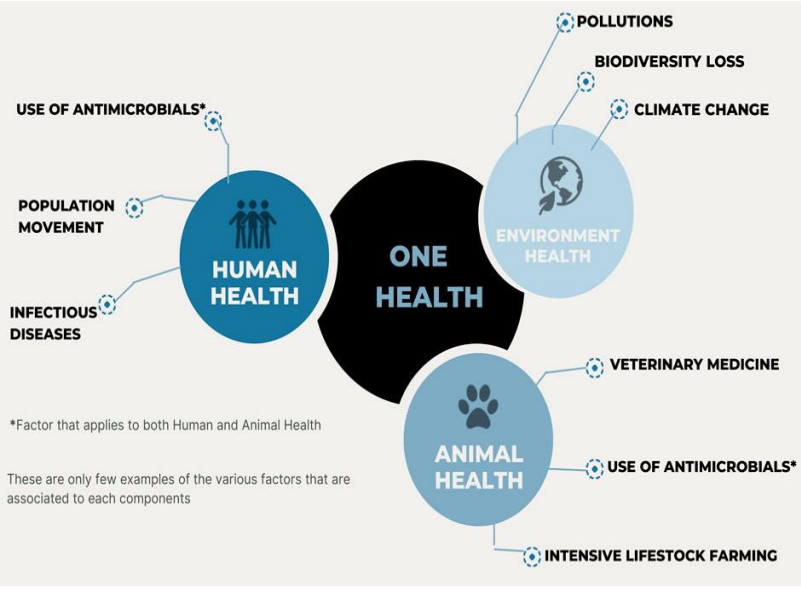

Fig. 2. Representing the concept of one health approach to address AMR [62]

6. CONCLUSION

In summary, antimicrobial resistance (AMR) and co-infections, including those caused by HIV, TB, and malaria, present serious challenges to global health. AMR complicates treatment, leading to longer illnesses, higher death rates, and increased healthcare expenses. Tackling this issue requires a comprehensive strategy involving better infection control, improved diagnostics, responsible use of antimicrobials, and the development of new treatments. Global cooperation, responsible antibiotic use, and advancing vaccine research are essential to reducing the impact of AMR. By uniting healthcare systems, governments, and international bodies, we can curb the spread of AMR and co-infections, protecting public health for future generations.

7. RECOMMENDATION

1. Strengthening surveillance systems for monitoring antibiotic resistance trends and co-infection rates. This entails implementing robust data collection systems that can provide real-time insights into AMR trends, particularly in high-burden areas such as Sub-Saharan Africa.
2. Investing in the development and implementation of rapid, cost-effective diagnostic tools like CRISPR-based technology. These techniques should be developed to identify AMR and co-infections with high sensitivity and specificity, allowing for prompt and effective treatments.
3. Healthcare institutions should implement comprehensive antimicrobial stewardship programs to optimize antibiotic usage. This comprises prescription guidelines, healthcare professional education, and patient awareness initiatives aimed at reducing needless antibiotic usage.
4. Funding and support for research into novel antimicrobial medicines, alternative therapeutics (such as bacteriophages), and vaccines is critical. Governments, academia, and the pharmaceutical sector may work together to develop creative ways to tackle AMR
5. Healthcare systems should take an integrated strategy to managing co-infections, especially in vulnerable populations like those living with HIV or tuberculosis. This entails educating healthcare practitioners on how to successfully detect and treat co-infections, as well as providing access to comprehensive treatment.
6. Public awareness and education to the public about the hazards of antimicrobial resistance and the significance of safe antibiotic usage. Educational programs should target both the general public and specific high-risk populations to foster knowledge and behavior change.
7. Governments should create and execute national action plans by the World Health Organization's Global Action Plan on AMR. These plans should include specific objectives, quantifiable goals, and methods for tracking progress.

By implementing these suggestions, stakeholders may collaborate to reduce the burden of antibiotic resistance and improve health outcomes for those impacted by co-infections.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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