



## Review

# A Review of the Important Weapons against Antimicrobial Resistance in Sub-Saharan Africa

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**Abstract:** Antimicrobial resistance (AMR) is one of the top 10 global health threats facing humanity, and the sub-Saharan Africa (SSA) is among the heavily affected regions due to its weak health systems and limited resources. Due to an escalating number of AMR pathogens and the scarcity of new antimicrobials, efforts in the prevention of infections and the search for alternative treatment options are ongoing. The objective of this review was to assess important weapons against AMR in SSA. The highlighted weapons include vaccines, education and awareness, infection prevention and control (IPC) using water, sanitation, and hygiene (WASH), alternative treatment options, the One Health (OH) approach, AMR surveillance, operational national action plans (NAPs) on AMR, antimicrobial stewardship (AMS) programs, and good governance and regulations. Despite not being used at a satisfactory level in SSA, advanced techniques in dealing with AMR in SSA include (i) metagenomics, (ii) whole-genome sequencing (WGS) in AMR surveillance to track resistance trends and know when to intervene, and (iii) use of artificial intelligence in AMR prediction based on genomics data. The fight against AMR threat in SSA has embraced a number of currently available strategies, and developing new ones will lower the consequences of such a threat for future generations.

**Keywords:** antimicrobial resistance; One Health; alternative treatment; weapons; Africa



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## 1. Introduction

Antimicrobials have increased life expectancy through a drastic reduction in morbidity and mortality rates from infectious diseases such as pneumonia, influenza, and tuberculosis [1,2]. Although the development of resistance to antimicrobials is a natural phenomenon [3], the excessive use of antimicrobials in livestock and human medicine accelerates this resistance [4,5]. Alexander Fleming, the discoverer of penicillin, predicted resistance to the drug in case the prescribed dose is not completed [1]. Antimicrobial resistance (AMR) is defined as the ability of microbes to nullify the effect of drugs, thus making them ineffective, and leading to hard-to-treat infections.

Antimicrobial resistance is often equated with antibiotic resistance. However, AMR includes resistance to all the microbes (bacteria, fungi, viruses, and parasites) while antibiotic resistance is restricted to bacteria. With a few exceptions, resistance to fungi and parasites has received less attention and resources [6], yet some fungi have been linked to human diseases and sometimes deaths [7]. Fungi belonging to the (i) *Candida*, (ii) *Aspergillus*, (iii) *Cryptococcus*, and *Pneumocystis* are among the fungal pathogens showing notable rates of antifungal resistance [7,8]. Recently, the World Health Organization (WHO) published

the list of fungal priority pathogens to guide research, development, and public health action [9]. Moreover, resistance to antivirals significantly affects immunocompromised patients, which may underscore the urgent need to develop novel therapeutics [10]. For instance, resistance to first- and second-line regimens has been reported among human immunodeficiency virus (HIV) patients [11]. The current review focuses on antibiotic resistance, but the same principles apply to other antimicrobials.

Globally, AMR poses a significant threat to modern medicine [12], and it is regarded as an underappreciated pandemic [13]. A recent study reported that around five million deaths were associated with AMR in 2019, and these deaths were higher than those caused by HIV, breast cancer, and malaria [14]. In addition to deaths, AMR is associated with long hospitalizations, treatment failure, and the use of second/third-line antimicrobials, which are expensive for poor individuals [13,15]. Without effective antimicrobials, processes such as surgery, organ transplantation, and cancer treatment would become even riskier [2]. Furthermore, the use of antimicrobials, particularly broad-spectrum antimicrobials, negatively affects the gut microbiome (reduced microbial diversity, changes in formation and roles of the microbiota, and selection of AMR strains), thus giving rise to the predominance of AMR pathogens [16,17].

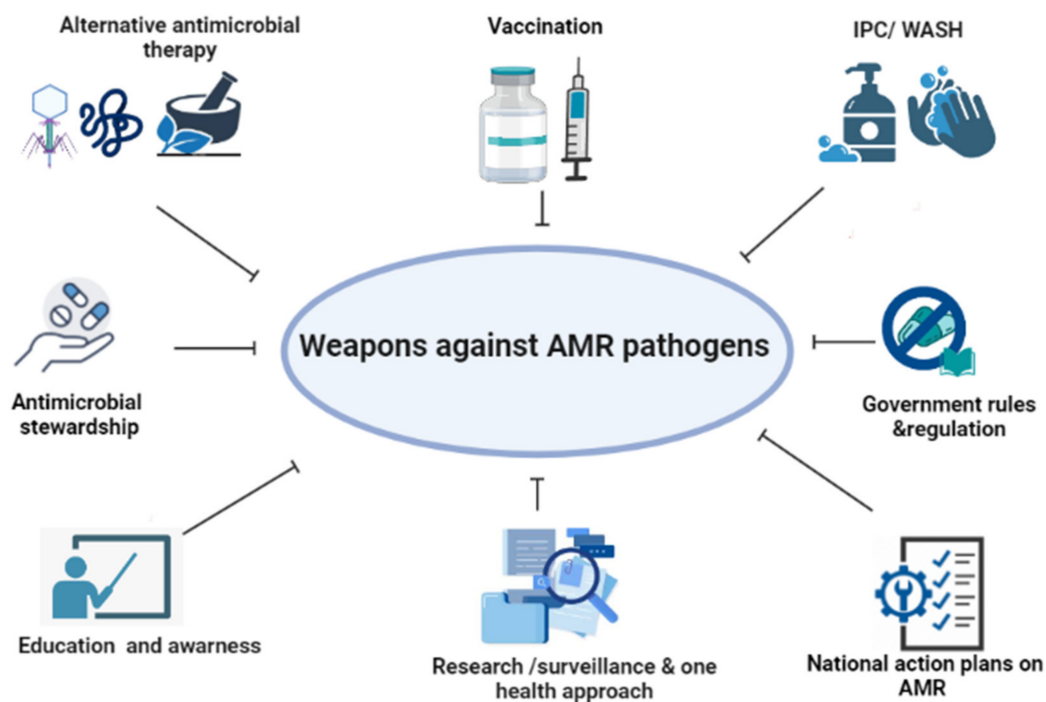
There are several mechanisms via which microorganisms resist antimicrobials. The two primary mechanisms of resistance are natural or intrinsic and acquired. Intrinsic resistance depends on the inherent structural/functional properties of the pathogen that stop the drug from reaching its target or produce enzymes that degrade it [18]. For instance, *Campylobacter* species are inherently resistant to  $\beta$ -lactams including ampicillin [19]. Contrarily, acquired resistance is the ability of a previously susceptible pathogen to develop or gain resistance to antimicrobials in different ways [20,21]. Furthermore, pathogens can be classified on the basis of how they acquire resistance genes. Vertical gene transfer (VGT) occurs when resistomes are passed from parent cells to offspring, whereas horizontal gene transfer (HGT) occurs when microbes transfer resistomes to neighboring cells in the environment [22]. The HGT occurs between pathogens of the same or different species, thus complicating the efforts to control AMR. HGT uses mobile genetic elements (MGEs) including phage transduction (mediated by a bacteriophage), conjugation (via direct cell-to-cell contact and transfer of plasmids or transposons), and transformation (uptake of free DNA that results from bacterial lysis) [23]. The HGT allows pathogens previously susceptible to become multidrug-resistant (MDR) by acquiring various resistance genes from the environment. The main mechanisms of acquired resistance are categorized into three groups: (i) those reducing the intracellular drug concentrations, modifying the membrane, or developing efflux pumps, (ii) those leading to target modification, and (iii) those degrading the drug [21,22].

The discovery of new antimicrobials is not satisfactory compared to the increased rates of AMR pathogens [24]. During the last 40 years, a limited number of new antibiotics have been licensed [25]. Pharmaceutical companies are afraid of not making a profit before the emergence of resistance to any antimicrobial put on the market, resulting in a nearly dry pipeline for new drugs [2]. It is known that resistance to a given antimicrobial emerges in less than 10 years after its introduction to the market [21]. However, this period may go to even less than 5 years if the new drug is misused. Due to the AMR pandemic, new control measures are urgently needed to counter their long-term consequences [18]. In sub-Saharan Africa (SSA), there is a paucity of drug discovery centers, highlighting the need to establish and equip them for a safe future of the subcontinent [26].

The problem of AMR in low- and middle-income countries (LMICs) is less documented, partly due to limited resources affecting their diagnostic capacities [15]. This leads to the use of broad-spectrum antibiotics for minor infections or without determining the disease etiologies [27]. In LMICs, especially in rural areas, the human–animal interaction, together with poor hygienic conditions, increases the risk of acquiring zoonotic diseases and their associated risk of AMR due to the use/misuse of antimicrobials [28]. In Africa, it has been reported that AMR data were missing in 42.6% of countries, but the available findings confirmed the resistance to commonly used antibiotics [29]. In SSA, the majority

of AMR-related studies have mainly been directed toward urban areas, but 60% of the human population lives in the countryside [30]. The scarcity of AMR data in SSA has been associated with the lack of real-time data recording and surveillance, as well as poor regulations [31]. A recent study in 14 countries of SSA showed that only 1.3% of the 50,000 medical laboratories forming the laboratory networks carry out bacteriology testing, underlining the insufficient laboratory capacity leading to misuse of antibiotics [32]. The same study found that a small percentage of the laboratories were geographically accessible (reachable within 1 h of travel by car or on foot) to less than 50% of the population [32]. In 2019, the SSA and South Asia were the predominant regions that experienced increased mortality rates associated with AMR [14]. Therefore, efforts to tackle the AMR threat should be doubled in SSA because the region could be more at risk.

There are several weapons that have been put in place to reduce the level of AMR in Africa. These include the use of vaccines [18,27], natural products [33–35], photosensitizers [36], bacteriophages [37], surveillance [38], the One Health approach [39], and infection prevention and control (IPC) via WASH [40] as depicted in Figure 1. The fight against AMR requires adopting current technologies and the discovery of new ones. Advanced techniques include (i) metagenomics, (ii) whole-genome sequencing (WGS) in AMR surveillance to track resistance trends and know when to intervene, and (iii) use of artificial intelligence in AMR prediction based on genomics data. Each of the weapons used to deal with AMR are detailed in the upcoming sections.



**Figure 1.** Different weapons against AMR in SSA. The image was created using [BioRender.com](https://www.biorender.com).

## 2. Important Weapons against AMR

### 2.1. Vaccines

Vaccines have been introduced to prevent several childhood diseases and eradicate some, such as smallpox and rinderpest [18]. Edward Jenner is considered the pioneer of vaccination for developing the vaccine for the smallpox virus but the same principle was used by Louis Pasteur for other pathogens including rabies virus and fowl cholera [41–43]. Vaccination fights against AMR both directly, by reducing the incidence of bacterial infections, and indirectly, via the various ways in which they can reduce the use of antibiotics [25]. Furthermore, vaccines can reduce both the inappropriate use of antibiotics prescribed in

case of viral infections (such as influenza) and the need for antibiotic treatment to cure secondary bacterial infections [18,25].

Vaccines differ from antibiotics because they target several immunogenic epitopes and are often used to prevent infections [18,44]. When used prophylactically, vaccines train the immune system to recognize and effectively respond to future infections by preventing their occurrence or reducing their severity [18,44]. When the majority of the population is vaccinated, the remainder is protected via herd immunity [45]. The reduced use of antimicrobials slows the pressure of developing resistance by pathogens and normal flora [25,27]. This leads to limited development of MDR pathogens and associated complications. Therefore, a drop in vaccination can be disastrous among nonvaccinated people protected via herd immunity and lead to recurrent epidemics.

Vaccination of children allows them to grow well until becoming adults by reducing morbidity and mortality. It is estimated that every dollar spent on vaccine production brings an economic return of 44 USD [43]. Rosini et al. [18] highlighted the importance of vaccines in increasing people's life expectancy by decreasing mortality rates. Vaccination has been associated with increasing national economic growth and poverty reduction [46]. The economic gains of vaccination can be seen in terms of reduced treatment and health-care costs, productivity gains where healthy children demonstrate improved educational attainment at school through increased attendance and better cognitive performance, and minimizing impact on families as sick people require a caregiver, mainly a parent, to spend time and money [47]. Despite the facts on the efficacy of vaccines in disease prevention, reducing mortality rates, and improving the economy, their contribution to addressing the threat of AMR is underappreciated [27,48].

The WHO report on the pipeline for vaccines targeting bacterial priority pathogens showed that 61 candidates are at different levels of clinical development [49]. Resistance to commonly used antimicrobials has been reported in SSA. For instance, a study by Musa et al. [50] reported a pooled prevalence of 2.1% (95% CI; 1.7–2.5%) for multidrug-resistant tuberculosis (MDR-TB) in new cases. Hlashwayo et al. [51] reported that 30% of *Campylobacter* isolates were resistant to ciprofloxacin. Of the 12 priority pathogens [52], licensed vaccines exist for only four species: pneumococcal disease (*Streptococcus pneumoniae*), Hib (*Haemophilus influenzae* type b) Tuberculosis (*Mycobacterium tuberculosis*), and Typhoid fever (*Salmonella typhi*) [49]. The same report highlighted that, for extraintestinal pathogenic *Escherichia coli* (ExPEC), *Salmonella enterica* ser. Paratyphi A, *Neisseria gonorrhoeae*, and *Clostridioides difficile*, vaccines are in late-stage clinical trials with high development feasibility.

Although vaccines against a number of pathogens are available, there is a shortage of vaccines against infectious diseases including, malaria, tuberculosis, and HIV-1 [43]. The development of vaccines against enterotoxigenic *E. coli* (ETEC), *Klebsiella pneumoniae*, nontyphoidal *Salmonella* (NTS), *Campylobacter* spp., and *Shigella* spp. will not yield positive results in the near future [49]. The lack of vaccine for a number of pathogens has been associated with different reasons, including (i) having several antigens making the selection of a vaccine target very challenging, (ii) difficulty in generating a memory (B and T-cells) response for antigenically diverse pathogens, and (iii) difficulty in finding suitable and effective animal models. Moreover, vaccine development is costly and a vaccine candidate to reach the market should pass through lengthy regulatory processes, limiting the investment by pharmaceutical companies. Therefore, efforts in financing vaccine development against various AMR pathogens should be encouraged.

The SSA is known to have high birth rates, as well as high childhood death rates, partly attributable to a disproportionate lack of vaccines for preventable infections [53]. Although there is progress in immunization, Africa still lags behind in terms of introducing new vaccines and eliminating vaccine-preventable diseases (VPDs) [54]. It is reported that 50% of the world's unvaccinated or under-vaccinated children are in Africa [55]. In SSA, immunization delays also compromise efforts to prevent morbidity and mortality associated with infectious diseases. For instance, 63% of children in SSA missed the first

dose of the measles vaccines (at 9 months), and the majority of these cases were reported from mothers with limited literacy [56]. Another study reported that the BCG vaccine had the highest coverage at 86.2% (95% CI: 85.6% to 86.8%); whereas three doses of oral polio vaccine had the lowest coverage at 68.2% (95% CI: 67.5% to 68.9%) [57]. In addition to education status, the distance of households from clinical settings, the vaccine supply chain, poverty, and training of healthcare workers have been highlighted as factors contributing to incomplete immunization [53,54].

Efforts toward equitable access to vaccines are needed to reduce both the morbidity and the mortality of VPDs. It is assumed that Africa consumes 25% of the world's vaccines but only 1% of them are manufactured in Africa [58]. This creates a dependency on external support and hampers the control of infectious diseases. However, efforts to reverse the trend are ongoing, and there is a target to reach production on the continent for 60% of vaccines needed by Africans [58]. Initiatives of various pharmaceutical companies to establish vaccine manufacturing plants in SSA will boost immunization coverage and reduce the cost of production, as such vaccines will be manufactured on the African continent.

## 2.2. Education and Awareness

One way to reduce the burden due to AMR is through promoting its awareness and designing curricula/teaching materials for different categories of people [59]. Education can focus on antibiotic misuse, behavioral change, and the advantages of wise use of antimicrobials.

### *Training healthcare professionals*

Healthcare professionals are at the frontline in the fight against AMR. However, the lack of teaching materials or specific modules hampers efforts to control and contain the AMR threat [60]. Training should start with a review of the curricula to integrate AMR topics. A study in the US showed that the majority of medical students learned about antibiogram during clinical placements, and 73% of them suggested formal training on antibiogram interpretation [61]. A study conducted in the East Africa showed that final-year medical and pharmacy students have limited knowledge of both AMR and antibiotic use in clinical scenarios [62]. Moreover, the awareness of AMR threat was reported to be limited even among healthcare students in Rwanda [12,63]. Nisabwe et al. [12] reported that 96% and 83% of dental and pharmacy students heard about AMR from non-curricula sources and were unfamiliar with antimicrobial stewardship, respectively. In LMICs, this is worrying as final-year medical and pharmacy students are involved in prescribing or dispensing antimicrobials due to a shortage of qualified personnel [63]. Furthermore, the full potential of pharmacists is not exploited considering that they are mainly used in stocking and supplying drugs [64]. There is a need to remind prescribers and pharmacists about their role in educating patients on the importance of completing the prescribed antimicrobials. Curricula for healthcare professionals need revisions to include special modules on AMR or provide specific extracurricular training. Medical or health professional councils are recommended to organize training sessions for their members on AMR. To motivate the enrolment of members, such training can be counted as continued professional development (CPD), often required to renew members' licenses.

### *Public awareness/engagement*

To address the AMR threat, it is important to stimulate behavioral change among different categories of the society. Studies have reported higher AMR where the level of public awareness was low [65,66]. The training about AMR should not be restricted to healthcare professionals because everyone has a role to play. Engaging the community about the appropriate use of antimicrobials can help preserve the limited arsenal of existing antimicrobials [25,67]. Public engagement has proven to be effective in tackling the AMR problem [68] via the use of healthcare professionals, social media, and apps [69,70]. A study conducted in Cyprus showed that 72.3% of the respondents were informed about AMR



from healthcare professionals or social media [70]. However, social media, television, and newspapers can be damaging because wrong information about AMR can also be shared. Therefore, information on AMR from social media should be handled with care in case it is from untrusted sources.

Training sessions proved to be effective in increasing the knowledge about AMR. A study in Tanzania showed that the AMR-related knowledge among secondary school students was 37% but increased to 90% after getting training on AMR [66]. Through community engagement, the community takes ownership of the issue and seeks solutions that are specific to the settings [67]. Experience has shown that media campaigns are more effective than healthcare professionals for raising awareness of antibiotics but healthcare professionals are known to influence behavioral change [71]. The behavioral change by healthcare personnel is thought to be associated with physical contact with the community and being an expert in the field [67]. In addition to the general public, it is crucial to educate and engage patients on AMR. Patients should be taught about adhering to prescriptions and warned of the possible consequences of not taking antimicrobials as prescribed by the clinician [59]. However, In LMICs, doctors are overwhelmed due to the high patient–doctor ratio affecting the time spent on patients at clinical settings [72]. Everyone should be taught about the safe disposal of expired, unused, or unwanted antimicrobials, considering that mishandling of drugs contributes to the spread of AMR threat.

The problem of AMR goes beyond human medicine and also touches veterinary medicine and the environment. The burden of AMR is expected to reduce livestock production by approximately 11% of the yield by 2050, with a particularly severe impact on LMICs [73]. Antimicrobials have been used in animals for therapy, growth promotion, and prophylaxis [4,15]. Additionally, some antimicrobials (erythromycin, ampicillin, and colistin) are used in both people and animals. Antimicrobials or antimicrobial residues from humans and animals or animal products end up in the environment, affecting aquatic lives [74]. Furthermore, livestock waste and manure are used as fertilizers yet carry many zoonotic pathogens, including MDR ones. Therefore, farmers and the community at large should be involved in awareness and education programs aimed at the proper use of existing antimicrobials and the management of livestock waste that can spread AMR pathogens.

### 2.3. Infection Prevention and Control by Improving WASH

Healthcare facilities are crucial in reducing disease, but the lack of basic WASH services contributes to more infections, extended hospitalizations, and preventable deaths [75]. Infection prevention and control (IPC) by improving WASH is one of five objectives in the World Health Organization's (WHO) Global Action Plan on AMR [76]. The WHO and the United Nations Children's Fund (UNICEF), through the Joint Monitoring Program (JMP), are responsible for global monitoring of the Sustainable Development Goal (SDG) targets for WASH [77]. WASH is essential on battlefronts for reducing and controlling the rising of AMR. Poor sanitation and hygiene lead to infections that promote extensive use of antimicrobials. Providing WASH and improving wastewater systems will lead to a major decline in infection and AMR pathogens around the world [78,79]. The lack of WASH may account for much of the AMR spread in LMICs and beyond health facilities [80].

Wastewater and sludge from animals, humans, and plants are overloaded with AMR pathogens and antimicrobial residues that contaminate water bodies [81]. This could result in the widespread of AMR microorganisms, thus increasing the risk of human exposure to AMR pathogens. The effectiveness of hygiene has a significant impact on lowering infection rates and the need for antimicrobial treatment, thus reducing the spread and development of AMR [82]. A previous study conducted in Guatemala showed that improved hygiene was associated with a 30–50% decrease in the odds of detecting resistance to all antimicrobials [83]. Ramay et al. [83] found that, for nine out of 10 antibiotics, the odds of detecting resistant bacteria decreased by ~32% (odds ratios, OR 0.53–0.8,  $p < 0.001$ ) for every unit of improvement on a hygiene scale. Moreover, this study highlighted that

differences in hygiene practices between households significantly impacted the AMR rate associated with antimicrobial use. Thus, understanding and addressing the role of WASH in combatting AMR is a critical element to be included in a One Health approach. Therefore, improving the quality of drinking water, sanitation systems, and treatment of wastewater and sludge are needed.

Healthcare facilities in SSA are lagging behind when it comes to hygiene services. While 73% of healthcare facilities in the region overall have alcohol-based handrub or water and soap at points of care, only 37% have handwashing facilities with water and soap at toilets [84]. In SSA, coverage of basic drinking water services remains below 50%. Therefore, promoting WASH and IPC could help reduce the number of infectious diseases and, thus, the unnecessary use of antimicrobials. This would contribute to a reduction in AMR rates.

#### 2.4. Natural Products

Currently, available treatments are failing to treat some of the microbial infections due to increasing reports of AMR [85]. Biofilms form a layer that prevents the entry of antimicrobials, thus making them ineffective [86]. Considering the problems associated with AMR pathogens and biofilm, there is an increasing need to develop alternative methods for treating microbial infections [35,87]. Worldwide, various alternatives to conventional antimicrobials have been developed, including herbal antimicrobial compounds, antimicrobial peptides, bacteriophages, and nanomaterials. The literature shows that over 80% of modern drugs are manufactured from natural products [88], and 88% of people in Africa rely on complementary and alternative medicine.

##### 2.4.1. Phytochemical Compounds

Plant-based antimicrobials have been reported to have antimicrobial properties against pathogenic microorganisms with limited side effects [85]; thus, they are being extensively researched as promising sources of effective compounds that can be used as alternative antimicrobials [89–91]. In recent decades, there has been a growing interest in herbal medicine and phytotherapy due to an escalating number of AMR pathogens and a decline in research and development of new antibiotics [2,35].

In SSA, people living in rural areas use medicinal plants for treatment [92] and this preference over conventional medicine is favored due to easy access, affordability, environmental friendliness, lower toxicity, and perceived safety [93,94]. A number of medicinal plants are used for the management of diseases in Africa. For example, *Vernonia amygdalina* Delile, *Tetradenia riparia* (Hochst.) Codd, *Clerodendrum myricoides* R. Br., and *Chenopodium ugandae* (Aellen) are used to treat diarrhea [35] while Beressa et al. [95] discussed medicinal plants used for the management of viral infections. Medicinal plants and their phytochemicals have been reported to have antimicrobial activities. They can be excellent alternative sources of effective antimicrobials due to their wide range of biological activities, lower toxicity, lower environmental friendliness, lower resistance development, and cost-effectiveness compared to synthetic antimicrobials. Phytochemicals mainly include quinines, lectins, polypeptides, flavones, coumarin, essential oils, terpenoids, phenolic, alkaloids, flavonoids, tannins, saponins, and glycosides [85,96]. Phenolics and terpenoids are the most common herbal antimicrobial compounds [97]. Phytochemicals inhibit bacteria through various mechanisms of action including the effect on DNA, enzyme, ion channels, specific receptors, and metabolic pathways of the microbial cells [98]. This can lead to increased permeability, disturbance of membrane-embedded proteins, inhibition of respiration, and alteration of ion transport processes in both Gram-positive and Gram-negative bacteria [99]. However, a limited number of studies have evaluated the toxicity of medicinal plants. This requires further investigations to ensure the safety of medicinal plants before a full integration of traditional medicine into conventional medicine [100].

#### 2.4.2. Antimicrobial Peptides (AMPs)

AMPs are small-sized protein molecules (10–50 amino acids), amphiphilic, and positively charged. They are key elements in host immune defense in most living organisms, including humans, animals, insects, fish, and plants [101]. AMPs represent an excellent alternative antimicrobial therapy considered as a solution to the rising threat of AMR [5] due to their unique properties including wide-spectrum antimicrobial activity, low toxicity, and low propensity to induce microbial resistance [102,103]. These features allow AMPs to bind and penetrate into the microbial membrane bilayer to induce pores through “toroidal-pore”, “barrel-stave”, and “carpet” mechanisms, causing intracellular leakage [101]. Furthermore, AMPs are believed to inhibit cell walls, nucleic acid and protein synthesis, and inhibition of enzymatic activity. The antimicrobial activity of AMPs has been particularly linked with their corresponding amino-acid composition and physicochemical characteristics [104]. Approximately 140 AMPs have entered clinical trials, and some of them have been approved for use in clinical settings [103]. In Africa, there is no evidence of using AMPs to combat AMR.

#### 2.4.3. Bacteriophage Therapy

Bacteriophages, also called “phages”, are viruses that infect and replicate within bacteria [101]. The use of phages for treatment is even older than the discovery of antibiotics but this practice declined after antibiotics came into use [105]. Phage therapy has shown several advantages for treating bacterial infections compared to conventional antimicrobials. Phage therapy has been proposed as one of the most promising alternative antimicrobials due to properties such as antibacterial activities, high specificity, ability to multiply (amplification) at the site of infection, lower toxicity and cost, and availability [105,106]. The ability of phages to multiply at the site of infection means that a single dose will be sufficient to have the desired effect [106]. They are able to kill both AMR and susceptible pathogens [105,107]. Phages are known to be highly specific and may not affect the gut microbiota [106]. There is a limited ability of bacteria to develop resistance toward phages, which makes them good alternatives to conventional therapy [105]. Furthermore, extending the utility of phage formulations, phage cocktails may also be useful in preventing the development of phage-resistant strains during individual treatments [105,106].

In SSA, the Phages for Global Health (PGH) organized practical training for scientists on the isolation and characterization of phages in countries including Tanzania, Uganda, Kenya, and Ghana [105]. Over the last decade, phage-related research in Africa has focused on livestock, human, aquaculture, and the environment, including isolation, characterization, sequencing, and metaviromes [105]. For instance, three novel bacteriophages were characterized in the East African Rift Valley [108]. However, Makumi et al. [105] mentioned that the work in Africa is still nascent; gaps include (i) a lack of manufactured products from phages, (ii) a lack of regulations, (iii) a lack of in vivo studies to test the efficacy and safety of phages, and (iv) the lack of a phage bank. Therefore, phage therapy still needs advocacy and support from various collaborators and experts from countries that have used such technology, e.g., Georgia and Poland.

#### 2.4.4. Carbon-Based Nanomaterials

Carbon-based nanomaterials (CBNMs) are defined as nanomaterials composed of carbon atoms, including fullerene, carbon nanotubes, graphene, and diamond-like carbon (DLC) [109]. Recently, CBNMs have received great attention due to their unique mechanical, electronic, and biological properties. These materials have emerged as promising novel alternative antimicrobials due to their potency against a wide range of bacteria [110]. The antibacterial activities of nanomaterials occur through unique mechanisms, making it difficult for bacteria to develop drug resistance [111,112]. Nanomaterials are less prone to induce bacterial resistance as compared to traditional antimicrobials due to their increased membrane permeability, their capacity to act as efflux pump inhibitors, and their potential for multiple antibacterial actions [113]. Furthermore, nanomaterials have the possibility to

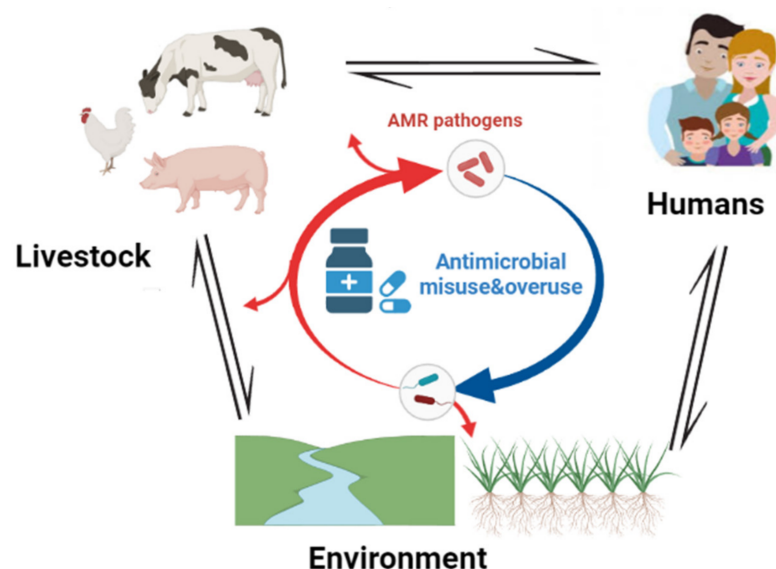


enter mammalian cells and accumulate in different cellular compartments owing to their small size and large surface area, making them good candidates to fight against intracellular bacteria [113]. To the best of our knowledge, CBNM technology has not been used in SSA for treating infectious diseases.

### 2.5. One Health Approach

The One Health (OH) approach has historically ingrained the fundamentals of social, medical, and ecological concepts. This approach can be traced back prior to the 21st century, to researchers such as Louis Pasteur, Robert Koch, William Osler, Rudolph Virchow, and others who sought to challenge boundaries across the field of animal and human health [114]. One Health is defined as an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals, and ecosystems. It recognizes that the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) is closely linked and interdependent. The approach mobilizes multiple sectors, disciplines, and communities at varying levels of society to work together to foster wellbeing and tackle threats to health and ecosystems while addressing the collective need for clean water, energy and air, and safe and nutritious food, taking action on climate change and contributing to sustainable development [115]. OH has been reconceptualized to manage the health catastrophes caused by accelerating environmental changes, as well as human and animal population growth [116].

AMR is among the major global health challenges that necessitate an OH approach (Figure 2). It is known that one of the drivers of AMR is the misuse of antimicrobials in human, animal, and environmental sectors [117]. Furthermore, today's AMR issues are complex; there are multifactorial issues that arise in humans, animals, or the environment, as well as food safety. There is a correlation between the occurrence of AMR from human samples and that from farm animals and the wider environment [118]. Waste from livestock is loaded with AMR pathogens and antimicrobial residues that reach the environment through sewage disposal and agricultural runoff [23]. To find solutions to such issues from a single discipline, whether medical, veterinary, or ecological, is unlikely to provide sustainable solutions. Therefore, human, animal, and environmental health is interdependent and must be confronted together.



**Figure 2.** Schematic illustration of the transmission paths of AMR pathogens between animals, humans, and the environment. The image was created using [BioRender.com](https://www.biorender.com/).

The One Health Global Leaders Group (OH-GLG) on AMR has called for urgent support and prioritization of actions to reduce drug-resistant infections through sustainable

and responsible access to and use of antimicrobials. The OH-GLG has also established a tripartite joint secretariat on AMR, including the World Health Organization (WHO), the Food and Agriculture Organization (FAO), and the World Organization for Animal Health (WOAH), emphasizing the importance of seizing the opportunity to use the One Health approach [119]. To establish an OH approach for tackling AMR, the tripartite became quadripartite after being joined by the United Nations Environment Program (UNEP) [120]. The quadripartite joint secretariat organized a World Antimicrobial Awareness Week (WAAW), celebrated between 18 and 24 November every year [6,121]. The aim of WAAW is to promote awareness and understanding of AMR and to inform of best practices to reduce its emergence and spread. The theme for the year 2022 was “preventing antimicrobial resistance together” [122].

In SSA, the OH approach has quickly spread across several regions, and the number of initiatives is increasing in Africa [123,124]. In general, OH initiatives in SSA are most prevalent in East Africa, with over 100 initiatives/activities, followed by Southern Africa and Central Africa, with fewer in West Africa [125]. The main OH initiatives include Afrique One, the Southern African Center for Infectious Disease Surveillance (SACIDS Foundation for One Health), and One Health Central and Eastern Africa (OHCEA) [126]. For instance, at SACIDS, AMR research activities are led by the antimicrobial resistance community of practice (AMR CoP) specific for bacterial diseases and AMR. The SACIDS Foundation for One Health is a key partner in implementing the Tanzania National Action Plan on AMR to support the AMR surveillance strategy [127] and in establishing the OH strategy in the region including Zambia, the Democratic Republic of the Congo (DRC), Mozambique, and Tanzania [128]. OHCEA countries include Cameroon, Côte d’Ivoire, Democratic Republic of the Congo, Ethiopia, Kenya, Rwanda, Senegal, Tanzania, and Uganda [123]. OHCEA became AFROHUN, a network of 23 schools of veterinary and public healthcare promoting the OH approach in academic institutions in Africa [129]. Afrique One is a consortium of university and research institutions in East, Central, and West Africa in the countries of Chad, Côte d’Ivoire, Ghana, Tanzania, Uganda, and Senegal, promoting OH through multidisciplinary research and training at the MSc and PhD levels [127].

One Health initiatives addressing AMR challenges have also extended to SSA regions. The threat of AMR is recognized by the Africa Centers for Disease Control and Prevention. It is a priority public health issue that led to the establishment of multi-institutional collaboration in capacity development, organization, and research [130].

## 2.6. AMR Surveillance Program

Disease surveillance is an ongoing systematic collection, analysis, visualization, and interpretation of disease-related data [131]. In 2015, the WHO launched the Global Antimicrobial Resistance and Use Surveillance System (GLASS), the first global collaborative effort to standardize AMR surveillance. GLASS has enrolled 109 countries and territories worldwide since its inception. The system monitors antimicrobial consumption (AMC) and AMR at the national level. GLASS has been gradually expanding on the basis of the number of covered sites. For example, GLASS recorded data from 24,803 surveillance sites in 70 countries, while only 729 surveillance sites were covered in 2017 [132]. GLASS keeps track of AMC and AMR in humans, as well as in the food chain and the environment.

In Africa, the joint collaborative effort was established by Africa CDC and formed the Antimicrobial Resistance Surveillance Network (AMRSNET) in 2017. The implemented framework aligns with the WHO GLASS action plan to fight AMR and to improve the detection of antibiotic-resistant pathogens in humans and animals on a continental scale [133]. Moreover, the network primarily coordinates AMR surveillance, prevention, and control with Ministries of Health and other key partners following the OH model. The global action plan has been adopted in most SSA countries and integrated into the strategies for prevention and combating AMR. However, full implementation of country-specific action plans remains challenged by existing barriers [134].

Countries such as Tanzania, Ghana, and South Africa are at an advanced level of implementing their NAP for AMR surveillance [135]. For instance, the NAP in Kenya uses an integrated OH model, and it was jointly endorsed by cabinet secretaries responsible for human health, animal health, and crop production [135]. Data from Environmental Health and Water Quality monitoring captured by local municipalities also contribute to strategic information in the prevention and control of AMR in South Africa [136]. In Tanzania, the strategic framework for AMR surveillance is overseen by a National Multi-sectoral Coordinating Committee (MCC). It also uses the OH model, and it is expected to mitigate AMR and antimicrobial misuse in the human, animal, crop, food, and environment sectors, where priority pathogens have been identified based on prevalence, zoonotic disease, food-borne illness, and potential pathogenicity [137]. A joint effort of multisectoral stakeholders seen in Ghana formed the AMR Policy Platform, with the governing structure strongly influencing the AMR policy development and national action plan adaptation at the global standard [138]. Challenges in integrating a multidisciplinary model arise in the absence of coordination effort and having systems operating in silos. However, the adoption of a global action plan for AMR encouraged the effort of the OH model. It also bolstered the standardization of AMR surveillance, prevention, and control in various countries. It is important to mention that countries are scaling up surveillance efforts to tackle AMR through the OH lens in an attempt to implement effective and sustainable interventions [139].

### 2.7. Antimicrobial Stewardship Programs

Antimicrobial stewardship (AMS) programs are hospital-based programs, aiming at promoting the appropriate use of antimicrobials, which proved to be effective in increasing compliance with antibiotic policy and reducing the duration of antimicrobial therapy, cost of antibiotics, AMR, and healthcare-associated infections [140]. AMS programs also improve patient care and safety [141], reducing treatment failure rates [142,143]. In 2019, the WHO published a practical implementation toolkit for AMS programs in healthcare facilities in LMICs which face a disproportionate burden of antimicrobial resistance, as well as challenges related to resource availability [144]. A study showed that reducing antimicrobial prescriptions for inpatients significantly improved microbiological and clinical outcomes, as well as reduced rates of AMR pathogens [145].

There is a shortage of data on the implementation of AMS programs in African countries [146], but the available data showed that only 12% of respondents in Africa had any form of AMS in place [147]. Howard et al. [147] mentioned that respondents were representatives from the hospitals of selected countries, but no information was included about the names of countries involved. Despite a limited number of AMS programs, there has been an improvement in outcome measures (e.g., decrease in antibiotic consumption, compliance with antibiotic policy, and reduction in surgical site infections) where the AMS program was implemented [140]. A study conducted in South Africa at an academic teaching hospital showed a 19.6% reduction in antibiotic consumption after introducing an AMS program [148]. Akpan et al. [140] reported that AMS programs were mainly found in the Southern African region, followed by the East African region. Unfortunately, there were no AMS programs in West Africa, which has the highest number of countries. This highlights the need to sensitize governments in SSA to initiate AMS programs due to their contribution to improving the quality of health and reducing the AMR problem.

### 2.8. Functional National Action Plans (NAPs) on AMR

NAP is a nationwide multisectoral document aimed at controlling and combating AMR through a One Health approach including all sectors, especially human health, animal health, and the environment, in order to contribute to the welfare of the population, as well as contribute to global health security. The plan requires a coordinated response to address its complex, multifaceted nature. In May 2015, 194 member states of the WHO endorsed the Global Action Plan (GAP) on AMR and committed to developing and integrating the

five objectives and corresponding actions of the GAP into national action plans (NAPs) to address AMR [149,150]. As of October 2021, 148 countries globally have finalized their NAPs that are consistent with the objectives of the GAP. Furthermore, 38 (81%) out of 47 countries in the WHO African region have developed NAPs, of which 29 are approved by their national authorities [151]. In several LMICs, implementation of NAPs for AMR remains fragmented and lacks an OH approach [152].

### 2.9. Political Will/Governance/Regulations

AMR is a multisectoral issue requiring diverse actors to collaborate across issue areas and national borders. This is reflected in the GAP on AMR, which brings together the WHO, the WOA, the FAO, and the UNEP in an unprecedented attempt to build an effective AMR global governance apparatus based on a holistic “One Health” approach [149].

At the country level, governance mechanisms are critical for effective intersectoral coordination of activities to combat AMR. They are also important while engaging key stakeholders in developing and implementing NAPs. Governance mechanisms need political support and authority to take action. Governance mechanisms are more likely to be effective if terms of reference are clearly defined. Under the fourth objective of GAP, which is to optimize the use of antimicrobial medicines in human and animal health, countries are urged to put in place effective and enforceable regulation and governance for licensing, distribution, use, and quality assurance of antimicrobial medicines in human and animal health. Such regulations also include a regulatory framework for the preservation of new antimicrobials. This will enable us to tackle the AMR threat successfully while ensuring access to appropriate and affordable antimicrobial treatment in LMICs [149].

The International Health Regulations (IHR) 2005 and the Good Manufacturing Practice (GMP) offer additional global regulatory tools to address AMR. The IHR provides a legally binding framework for 194 State Parties on how to report and contain public health threats that have the potential to cross borders. They can contribute to the response to emerging AMR threats such as carbapenem-resistant Enterobacteriaceae (CRE) [153]. GMP represents the gold standard in certifying the quality of pharmaceutical products and, thus, preventing the sale of substandard medicines, which can accelerate the emergence of resistant pathogens [154].

## 3. Advanced Techniques in Deciphering AMR

The cost of pandemics is devastating for human health, and a greater burden is placed on low-resource settings [14]. According to the World Bank Group, the negative impact of AMR on the gross domestic product (GDP) can be as severe as during the financial crisis that started in 2008 and ended in 2009 [73]. In contrast to the financial crisis of 2008–2009, the damage caused by the AMR threat could last longer, and LMICs will be the most affected [73]. The AMR diagnosis in most SSA countries relies on phenotypic characterization methods such as disc diffusion and the minimal inhibitory concentration (MIC) approach [135,155] with little or no data regarding the resistance mechanisms, and with varying clones showing similar resistance profiles [156]. With the recent advancement of cutting-edge next-generation sequencing (NGS) technologies, there is a need to complement phenotypical characterization with genomic-level interpretation for effective AMR risk management [157]. However, the routine use of whole-genome sequencing (WGS) in pathogen genotyping is difficult due to the need for bioinformaticians, resources, and validated workflows during the interpretation [158].

Genomics and metagenomics offer unprecedented opportunities, and SSA should embrace these new technologies for improved AMR preparedness and response. Genomics provides important insights into the host–pathogen interaction, reservoirs, and the mechanism of AMR in animals, humans, and the environment. On the other hand, metagenomics, through the taxonomic classification of microbes, as well as the identification of AMR and virulence genes, provides an opportunity for understanding the mechanisms of AMR for

effective prevention and control. Furthermore, the generated genomics data can be used for AMR prediction using artificial intelligence (AI).

### 3.1. Metagenomics

The alarming increase in AMR pathogens calls for the use of innovative diagnostic tests able to detect more mutations and resistomes. Through the metagenomics approach, a significant amount of AMR data can be generated from a diverse microbial community through one detection instead of focusing on a specific pathogen [159]. Metagenomics allows access to genomic data from environmental samples without the need to isolate and culture microorganisms [160]. The superiority of the metagenomics approach over conventional methods in AMR surveillance in domestic pig herds has been reported [161]. The ability to perform high-throughput DNA sequencing without prior bacteria culture make this tool cost-effective and suitable for deciphering the complexity of AMR in animals, humans, and the environment [162].

Through metagenomics, the microbial diversity and genes coding for resistance and virulence can be identified without prior knowledge and selection of the pathogen, thus offering an opportunity for a comprehensive understanding of AMR dissemination [163]. While identifying bacteria or genes of interest, the generated high-throughput sequencing data can be reanalyzed in detail. Deployment of metagenomics tools holds promise to develop a system of One Health surveillance of AMR when applied to samples from recalcitrant human clinical cases, animals, and potential reservoirs for the identification of resistance genes. In addition, these strategies need to be accompanied by efforts to design and develop alternative drugs and a better understanding of the AMR mechanisms through sustained and real-time genomic data sharing. NGS technologies are becoming more affordable, and SSA needs to invest in such technologies and strengthen bioinformatics capabilities for an improved understanding of changes in the epidemiology of AMR organisms.

### 3.2. Whole-Genome Sequencing (WGS)

WGS is an effective and powerful tool for AMR surveillance and monitoring [164]. It is crucial for monitoring the trend and mechanisms underlying specific resistances required for understanding AMR transmission dynamics in different OH niches. Through phylogenetic analysis, WGS offers an opportunity to compare sequencing data from different hosts including humans, animals, and the environment, which aligns very well with the OH approach for AMR surveillance [163]. Therefore, WGS is important in tracing the sources of outbreaks and establishing relationships among AMR strains. Africa has a high burden of diseases but with inadequate genomic programs necessary for developing new disease prevention technologies [165]. The WGS has been used to identify drivers of AMR burden in LMICs (South Asia and SSA), and it was found that 65% of *E. coli* isolates were resistant to three or more antimicrobial classes, and that resistance correlated with geography and antimicrobial usage, rather than lineage [166]. The SSA needs to train enough bioinformaticians and allocate some budget for WGS facilities and their use. There is a need for staff retention programs to avoid disrupting genomic systems when a staff member leaves an institution. Furthermore, training a team at each institution would be more beneficial so that if one staff member leaves, the remainder will continue the work without interruption. The Collaborative African Genomics Network (CAfGEN) provides training for PhD students from Uganda and Botswana in genomics [166]. Establishing regional diagnostic centers of excellence in SSA would help communicate and coordinate WGS activities that can be ready for outbreak investigations [167].

### 3.3. AMR Prediction Using AI Based on Genomics Data

With several shortfalls of traditional antimicrobial susceptibility testing, including a long turn-around time and the applicability to cultivable bacteria only, AI offers an opportunity for AMR prediction based on genomic data generated for different bacteria



species [168]. For instance, highly accurate AMR prediction has been achieved using machine learning algorithms trained on WGS [169,170]. With AI, one can efficiently predict and identify AMR genes in bacteria. Furthermore, machine learning algorithms combined with laboratory testing accelerate the process of discovering new antimicrobials [171]. AI can analyze routine microbiology laboratory results to detect outbreaks associated with MDR pathogens, improve the quality of laboratory processes, increase pathogen detection rates, reduce turn-around time, and improve clinical decision making [172]. This helps to assess the trends in resistance to certain antimicrobials and allows policymakers and scientists to intervene when it is not too late. However, there is no evidence of using AI to predict AMR in SSA and the cited reasons include dearth of technical expertise, lack of infrastructure and a regulatory framework, and the increased cost of deployment [172].

#### 4. Conclusions

AMR is a public health crisis, which halts the progress in controlling infectious diseases. The pace of making new antimicrobials is very slow when compared to the rate of AMR emergence and spread. The SSA is among the regions heavily affected by the AMR burden due to the limited infrastructure, financial resources, and qualified personnel. There is a serious problem of not enough microbiology laboratories in Africa and lack of basic utilities and equipment for the operational laboratories. Several weapons have been deployed in the efforts to curb the increasing number of AMR pathogens on the subcontinent. These include vaccine production in Africa, education and awareness of AMR among health professionals and the community at large, strengthening IPC by improving WASH facilities, using alternative treatment options, developing and implementing NAPs on AMR, adopting an OH approach in dealing with the AMR threat, initiating AMR surveillance and empowering AMS programs, and promoting good governance and regulations. Advanced techniques such as metagenomics, WGS, and AI are still nascent in SSA but help in the quick identification of outbreak etiologies. To reduce the consequences of AMR, everyone must play a part, and the speed has to be increased to remain ahead of microorganisms. Financial support is paramount for stimulating research and improving the diagnostic capacities of healthcare settings on the continent.

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