Review

Exploring Phage Therapy as a Sustainable Solution to Combat Antimicrobial Resistance in Africa: Challenges, Applications, and Future Directions

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Exploring Phage Therapy as a Sustainable Solution to Combat Antimicrobial Resistance in Africa: Challenges, Applications, and Future Directions

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ABSTRACT: The increasing threat of antibiotic resistance in Africa, coupled with limited access to advanced antibiotics and high rates of bacterial infections, poses a 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's beneficial microbiota. It is an effective tool against multi-drug-resistant infections, particularly in resource-limited settings. This paper explores the potential 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 antibiotic-resistant infections. It reviews current research and collaborations, including case studies from Nigeria, Benin, and South Africa, that demonstrate the efficacy of phage therapy against pathogens like *Staphylococcus aureus* and *Klebsiella pneumoniae*. Furthermore, it discusses the challenges to implementation, such as regulatory hurdles, public scepticism, and infrastructure limitations, while emphasising the importance of developing local production and awareness campaigns. The paper concludes by recommending the integration of phage therapy into Africa's 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.

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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 bacterial cell's machinery to replicate. This 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).

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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, particularly in Eastern Europe, as an effective method for treating bacterial infections (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 bacterial strains, which are becoming more common worldwide. This adaptability, along with their 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 potential in addressing multi-drug-resistant 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 a broader spectrum of bacterial pathogens, further increasing the feasibility of phage therapy in clinical settings (8,11).

Africa faces a growing burden of antibiotic-resistant 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 antibiotic resistance 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).

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ANTIMICROBIAL RESISTANCE (AMR) 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. Key multidrug-resistant (MDR) pathogens in Africa including *E. coli*, *K. pneumoniae*, *S. aureus*, *P. aeruginosa*, and *A. baumannii,* often cause severe infections like UTIs, bloodstream infections, respiratory infections, and wound infections. *E. coli* and *K. pneumoniae* which are also common culprits of UTIs and bloodstream infections, currently have increased resistance to crucial antibiotics like fluoroquinolones and third-generation cephalosporins due to ESBL production. *S. aureus*, particularly MRSA, is 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), the African region faces a particularly high burden of antimicrobial resistance, 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 Antibiotic Resistance 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 a prescription, further fuelling 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: The Threat of Multidrug-Resistant Bacteria and the Urgent Demand 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).

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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's 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's 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 multidrug-resistant (MDR) bacteria. Phages can target bacterial strains that have developed resistance to antibiotics, 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 *Staphylococcus aureus*, *Klebsiella pneumoniae*, and those responsible for diarrhoeal diseases are common targets of phage therapy. For instance, *Staphylococcus aureus*, including methicillin-resistant strains (MRSA), 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

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Africa. Phages have been successfully used to treat *Escherichia 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 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's 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 antimicrobial resistance (AMR) on the continent.

Case Studies in Africa

Staphylococcus aureus infections in Nigeria

A study conducted in Nigeria demonstrated the effectiveness of bacteriophages in targeting drug-resistant Staphylococcus aureus. Researchers isolated phages specific to methicillin-resistant *S. aureus* (MRSA) strains and observed significant reductions in bacterial load in vitro. This is particularly relevant as MRSA is a major cause of hospital-acquired infections in the region, where access to advanced antibiotics is limited (50).

Urinary Tract infections by *Escherichia coli*

Another case study in West Africa explored the use of phages to treat *Escherichia coli*-induced urinary tract infections (UTIs). Clinical isolates resistant to multiple antibiotics were treated with customized phage cocktails, leading to the successful eradication of the pathogens. This outcome supports phage therapy as an effective alternative to antibiotics for managing UTIs caused by drug-resistant strains (8).

Joint Initiatives in Benin

Collaborative research projects in Benin focused on phage therapy for diarrhoeal diseases caused by resistant bacteria such as *Klebsiella pneumoniae*. Early results indicate that phage therapy can be integrated into local healthcare strategies, showing high specificity and minimal side effects compared to traditional antibiotic treatments (32).

Compassionate Use in South Africa

South African healthcare settings have implemented phage therapy under compassionate use programs. For instance, a patient with a chronic infection caused by drug-resistant *Pseudomonas aeruginosa* was successfully treated using a personalized phage cocktail. The therapy not only

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eradicated the infection but also reduced inflammation, illustrating its dual therapeutic role in infection control and immune modulation (51).

CHALLENGES TO 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 scepticism, and infrastructure limitations for production and storage.

A. Regulatory Hurdles

The lack of clear and standardized regulatory frameworks for phage therapy in most African countries presents a significant barrier to its implementation.

- ✓ Absence of Guidelines: Unlike antibiotics, which have well-established pathways for approval, phage therapy lacks formalized protocols for preclinical and clinical trials in Africa. This ambiguity hampers the widespread adoption of phage-based treatments (6, 52).
- ✓ Global Inconsistencies: Even globally, regulatory frameworks for phages are fragmented, with countries like Georgia and Poland having established systems, while others, including most African nations, lag. Efforts by the WHO to streamline regulatory processes for novel therapies could help, but these measures are still in the early stages (8).
- ✓ Example: In South Africa, researchers have faced delays in receiving approvals for clinical trials involving phages, despite their promise in treating resistant infections (53).

B. Public and Healthcare Sector Skepticism

Phage therapy is often viewed with scepticism due to its novelty and historical associations with limited regions.

- ✓ Healthcare Professionals: Many doctors and healthcare providers in Africa are unfamiliar with phage therapy, leading to resistance to adopting it over traditional antibiotics (36).
- ✓ Public Awareness: 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 is essential (32).
- ✓ Cultural Factors: In some communities, distrust of modern medicine complicates the introduction of phage therapy, requiring culturally sensitive awareness campaigns (53).

C. Production and Storage Challenges

The practicalities of producing and storing bacteriophages present hurdles in regions with limited resources.

- ✓ Production: Producing phages requires advanced laboratory facilities to ensure safety, efficacy, and specificity. Few African countries have the infrastructure for large-scale, high-quality phage production (54).
- ✓ Formulation: Developing formulations suitable for different infections (e.g., topical, oral, or injectable) demands significant investment in research and development.
- ✓ Storage: Phages are temperature-sensitive and often require cold-chain storage to maintain viability, which is a challenge in regions with unreliable electricity or refrigeration (8). 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.
- ✓ Cost Implications: 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 (6).

6. 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

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phages. Trials focused on region-specific infections, such as typhoid fever or cholera, can validate phage therapy's relevance 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's burden of infectious diseases, limited access to new antibiotics, and increasing prevalence of antimicrobial resistance (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, 53, 55).

Call to Action

To fully harness the potential of phage therapy in Africa, coordinated efforts are required from policy-makers, researchers, and healthcare providers:

- ✓ Policy-makers: Governments must prioritize the establishment of regulatory frameworks that facilitate phage therapy's development and integration into healthcare systems. Investing in infrastructure for local phage production and quality assurance is crucial.
- ✓ Researchers: African research institutions should focus on conducting clinical trials, optimizing phage formulations, and studying phage-host interactions in the context of regional pathogens.
- ✓ Healthcare Providers: 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's leadership in advancing phage therapy could also position it as a global pioneer in this promising field.

REFERENCES

1. Abedon, S. T., García, P., Mullany, P., & Aminov, R. (2017). Editorial: Phage Therapy: Past, Present and Future. Frontiers in microbiology, 8, 981. https://doi.org/10.3389/fmicb.2017.00981
2. Burrowes, B., Harper, D. R., Anderson, J., McConville, M., & Enright, M. C. (2011). Bacteriophage therapy: potential uses in the control of antibiotic-resistant pathogens. Expert review of anti-infective therapy, 9(9), 775–785. https://doi.org/10.1586/eri.11.90
3. Chan, B. K., Abedon, S. T., & Loc-Carrillo, C. (2013). Phage cocktails and the future of phage therapy. Future microbiology, 8(6), 769–783. https://doi.org/10.2217/fmb.13.47
4. Chang, C., Yu, X., Guo, W., Guo, C., Guo, X., Li, Q., & Zhu, Y. (2022). Bacteriophage-Mediated Control of Biofilm: A Promising New Dawn for the Future. Frontiers in microbiology, 13, 825828. https://doi.org/10.3389/fmicb.2022.825828
5. Doss, J., Culbertson, K., Hahn, D., Camacho, J., & Barekzi, N. (2017). A Review of Phage Therapy against Bacterial Pathogens of Aquatic and Terrestrial Organisms. Viruses, 9(3), 50. https://doi.org/10.3390/v9030050
6. Pires, D. P., Cleto, S., Sillankorva, S., Azeredo, J., & Lu, T. K. (2016). Genetically Engineered Phages: a Review of Advances over the Last Decade. Microbiology and molecular biology reviews: MMBR, 80(3), 523–543. https://doi.org/10.1128/MMBR.00069-15
7. Dufour, N., Debarbieux, L., Fromentin, M., & Ricard, J. D. (2015). Treatment of Highly Virulent Extraintestinal Pathogenic Escherichia coli Pneumonia With Bacteriophages. Critical care medicine, 43(6), e190–e198. https://doi.org/10.1097/CCM.0000000000000968
8. Kortright, K. E., Chan, B. K., Koff, J. L., & Turner, P. E. (2019). Phage Therapy: A Renewed Approach to Combat Antibiotic-Resistant Bacteria. Cell host & microbe, 25(2), 219–232. https://doi.org/10.1016/j.chom.2019.01.014

9. Rogovski, P., Cadamuro, R. D., da Silva, R., de Souza, E. B., Bonatto, C., Viancelli, A., Michelon, W., Elmahdy, E. M., Treichel, H., Rodríguez-Lázaro, D., & Fongaro, G. (2021). Uses of Bacteriophages as Bacterial Control Tools and Environmental Safety Indicators. Frontiers in microbiology, 12, 793135. https://doi.org/10.3389/fmicb.2021.793135
10. O'Neill, J. (2016) Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. Review on Antimicrobial Resistance. Wellcome Trust and HM Government. https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf
11. Górski, A., Międzybrodzki, R., Węgrzyn, G., Jończyk-Matysiak, E., Borysowski, J., & Weber-Dąbrowska, B. (2020). Phage therapy: Current status and perspectives. Medicinal research reviews, 40(1), 459–463. https://doi.org/10.1002/med.21593
12. Tadesse, B. T., Ashley, E. A., Ongarello, S., Havumaki, J., Wijegoonewardena, M., González, I. J., & Dittrich, S. (2017). Antimicrobial resistance in Africa: a systematic review. BMC Infectious Diseases, 17(1), 616. https://doi.org/10.1186/s12879-017-2713-1
13. Essack, S. Y., Desta, A. T., Abotsi, R. E., & Agoba, E. E. (2017). Antimicrobial resistance in the WHO African region: current status and roadmap for action. Journal of Public Health (Oxford, England), 39(1), 8–13. https://doi.org/10.1093/pubmed/fdw015
14. Ekpunobi, N. F., Adesanoye, S., Orababa, O., Adinnu, C., Okorie C, et.al (2024) Public health perspective of public abattoirs in Nigeria, challenges and solutions. *GSC Biological and Pharmaceutical Sciences* 26(2): 115-127
15. Favour, E. N. and Isaac, A. A. (2020). Phenotypic characterization of biofilm formation and efflux pump activity in multi-drug resistant *staphylococcus* species isolated from asymptomatic students *J Microbiol Exp,* **8:** 223–229
16. World Health Organization (2018). Antibacterial agents in clinical development: An analysis of the antibacterial clinical development pipeline, including tuberculosis.
17. Monteiro, R., Pires, D. P., Costa, A. R., & Azeredo, J. (2019). Phage Therapy: Going Temperate? Trends in microbiology, 27(4), 368–378. https://doi.org/10.1016/j.tim.2018.10.008
18. Luong, T., Salabarria, A. C., & Roach, D. R. (2020). Phage Therapy in the Resistance Era: Where Do We Stand and Where Are We Going? Clinical therapeutics, 42(9), 1659–1680. https://doi.org/10.1016/j.clinthera.2020.07.014
19. Newman, M. J., Frimpong, E., Donkor, E. S., Opintan, J. A., & Asamoah-Adu, A. (2011). Resistance to antimicrobial drugs in Ghana. Infection and drug resistance, 4, 215–220. https://doi.org/10.2147/IDR.S21769
20. Bunduki, G. K., Masoamphambe, E., Fox, T., Musaya, J., Musicha, P., & Feasey, N. (2024). Prevalence, risk factors, and antimicrobial resistance of endemic healthcare-associated infections in Africa: a systematic review and meta-analysis. BMC Infectious Diseases, 24(1), 158. https://doi.org/10.1186/s12879-024-09038-0
21. Ekpunobi, N.; Markjonathan, I.; Olanrewaju, O.; Olanihun, D. (2020). Idiosyncrasies of COVID-19; A Review. *Iran. J. Med. Microbiol. 14*, 290–296.
22. Bebell, L. M., & Muiru, A. N. (2014). Antibiotic use and emerging resistance: how can resource-limited countries turn the tide? Global Heart, 9(3), 347–358. https://doi.org/10.1016/j.gheart.2014.08.009
23. Okeke, I. N., Laxminarayan, R., Bhutta, Z. A., Duse, A. G., Jenkins, P., O'Brien, T. F., Pablos-Mendez, A., & Klugman, K. P. (2005). Antimicrobial resistance in developing countries. Part I: recent trends and current status. The Lancet. Infectious diseases, 5(8), 481–493. https://doi.org/10.1016/S1473-3099(05)70189-4
24. Ocan, M., Obuku, E. A., Bwanga, F., Akena, D., Richard, S., Ogwal-Okeng, J., & Obua, C. (2015). Household antimicrobial self-medication: a systematic review and meta-analysis of the burden, risk factors and outcomes in developing countries. BMC Public Health, 15, 742. https://doi.org/10.1186/s12889-015-2109-3
25. Aslam, A., Gajdács, M., Zin, C. S., Ab Rahman, N. S., Ahmed, S. I., Zafar, M. Z., & Jamshed, S. (2020). Evidence of the Practice of Self-Medication with Antibiotics among the Lay Public in Low- and Middle-Income Countries: A Scoping Review. Antibiotics (Basel, Switzerland), 9(9), 597. https://doi.org/10.3390/antibiotics9090597
26. Mendelson, M., & Matsoso, M. P. (2015). The World Health Organization Global Action Plan for Antimicrobial Resistance. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde, 105(5), 325. https://doi.org/10.7196/samj.9644
27. Founou, R. C., Founou, L. L., & Essack, S. Y. (2017). Clinical and economic impact of antibiotic resistance in developing countries: A systematic review and meta-analysis. PloS one, 12(12), e0189621. https://doi.org/10.1371/journal.pone.0189621
28. Tessema, G. A., Kinfu, Y., Dachew, B. A., Tesema, A. G., Assefa, Y., Alene, K. A., Aregay, A. F., Ayalew, M. B., Bezabhe, W. M., Bali, A. G., Dadi, A. F., Duko, B., Erku, D., Gebrekidan, K., Gebremariam, K. T., Gebremichael, L. G., Gebreyohannes, E. A., Gelaw, Y. A., Gesesew, H. A., Kibret, G. D., … Tesfay, F. H. (2021). The COVID-19 pandemic and healthcare systems in Africa: a scoping review of preparedness, impact and response. BMJ Global Health, 6(12), e007179. https://doi.org/10.1136/bmjgh-2021-007179

29. Ayukekbong, J. A., Ntemgwa, M., & Atabe, A. N. (2017). The threat of antimicrobial resistance in developing countries: causes and control strategies. Antimicrobial resistance and infection control, 6, 47. https://doi.org/10.1186/s13756-017-0208-x
30. Kakkar, A. K., Shafiq, N., Singh, G., Ray, P., Gautam, V., Agarwal, R., Muralidharan, J., & Arora, P. (2020). Antimicrobial Stewardship Programs in Resource-Constrained Environments: Understanding and Addressing the Need of the Systems. Frontiers in public health, 8, 140. https://doi.org/10.3389/fpubh.2020.00140
31. Enyi E, Ekpunobi N. (2022). Secondary metabolites from endophytic fungi of Moringa oleifera: Antimicrobial and antioxidant properties. *J Microbiol Exp.* 10:150-154. http://doi.org/10.15406/jmen.2022.10.00367
32. Reardon S. (2014). Antibiotic resistance sweeping the developing world. Nature, 509(7499), 141–142. https://doi.org/10.1038/509141a
33. Ekpunobi NF, Mgbedo UG, Okoye LC, Agu KC. (2024). Prevalence of ESBL genes in *Klebsiella pneumoniae* from individuals with community-acquired urinary tract infections in Lagos state, Nigeria. *J RNA Genomics* 20(2):1-6.

34. Aslam, B., Wang, W., Arshad, M. I., Khurshid, M., Muzammil, S., Rasool, M. H., Nisar, M. A., Alvi, R. F., Aslam, M. A., Qamar, M. U., Salamat, M. K. F., & Baloch, Z. (2018). Antibiotic resistance: a rundown of a global crisis. Infection and drug resistance, 11, 1645–1658. https://doi.org/10.2147/IDR.S173867
35. Helmy, Y. A., Taha-Abdelaziz, K., Hawwas, H. A. E., Ghosh, S., AlKafaas, S. S., Moawad, M. M. M., Saied, E. M., Kassem, I. I., & Mawad, A. M. M. (2023). Antimicrobial Resistance and Recent Alternatives to Antibiotics for the Control of Bacterial Pathogens with an Emphasis on Foodborne Pathogens. Antibiotics (Basel, Switzerland), 12(2), 274. https://doi.org/10.3390/antibiotics12020274
36. Sulakvelidze, A., Alavidze, Z., & Morris, J. G., Jr (2001). Bacteriophage therapy. Antimicrobial agents and chemotherapy, 45(3), 649–659. https://doi.org/10.1128/AAC.45.3.649-659.2001
37. Nobrega, F. L., Costa, A. R., Kluskens, L. D., & Azeredo, J. (2015). Revisiting phage therapy: new applications for old resources. Trends in microbiology, 23(4), 185–191. https://doi.org/10.1016/j.tim.2015.01.006
38. Pirnay, J. P., Verbeken, G., Ceyssens, P. J., Huys, I., De Vos, D., Ameloot, C., & Fauconnier, A. (2018). The Magistral Phage. Viruses, 10(2), 64. https://doi.org/10.3390/v10020064
39. Kakasis, A., & Panitsa, G. (2019). Bacteriophage therapy as an alternative treatment for human infections. A comprehensive review. International journal of antimicrobial agents, 53(1), 16–21. https://doi.org/10.1016/j.ijantimicag.2018.09.004
40. Górski, A., Międzybrodzki, R., Łobocka, M., Głowacka-Rutkowska, A., Bednarek, A., Borysowski, J., Jończyk-Matysiak, E., Łusiak-Szelachowska, M., Weber-Dąbrowska, B., Bagińska, N., Letkiewicz, S., Dąbrowska, K., & Scheres, J. (2018). Phage Therapy: What Have We Learned? Viruses, 10(6), 288. https://doi.org/10.3390/v10060288
41. Bernabé, K. J., Langendorf, C., Ford, N., Ronat, J. B., & Murphy, R. A. (2017). Antimicrobial resistance in West Africa: a systematic review and meta-analysis. International journal of antimicrobial agents, 50(5), 629–639. https://doi.org/10.1016/j.ijantimicag.2017.07.002
42. Iseppi, R., Mariani, M., Condò, C., Sabia, C., & Messi, P. (2021). Essential Oils: A Natural Weapon against Antibiotic-Resistant Bacteria Responsible for Nosocomial Infections. Antibiotics (Basel, Switzerland), 10(4), 417. https://doi.org/10.3390/antibiotics10040417
43. Caflisch, K. M., Suh, G. A., & Patel, R. (2019). Biological challenges of phage therapy and proposed solutions: a literature review. Expert review of anti-infective therapy, 17(12), 1011–1041. https://doi.org/10.1080/14787210.2019.1694905
44. Melo, L. D. R., Pinto, G., Oliveira, F., Vilas-Boas, D., Almeida, C., Sillankorva, S., Cerca, N., & Azeredo, J. (2020). The Protective Effect of Staphylococcus epidermidis Biofilm Matrix against Phage Predation. Viruses, 12(10), 1076. https://doi.org/10.3390/v12101076
45. Ekpunobi NF, Mgbedo UG, Okoye LC, Agu KC. Prevalence of Esbl Genes in *Klebsiella pneumoniae* from Individuals with Community-Acquired Urinary Tract Infections in Lagos State, Nigeria. *Preprints* 2024, https://doi.org/10.20944/preprints202403.1702.v1
46. Salmond, G. P., & Fineran, P. C. (2015). A century of the phage: past, present and future. Nature reviews. Microbiology, 13(12), 777–786. https://doi.org/10.1038/nrmicro3564
47. Manohar, P., Tamhankar, A. J., Lundborg, C. S., & Nachimuthu, R. (2019). Therapeutic Characterization and Efficacy of Bacteriophage Cocktails Infecting *Escherichia coli, Klebsiella pneumonia*e, and *Enterobacter* Species. Frontiers in microbiology, 10, 574. https://doi.org/10.3389/fmicb.2019.00574
48. Międzybrodzki, R., Borysowski, J., Weber-Dąbrowska, B., Fortuna, W., Letkiewicz, S., Szufnarowski, K., Pawełczyk, Z., Rogóż, P., Kłak, M., Wojtasik, E., & Górski, A. (2012). Clinical aspects of phage therapy. Advances in virus research, 83, 73–121. https://doi.org/10.1016/B978-0-12-394438-2.00003-7

 doi:10.20944/preprints202411.1597.v1

49. Anastassopoulou, C., Ferous, S., Petsimeri, A., Gioula, G., & Tsakris, A. (2024). Phage-Based Therapy in Combination with Antibiotics: A Promising Alternative against Multidrug-Resistant Gram-Negative Pathogens. Pathogens (Basel, Switzerland), 13(10), 896. https://doi.org/10.3390/pathogens13100896
50. Plumet, L., Ahmad-Mansour, N., Dunyach-Remy, C., Kissa, K., Sotto, A., Lavigne, J. P., Costechareyre, D., & Molle, V. (2022). Bacteriophage Therapy for Staphylococcus Aureus Infections: A Review of Animal Models, Treatments, and Clinical Trials. Frontiers in cellular and infection microbiology, 12, 907314. https://doi.org/10.3389/fcimb.2022.907314
51. Abedon, S. T., Kuhl, S. J., Blasdel, B. G., & Kutter, E. M. (2011). Phage treatment of human infections. Bacteriophage, 1(2), 66–85. https://doi.org/10.4161/bact.1.2.15845
52. Henein A. (2013). What are the limitations on the wider therapeutic use of phage?. Bacteriophage, 3(2), e24872. https://doi.org/10.4161/bact.24872
53. Fokou, P. V. T., et al. (2023). Bacteriophages as Antimicrobial Agents in African Healthcare: Current Research and Future Directions. *FEMS Microbiology Reviews*, *47*(1), 1–DOI: 10.1093/femsre/fuad023.
54. Kutateladze, M., & Adamia, R. (2010). Bacteriophages as potential new therapeutics to replace or supplement antibiotics. Trends in biotechnology, 28(12), 591–595. https://doi.org/10.1016/j.tibtech.2010.08.001
55. Ekpunobi, N. F. and Agu, K.C Emergence and Re-Emergence of Arboviruses: When Old Enemies Rise Again. *Cohesive J Microbiol Infect Dis*. 7(2). CJMI. 000658. DOI: 10.31031/CJMI.2024.07.000658.