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Review Article **Open Access**

A narrative review exploring phage therapy as a sustainable alternative solution to combat antimicrobial resistance in Africa: Applications, challenges and future directions

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Abstract:

The increasing threat of antimicrobial resistance (AMR) in Africa, coupled with limited access to advanced antibiotics and high rates of bacterial infections poses serious public health challenge. Bacteriophages, viruses that target and destroy bacteria, present a promising alternative or complementary therapy to traditional antibiotics. Phage therapy leverages its unique ability to target specific bacterial strains without affecting the host beneficial microbiota. It is an effective tool against multi-drug-resistant (MDR) microbial pathogens, particularly in resource-limited settings. This narrative review explores the potentials of phage therapy in Africa, highlighting its advantages, such as specificity, minimal side effects, and cost-effectiveness, alongside its capability to tackle biofilm-associated and AMR infections. It discusses current research and collaborations, including case studies from Nigeria, Benin, and South Africa that demonstrate the efficacy of phage therapy against bacterial pathogens such as *Escherichia coli, Acinetobacter baumannii* and *Klebsiella pneumoniae*. Furthermore, it discusses the challenges to phage therapy implementation such as regulatory hurdles, public skepticism, and infrastructure limitations, while emphasizing the importance of developing local production and awareness campaigns. The review concludes by recommending the integration of phage therapy into Africa healthcare strategies to address AMR. Through strategic partnerships, education and regulatory frameworks, phage therapy could become a transformative solution, particularly for neglected diseases and infections common in low-resource settings. As Africa seeks innovative approaches to its growing AMR crisis, phage therapy stands out as a viable and adaptable option.

Keywords: Bacteriophage; therapy; application; antimicrobial resistance; review; Africa

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Une revue narrative explorant la phagothérapie comme solution alternative durable pour lutter contre la résistance aux antimicrobiens en Afrique: applications, défis et orientations futures

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Résumé:

La menace croissante de la résistance aux antimicrobiens (RAM) en Afrique, associée à un accès limité aux antibiotiques avancés et à des taux élevés d'infections bactériennes, pose un sérieux problème de santé publique. Les bactériophages, des virus qui ciblent et détruisent les bactéries, présentent une alternative prometteuse ou une thérapie complémentaire aux antibiotiques traditionnels. La phagothérapie exploite sa capacité unique à cibler des souches bactériennes spécifiques sans affecter le microbiote bénéfique de l'hôte. C'est un outil efficace contre les agents pathogènes microbiens multirésistants (MDR), en particulier dans les environnements aux ressources limitées. Cette revue narrative explore le potentiel de la phagothérapie en Afrique, en soulignant ses avantages, tels que la spécificité, les effets secondaires minimes et la rentabilité, ainsi que sa capacité à lutter

contre les infections associées aux biofilms et à la RAM. Elle aborde les recherches et collaborations actuelles, notamment les études de cas du Nigéria, du Bénin et de l'Afrique du Sud qui démontrent l'efficacité de la phagothérapie contre des agents pathogènes bactériens tels qu'*Escherichia coli, Acinetobacter baumannii* et *Klebsiella pneumoniae*. En outre, elle aborde les défis liés à la mise en œuvre de la phagothérapie, tels que les obstacles réglementaires, le scepticisme du public et les limitations des infrastructures, tout en soulignant l'importance de développer une production locale et des campagnes de sensibilisation. La revue conclut en recommandant l'intégration de la phagothérapie dans les stratégies de santé en Afrique pour lutter contre la RAM. Grâce à des partenariats stratégiques, à l'éducation et aux cadres réglementaires, la phagothérapie pourrait devenir une solution transformatrice, en particulier pour les maladies négligées et les infections courantes dans les milieux à faibles ressources. Alors que l'Afrique cherche des approches innovantes pour faire face à la crise croissante de la RAM, la phagothérapie apparaît comme une option viable et adaptable.

Mots-clés: Bactériophage; thérapie; application; résistance aux antimicrobiens; revue; Afrique

Introduction:

Bacteriophages, often referred to as phages, are viruses that target and replicate inside bacterial cells. These viruses are incredibly abundant and diverse, inhabiting environments rich in bacterial life, including soil, water, and the human microbiome. Each type of bacteriophage typically has a high degree of specificity, often infecting a specific species of bacteria, which allows them to precisely target harmful bacteria without affecting beneficial microbiota (1,2). Phages combat bacterial infections by attaching to bacteria, injecting their genetic material, and hijacking the bacteria machinery to replicate. The process ultimately results in cell lysis, releasing new phage particles to infect other bacteria. This selective bacterial killing process is particularly valuable in treating infections, as phages reduce the bacterial population while sparing the surrounding non-targeted bacteria (3,4).

Phage therapy, a treatment that uses viruses to combat bacterial infections, was initially investigated in the early 20th century. However, with the advent and widespread use of antibiotics, it was largely abandoned. This concept capitalizes on the natural predator-prey relationship between phages and bacteria. After its discovery, phage therapy showed early promise as an effective method for treating bacterial infections particularly in Eastern Europe (5,6). The recent surge in antibiotic-resistant bacteria has led to a renewed interest in phage therapy as a potential alternative or complementary approach to conventional antibiotic treatments. Unlike broad-spectrum antibiotics, phages can penetrate biofilms, which are dense bacterial communities that protect bacteria from many conventional treatments. This characteristic makes them especially effective against biofilm-associated infections, which are often resistant to traditional antibiotics (7).

Current studies highlight phages adaptability in addressing multi-drug-resistant (MDR) bacterial infections, which are becoming increasingly common worldwide. This adaptability, along with the ability to evolve alongside bacterial resistance mechanisms, places phages as a valuable tool in combating antibiotic resistance, especially in regions where resources and access to advanced antibiotics are limited (8,9).

The resurgence of phage therapy is closely tied to the global rise in antibiotic-resistant infections, which pose a major threat to public health. By 2050, it is estimated that antibiotic-resistant infections could cause up to 10 million deaths annually if left unchecked (10). Phage therapy has demonstrated pot- ential in addressing MDR bacterial strains and is increasingly recognized as a viable complement to traditional antibiotics. Advances in phage research have led to the development of engineered phages and phage cocktails capable of targeting broader spectrum of bacterial pathogens, further increasing the feasibility of phage therapy in clinical settings (8,11).

Africa faces a growing burden of AMR infections, exacerbated by limited healthcare resources, high infection rates, and restricted access to advanced antibiotics. In regions where sanitation and healthcare infrastructure are underdeveloped, the incidence of bacterial infections and their antibiotic-resistant forms is high, contributing to significant morbidity and mortality (12,13,14). The World Health Organization (WHO) has highlighted antibiotic resistance as a critical health concern in Africa, particularly with resistant strains of *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* increasingly detected (15,16).

Phage therapy offers an innovative solution to the AMR crisis in Africa by providing a targeted, adaptable, and cost-effective alternative for treating bacterial infections. Since bacteriophages can be isolated from local environments and even tailored to specific bacterial strains, phage therapy could provide a viable and accessible treatment for infections in African countries (17). In recent years, international and local initiatives have sought to develop phage therapy in Africa to address antibiotic-resistant pathogens. With collaborations between African research institutions and international bodies, phage research and application in the African healthcare system could become an effective approach to curbing resistant infections and reducing the reliance on imported antibiotics (18).

Antimicrobial resistance in Africa: A growing threat

Antibiotic resistance is a major public health issue in Africa, with rising resistance rates among many bacterial pathogens. Treatment for these infections is particularly difficult in resource-limited settings due to limited access to advanced antibiotics and alternative therapies. The major MDR pathogens in Africa, such as *E. coli*, *K. pneumoniae*, *S. aureus*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii,* often cause severe infections like urinary tract infections (UTIs), bloodstream infections, respiratory and wound infections. *Escherichia coli* and *K. pneumoniae*, which are also commonly implicated in UTIs and bloodstream infections, have currently demonstrated increased resistance to crucial antibiotics such as fluoroquinolones and third-generation cephalosporins due to production of extended spectrum β-lactamase (ESBL) enzyme. *Staphylococcus aureus*, particularly methicillin-resistant strains (MRSA) are prevalent in both community and hospital settings, causing skin and soft tissue infections and worsening wound infections (12,13,19).

According to the World Health Organization (WHO), African region faces a particularly high burden of AMR, which has worsened due to inadequate surveillance systems, lack of diagnostic capabilities, and poor infection prevention and control practices. Reports from various African countries indicate that resistant strains are widespread and that MDR bacterial infections have increased mortality rates and prolonged hospital stays, straining already limited healthcare resources (16,20).

Limited healthcare infrastructure contributes to rising AMR in Africa:

Africa faces numerous healthcare challenges that contribute to the rising antibiotic resistance rates across the continent. One major issue is the limited healthcare infrastructure in many African countries, with shortages of healthcare facilities, trained medical personnel, and diagnostic equipment. Without adequate diagnostic capabilities, infections are often empirically treated with antibiotics, sometimes inappropriately, contributing to the development and spread of resistance (21-23). Self-medication is also prevalent in many parts of Africa due to easy accessibility to antibiotics without prescriptions. Many people buy antibiotics over-the-counter at pharmacies or from informal vendors, often using them improperly, such as by taking sub-therapeutic doses or using them to treat viral infections. This misuse accelerates the development of resistance (24,25).

Furthermore, poor regulation and oversight of antibiotic sales contribute significantly to resistance. In some countries, weak regulatory frameworks allow for unregulated distribution and sale of antibiotics, including counterfeit or substandard drugs that may have reduced efficacy. This lack of regulation complicates efforts to control antibiotic use, as patients can easily access antibiotics without medical authorization, further fueling misuse and resistance (26,27). Additionally, limited access to clean water, poor sanitation, and overcrowded hospitals facilitate the transmission of infections, particularly in low-resource settings, making it difficult to contain outbreaks of antibiotic-resistant bacteria (28).

Public health implications: Threat of AMR and urgent need for alternative treatment options:

The escalating crisis of antibiotic resistance in Africa poses a significant threat to public health. The increasing prevalence of drug-resistant bacteria, coupled with limited access to effective treatments in resource-constrained settings, makes these infections increasingly difficult to manage. The prevalence of MDR infections often results in extended hospital stays, limited treatment options, and higher healthcare expenses due to the need for last-resort antibiotics or alternative treatments. These impacts strain already limited healthcare resources in many African countries (29-31).

One of the most significant public health impacts of MDR bacteria is the threat they pose to vulnerable populations, such as neonates, immunocompromised patients, and individuals with chronic illnesses, thus, contributing to a high burden of preventable mortality in Africa, where limited access to advanced treatments exacerbates the impact of resistant infections (13,32,33). The urgent need for alternative therapies is underscored by the slow development of new antibiotics and the diminishing effectiveness of existing drugs.

Bacteriophage therapy, for instance, is emerging as a promising alternative for treating MDR infections by using viruses that specifically target and destroy pathogenic bacteria. Phage therapy and other alternatives like antimicrobial peptides and probiotics could offer valuable options to supplement or replace antibiotics, especially as the continent grapples with the severe consequences of antibiotic resistance (34,35).

The promise of phage therapy in tackling AMR in Africa:

As antimicrobial resistance continues to challenge healthcare systems globally, phage therapy presents an alternative and promising solution, particularly in Africa, where access to effective antibiotics is limited and AMR is widespread. Phage therapy unique benefits, such as its specificity to pathogens, minimal side effects, and effectiveness against drug-

resistant bacteria, make it a strong candidate for tackling AMR on the continent. In addition to clinical effectiveness, phage therapy also offers cost-effective production and ease of storage, making it a practical and accessible choice for resource-limited regions (6,8).

Advantages of phage therapy over antibiotics:

One primary benefit is its specificity to pathogens, which allows for targeted treatment without harming the host beneficial microbiota. Unlike broad-spectrum antibiotics, bacteriophages (phages) selectively infect and kill specific bacteria, reducing the risk of disrupting the natural microbial balance and decreasing the likelihood of secondary infections or adverse reactions (36,37).

Moreover, phage therapy is particularly effective against MDR bacteria, providing a viable treatment option where antibiotics have failed. This feature is essential in Africa, where AMR levels are high and last-resort antibiotics are scarce. Phages can also evolve alongside bacterial pathogens, potentially reducing the risk of resistance development and prolonging the efficacy of treatment (38,39).

Phage therapy generally has fewer side effects than antibiotics, as it is less likely to trigger allergic reactions or gastrointestinal disturbances commonly associated with antibiotic use. Additionally, because phages are natural components of the environment, they are usually well-tolerated by the human body, further enhancing their safety profile (34,40).

Suitability of phage therapy in the African context:

In Africa, where infections caused by drug-resistant pathogens are increasingly common, phage therapy offers a tailored solution to combating diseases prevalent on the continent. Pathogens such as *S. aureus*, *K. pneumoniae*, and those responsible for diarrhoeal diseases are common targets of phage therapy. For instance, *S. aureus*, including MRSA strain, is a frequent cause of wound and soft tissue infections. Phage therapy has demonstrated efficacy against MRSA in various settings, suggesting it could be valuable in Africa, where resistant infections are particularly problematic in hospital and community environments (41,42).

Klebsiella pneumoniae, known for causing severe respiratory and urinary tract infections, is another target for phage therapy. This pathogen is often resistant to multiple antibiotics, especially in African healthcare settings where treatment options are limited. Phages targeting *Klebsiella* strains have shown promise in experimental studies, providing a potential alternative treatment for these infections. Additionally, phage therapy could be adapted for use against pathogens causing diarrhoeal diseases, which are significant contributors to morbidity and mortality among children in Africa. Phages have been successfully used to treat *E. coli* and *Shigella* species, both major causes of bacterial diarrhoea on the continent, highlighting their potential to reduce the disease burden (43,44,45).

Cost and accessibility of phage therapy:

Phage therapy has the potential to be cost-effective and accessible, especially when compared to the high development and production costs associated with new antibiotics. Phages can be isolated from natural sources and adapted for therapeutic use with relatively low investment in laboratory infrastructure. Local production of phage preparations is feasible in many African countries, particularly with minimal equipment requirements, as opposed to the large-scale industrial facilities needed for conventional antibiotics. This adaptability is significant for low-resource settings in Africa, where healthcare budgets are often constrained (46,47).

Another advantage is the ease of storage and distribution. Phages are stable at a wide range of temperatures and can often be stored without refrigeration, making them suitable for regions where cold-chain storage is difficult. This storage advantage reduces logistical barriers and makes phage therapy especially viable in rural or remote areas with limited access to healthcare facilities. With these benefits, phage therapy could be implemented at a lower cost and with greater accessibility, providing a valuable alternative to traditional antibiotic treatments (48,49).

Current research and applications of phage therapy in Africa

Research into phage therapy has been gaining momentum in Africa as the continent grapples with high rates of antibiotic resistance. Various institutions and partnerships are involved in investigating phage therapy effectiveness, adaptability, and potential for implementation within African healthcare systems. This research spans experimental studies, clinical trials, and international collaborations aimed at exploring phage therapy as a sustainable solution to the growing crisis of AMR on the continent

Case study in Ethiopia:

A study in Ethiopia showed that ΦJHS and ΦSMK phages demonstrated broad lytic spectra on clinical MDR *P. aeruginosa* strains, as all strains tested were lysed by both phages. Seven MDR *P. aeruginosa* strains were infected, suggesting that the isolated phages might be used as biocontrol agents on abiotic surfaces or as candidates for clinical phage therapy.

Additionally, it may be possible to create

a phage cocktail using the isolated phages to target a specific type of bacterium. Such a cocktail that targets only a single rather than multiple bacterial species is described as generally emphasizing the spectrum of phage activity breadth in its design, rather than necessarily emphasizing the spectrum of phage activity depth. The promising outcomes of phages being used for both bacterial colonization prevention and bacterial biofilm removal are highlighted by the reduction of MDR *P. aeruginosa* biofilm development on catheter and endotracheal tube surfaces (50).

Lytic phages against *Escherichia coli* and *Pseudomonas aeruginosa* in Nigeria:

Another case study in Nigeria explored the use of phages to treat *E. coli* and *P. aeruginosa*. Clinical isolates resistant to multiple antibiotics were treated with phage cocktails, leading to the successful eradication of the pathogens. The phages recovered from wastewaters were exclusive *to E. coli* and MDR *P. aeruginosa*. These demonstrate the value of using phages as therapeutic agents to lessen the threat posed by AMR pathogens (51,52).

Joint initiatives in Benin:

From hospital wastewater in Benin, scientists discovered and described three new *A. baumannii* phages that belong to the Autographiviridae family. The opportunistic bacterium, *A. baumannii* is primarily linked to infections acquired in hospitals. The isolated phages satisfy the specifications needed to be employed in phage therapy. Their limited host range, however, may restrict their potential for therapeutic use (53).

Compassionate use in South Africa:

The South African healthcare settings have implemented phage therapy under compassionate use programs. In a study in South Africa, a significant log reduction in viable *E. coli* O177 cell counts was observed on beef samples upon phage treatment over the 7-day incubation period. *E. coli* cell counts were lowered by two single phages and three phage cocktails to values below the detection limit (1.0 log10 CFU/g).

For both individual phages and cocktails, log decrease in viable *E. coli* cell counts varied between 2.10 - 7.81 CFU/g and 2.86 - 7.81 CFU/g, respectively. Both single phage and phage cocktails prevented the growth of *E. coli* O177 biofilms, with phage cocktails demonstrating the highest level of effectiveness. Additionally, phage mixtures were more effective than single phage at eliminating pre-formed biofilm. These results led to the conclusion that phage cocktails created in this work may be utilized to decrease *E. coli* O177 infection (54).

Challenges of phage therapy implementation in Africa:

Despite the potential benefits of phage therapy, implementing it in African healthcare systems faces several challenges. These include regulatory hurdles, public and healthcare sector skepticism, and infrastructure limitations for production and storage.

Regulatory hurdles:

The lack of clear and standardized regulatory frameworks for phage therapy in most African countries presents a significant barrier to its implementation. Unlike antibiotic therapy that has well-established pathways for approval, phage therapy lacks formalized protocols and guidelines for preclinical and clinical trials in Africa. This ambiguity hampers the widespread adoption of phage-based treatments (55).

There are global inconsistencies in the regulatory frameworks for phage therapy, with fragmented regulations. While countries such as Georgia and Poland have established systems, others, including most African countries, have no established regulatory frameworks (56). Efforts by the WHO to streamline regulatory processes for novel therapies could help, but these measures are still in the early stages.

Public and healthcare sector Skepticism:

Phage therapy is often viewed with skepticism due to its novelty and historical associations with limited regions. Many doctors and healthcare providers in Africa are unfamiliar with phage therapy, leading to unwillingness and resistance to adopting it over traditional antibiotics (57). Public acceptance is low because phages are misunderstood, with fears rooted in their association with viruses and biological warfare.

Addressing these misconceptions through education campaigns and showcasing successful case studies are essential (58). Cultural factor is also a challenge. In some communities, distrust of modern medicine complicates the introduction of phage therapy, requiring culturally sensitive awareness campaigns (59).

Production and storage challenges:

The practicalities of producing and storing bacteriophages present hurdles in regions with limited resources. Producing phages requires advanced laboratory facilities to ensure safety, efficacy, and specificity (60). Few African countries have the infrastructure for large-scale, high-quality phage production. Developing formulations suitable for different infections e. g., topical, oral, or injectable demands significant investment in research and development.

Phages are temperature-sensitive and often require cold-chain storage to maintain viability (8), which is a challenge in regions with unreliable electricity or refrigeration. For instance, in rural areas of Africa, phages risk degradation due to inadequate cold storage, which undermines their effectiveness and limits their application in community healthcare settings. The cost implication of phage therapy is also a hurdle.

Establishing the necessary infrastructure for production and storage can be prohibitively expensive for many African nations, particularly those heavily reliant on international aid for healthcare needs (56,61).

Future prospects of phage therapy in Africa:

Further research is essential to realize the full potential of phage therapy in Africa. Large-scale, randomized controlled trials are needed to establish the safety, efficacy, and optimal dosing of phages. Trials focused on region-specific infections such as typhoid fever or cholera, can validate the relevance of phage therapy in African settings (1). Also, integrating phage therapy into healthcare systems requires strategic planning and partnerships. Collaborations with pharmaceutical companies can address challenges in mass production and distribution. Examples from Eastern Europe, such as the Eliava Institute, illustrate the viability of such models (8).

International collaborations such as those with WHO and the Africa CDC, aim to establish regional guidelines for phage therapy trials and usage. Incorporating phage therapy into national AMR strategies would promote its systematic use and scaling. For example, training hospital microbiologists to isolate and produce phages locally could support personalized therapy initiatives.

Conclusion:

With the continent burden of infectious diseases, limited access to new antibiotics, and increasing prevalence of AMR, phage therapy represents a transformative opportunity. Furthermore, its potential to address neglected tropical diseases and its adaptability to local healthcare needs underscore its relevance in improving public health outcomes across the region (6,62).

To fully harness the potential of phage therapy in Africa, coordinated efforts are required from policy-makers, researchers and healthcare providers. Governments must prioritize the establishment of regulatory frameworks that facilitate phage therapy development and integration into healthcare systems. Investing in infrastructure for local phage production and quality assurance is crucial. African research institutions should focus on conducting clinical trials, optimizing phage formulations, and studying phage-host interactions in the context of regional pathogens. Training and educating medical professionals about phage therapy can foster its acceptance and successful implementation in clinical settings.

By adopting phage therapy as part of a multi-pronged strategy to address AMR, Africa can strengthen its healthcare systems and provide innovative, sustainable solutions to its pressing public health challenges. The continent leadership in advancing phage therapy could also position it as a global pioneer in this promising field.

Contributions of authors:

NOO was involved in research conceptualization, design formulation and writing of the original draft; NFE was involved in research design, supervision, methodological activities, analysis, writing and review of the manuscript. All authors read and approved the manuscript for submission.

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