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Review Article

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Antimicrobial Resistance in Cholera: A Need for Quick Intervention in Nigeria, West Africa

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Abstract

Following the discovery and identification of *Vibrio cholerae*, cholera disease continues to be a burden on the global community, including Nigeria. In this article, we provide an inclusive review on antimicrobial resistance (AMR) in cholera and the need for its quick interventions. Cholera spread over Asia and other continents, majorly because of poor hygiene practises since 1817, and still exists. This agent secretes a toxin called cholera toxin (CT) after ingestion of contaminated water and/or food, which adheres to the cells in the intestinal epithelial, leading to symptoms such as watery diarrhea, fever, and even death if not treated. Many antimicrobials such as tetracycline, trimethoprim/sulfamethoxazole, and ampicillin, previously effective in cholera therapy, are now reported ineffective due to emerging and developing AMR strains of *V. cholerae*. AMR in cholera continues to be a major public health concern. Various outbreaks have been reported in Nigeria since the 1970s. This is as a result of the acquisition of resistance genes and/or mutation. Also, irrational usage of antibiotics by people. Promising approaches such as probiotics, vaccines, phage therapy, provision of safe water and proper hygiene are ways to avert the outbreak of cholera and resistant strains in Nigeria.

Keywords: Antimicrobial Resistance, Cholera, Cholera Toxin, Nigeria, Vaccine

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Introduction

Cholera is an infectious disease characterized by acute watery diarrhea, caused by Gram-negative curved bacilli called *Vibrio cholerae*. There are more than 200 serogroups of *V. cholerae* classified based on structural protein present on the bacterium's cell wall but only the O1 and 0139 serogroups are responsible for the most outbreak of cholera. The O139 serogroup is limited to some parts of Asia while the O1 serogroup (further classified as El Tor and Classical biotypes) are found globally.[1,2] The El Tor biotype persists much longer than the classical biotypes.[3] Indeed, the major cause of illness and death in underdeveloped countries is cholera.[4]

Cholera spread worldwide beyond Asia seven times (1817, 1829, 1852, 1863, 1881, 1889, and 1961) in the 18th and 19th centuries, and this is known as the cholera pandemic. 1961 is still in existence. Other continents are also affected at one time or another.[5] Of these seven pandemics, *V. cholerae* O1 biotype is presumed as the etiological agent of the first six, while El Tor lineage is dominant in the seventh pandemic, which began in the Sulawesi Archipelago in 1960 and spread to other parts of the world.[6]

The main virulence factors used by *V. cholerae* are the cholera toxin (CT) encoded by the bacteriophage CTXϕ and the toxin-coregulated pilus encoded by the vibrio seventh pandemic island 1 which aid in the colonization of the host. In recent times, a new strain of *V. cholerae* called Atypical or Hybrid El Tor emergence showing both markers of El Tor and Classical biotypes. This strain is frequently accountable for multidrug resistance (MDR).[2]

Cholera disease is an indicator of poor hygiene, and its transmission is intently interrelated to inadequate access to clean water and poor sanitation facilities. Areas with high risk include rural communities, refugee camps[3] and areas experiencing natural disasters such as floods.[7] All attributed to lack of safe water and poor sanitation facilities.[3]

Transmission

Aquatic milieus, particularly brackish riverine, estuarine, and coastal waters, are the natural habitat of O1 and O139 *V. cholerae* serogroups.[8] Human feces contain many pathogenic microorganisms that can be directly and/or indirectly transmitted from one human to another.[9] The fecal-oral route is the major route for cholera transmission. Cholera can be transmitted by ingesting the bacteria from an environment contaminated with an infected individual's feces, such as a river, lake, or stream, and this transmission route is

called environment-human transmission. Cholera can also be transmitted from infected individuals to susceptible individuals via consumption of food or water at the point of use contaminated by caring for existing cholera cases, which usually occur in households. This route is called "human-to-human transmission."[10]

Pathogenesis

Once the bacterium is ingested, a minimum infectious dose is 10^8 viable organisms are entailed to cause cholera, the incubation period ranges from a few hours to 5 days.[11,12] However, this dropped up to 10^4 in persons that produce less stomach acid such as young and old persons including those who take antacids.[13] The bacterium secretes CT, which adheres to the intestinal mucosal in the host's small intestine.[11] CT is composed of two subunits an enzymatically catalytic A subunit (CtxA) and a pentamer of B subunits (CtxB). The CtxB binds to the monosialoganglioside GM1 by receptors on the apical surface of the intestinal epithelial cells and this leads to the activation of an enzyme called adenylate cyclase, which leads to excessive secretion of water and chloride, leading to massive loss of fluid and electrolytes.[11] This causes watery diarrhea, fever, diarrhea, and abdominal cramps.[14] Other symptoms include hypovolemia and death if not treated due to dehydration.[12,15]

Incidence

Annually about 1.3 to 4.0 million cases and 21 000 to 143 000 deaths were reported worldwide due to cholera.[5] In Nigeria, a cholera outbreak was first reported in 1970 and Nigeria remained one of the foci of cholera endemic and epidemic in the world,[1] and most of these cases occur during the rainy season.[3] Several cases of high case fatalities are reported almost annually. In 2019, Nigeria reported 2497 suspected cases of cholera and 38 death.[16] In 2020, from January to September, Nigeria recorded 1,115 suspected cases of cholera with 61 deaths but only 40 were accurately confirmed by laboratory tests.[16] As of last year (2021), Nigeria has the highest rate of cases (102 684) and deaths (3519) of cholera in West Africa.[17] The Nigeria Centre for Disease Control (NCDC) recorded 3610 cases and 91 deaths in Nigeria from January to July 2022. The majority of these cases occur in Taraba State and the most affected are children less than 5,[18] because most northern states rely on hand dugs and contaminated rivers as a major source of drinking water.[19] Despite several exertions to control cholera, it is a major public health problem in Nigeria.[3]

Antimicrobials

Antimicrobials are agents used for the treatment of diseases such as cholera, typhoid fever, malaria, gonorrhea, etc. They are also used as a growth promoter in animals and antimicrobial prophylaxis.[20] These include penicillin, tetracycline, ciprofloxacin, etc. Antimicrobials are classified in many ways; the common, based on infectious agents (microorganisms) they attack and the mechanisms of attack. Antimicrobials are used in the treatment of diseases in animals and humans worldwide, in developing countries, they are commonly used without control and regulation. Based on the infectious agent they attack, we have antibacterial (antibiotics), antifungal, antiprotozoal, and antiviral that act against bacteria, fungi, protozoa, and viruses respectively. Based on the mechanism of action we have those that inhibit cell wall synthesis, nucleic synthesis, protein synthesis, and damage cell membrane.[20] Antimicrobials (antibiotics) are not administered solely in cholera therapy but with oral rehydration therapy to lessen the duration of the illness and also reduce the shedding of the pathogen in the stool.[12]

Tetracyclines (tetracycline and doxycycline) are broad-spectrum antibiotics and among the pioneer antibiotics used for treating severe cholera disease previously excluding pregnant women and young children globally[21] because of the teratogenic effect in pregnant women and dental complications in children. A single dose of doxycycline is required to reduce the duration of symptoms and stool in adults and children while multiple doses are required in adult.[21] These antibiotics target the bacterial 30S ribosomal subunits and protein synthesis. Resistance strains, mostly in serogroup O1 are responsible for a major outbreak of cholera in the world.[22] due to extensive inappropriate use of these regimens.[22] Resistance is mainly due to the presence of mobile genetic elements such as plasmids and transposons and other mechanisms such as decreased drug permeability, enzymatic degradation of the antibiotic, active efflux, and production of ribosomal protection proteins encoded by genes called *tet* genes.[22] Antimicrobial susceptibility testing before the administration of antibiotics would help to curb the development of resistance and failure of treatment.[22] Probiotics, vaccines, and phage therapy are notable approaches to reducing the resistance strain of *V. cholerae*.[22]

Antimicrobial Resistance in Cholera

Antimicrobial resistance (AMR) is a major threat to public health globally which call for quick intercession.[4,23] AMR is multifactorial and these include overuse, insufficient and/or incomplete dose, inadequate/lack of adequate water, lack of quality and/or high-cost medication, and lack of public awareness.[24] AMR is the situation in which microbe(s) developed the ability to withstand or become unaffected by drugs that usually inhibit or reduce their growth. Bacterial infections result in die of at least 700 000 individuals per annum as a result of AMR and it has been estimated that 10 million people will die per year by 2050.[25] Many individuals mistakenly believe that it is the host (human) developed resistance, not the microbes but AMR had been recorded to be transmitted between humans to humans through poor sanitation and fecal-oral route.[23] *V. cholerae* uses mechanisms such as (1) limiting uptake of a drug (2) modifying a drug target (3) inactivating a drug (4) active drug efflux. Many antimicrobials have been used for cholera therapy such as tetracycline, macrolides, and fluoroquinolones but resistance to all the drugs has been reported. However, the resistance is due to mutation in the chromosome and/or acquisition of mobile genetic elements such as plasmids, transposons, and

integrating conjugative elements.[26,27] AMR in cholera leads to an increase in healthcare costs, morbidities, mortalities, and prolonged hospitalization.[3] Antimicrobial multidrug resistance is most common among the atypical cholera strains, which is associated with the acquirement of genes and/or modification in the antibiotic target.[1] If humans continue to overuse/misuse antimicrobials, they would not be able to defeat cholera disease and many other infections.[28]

However, antimicrobial therapy is recommended for severe cases of cholera[2] to reduce the volume of the duration of diarrhea as well as the transmission of the bacterium.[12,28] and most of these agents are now ineffective. There is no specific strain that their AMR pattern is well studied and explained in Nigeria.[2] In Nigeria, high resistance in tetracycline and ampicillin[3] were reported, in contrast, to[3] Stephanie et al reported that the O1 cholera strain is highly sensitive to tetracycline in Bangladesh.[26] Resistance to antimicrobial among *V. cholerae* O1 varies considerably between regions and over time.[28] Garbati et al reported that amikacin, cefotaxime, and ciprofloxacin are sensitive, while tetracycline, trimethoprim/sulfamethoxazole are resistant.[3] Also Marin et al study showed that the El Tor *V. cholerae* strain has virulence alleles and resistance genes that result in the cholera outbreak in Nigeria which is resistant to some antibiotics such as quinolone, streptomycin, nalidixic acid, sulfamethoxazole/trimethoprim, sulphonamides and reduced in sensitivity to ciprofloxacin and chloramphenicol.[1] Reduced quinolone is attributed to the mutation in gyrA and in parC; all these genes are associated with integrative and conjugative elements.[1] Tetracycline was earlier considered most effective for cholera therapy, increase in tetracycline resistance among *V. cholerae* O1 strain is the major cause of cholera outbreak in Nigeria and Africa at large.[3] This may be due to the widespread use of this drug for treatment and prophylaxis.[3] O1 cholera strains are usually resistant to streptomycin, trimethoprim, and sulfonamides and this is associated with the presence of class 1 and 2 integrons and SXT elements.[1]

Recommendations/Solutions

Probiotics

The novel idea behind probiotics is the use of the host microbiome to prevent or treat infections by restoring the gut microbiome.[21] Severe cholera infection leads to disruption of the gut microbiome.[29] Various bacterial species such as *Lactobacillus lactis*, *Lactobacillus rhamnosus*, *Ruminococcus obeum*, and *Bifidobacterium longum* are used as probiotics. *Lactobacillus lactis* can be engineered to increase lactic acid production while resulting in disruption of *V. cholerae* due to a decrease in pH. Also engineered *Escherichia coli* was demonstrated to decrease colonization of *V. cholerae* by mimicking the binding CT (CtxB) to the monosialoganglioside GM1 by receptors on the apical surface of the intestinal epithelial cells.[21] Adopting the approach will reduce the extensive use of antibiotics and when vaccines are unavailable for cholera therapy.[21]

Phage Therapy

Phages are novel viruses that specifically infect bacteria. Following the discovery of the bactericidal effect of phages against bacteria by Frederick Twort and Felix d'Herelle, phages have been used for treating bacterial diseases prior to the discovery of antibiotics and this modality is called phage therapy.[30] Antibiotic discovery waned this approach but reawakened after the announcement of AMR as a global threat.[30] Adesola and Moses stressed the use of phage therapy as an alternative to fighting AMR in the world.[31] Phage therapy research in Nigeria and Africa at large needs more awareness.[32] Phages can infect and destroy bacteria including AMR strains.[21] Phages are subdivided into two based on their life cycle, the lytic and lysogenic phages. Lytic phages infect bacteria and hijack their replication machinery to replicate and lyse the bacteria to release its progeny[33] while the lysogenic phages infect and integrate the genome into the bacterial chromosome to become prophages and remain latent.[33] Prophages are triggered by environmental factors and transit to the lytic cycle thereby releasing their progeny.[33] This modality relies on lytic phages due to lysing ability.[34] Phages are first used in the treatment of bacterial dysentery in pediatric patients.[30] In one clinical trial in 1938, phage cocktails targeting a range of bacterial species were administered orally and rectally to 219 patients (138 children) where 132 patients showed alleviated symptoms.[35] Also, Jun et al showed that administration of phage cocktail via oral and intraperitoneal routes against MDR *Vibrio parahaemolyticus* showed 84% and 92% reduced mortality respectively.[36] This modality is also effective in treating cholera as 93% survived in one demonstration.[35] Antibiotics had been shown to have some adverse side effects on the kidney, heart, liver, and gastrointestinal tract as well as allergic reactions.[30] In contrast, phages had been shown to have minimal effects on host organs and microbiomes. Moreover, a single dose of phage is sufficient in some treatments because of their self-replicating ability.[37] The major drawback of phage therapy is the cocktail preparation, the major determinant of the success of this therapy. Preparation of cocktails for specific infections especially those caused by many pathogens is tedious, time-consuming, and pricey. Many researchers found that oral routes are more effective than other routes in model animals.[38]

Vaccine

Vaccination is the most successful tool for the prevention of cholera. One of the factors contributing to the cholera outbreak is the non-use of the cholera vaccine in rural areas. WaldemarHaffkine developed the first effective human cholera vaccine in July 1892.[39] Presently, three WHO pre-qualified oral cholera vaccines including lived attenuated and inactivated whole cell (WC) vaccines and can provide herd immunity in unvaccinated adults, i.e. Dukoral Shanhol and Euvichol.[21] These vaccines are administered to stimulate immune responses against CT and O1-specific polysaccharides.[40] Euvichol and Shanchol are WC vaccines composed of inactivated O1 Inaba, O1 Ogawa, and O139 strains, but these vaccines do not contain CTB. These two

vaccines showed to be effective in all individuals for 1 year excluding pregnant women while Dukoral contains WC dead *V. cholerae* O1 (El Tor and classical biotypes) with recombinant B subunits of CT (CTB).[41] Shanhol™ provides durability immunity in individuals above 5 years.[41] For full protection, all these vaccines are required in two doses.[21] US Food and Drug Administration–approved recently approved the oral live-attenuated vaccine Vaxchora (CVD 103-HgR) which is effective against either the Inaba or Ogawa serotype with the administration of single-dose and contains CTB from both classical and El Tor biotypes.[21] This vaccine require more clinical trial in cholera-endemic regions such as Nigeria.[42]

Conclusion

Cholera outbreaks have been ongoing in Nigeria for the past 4 decades, but the specific strains responsible and their AMR pattern are not well elucidated and their distribution pattern in Nigeria is dynamic. This study suggested some solutions and call for more studies and development of alternatives to curb cholera and AMR in Nigeria. Antimicrobials seem not to be more effective in cholera therapy. New clinical and non-clinical approaches have to be adopted to prevent future cases, outbreaks, and spread of resistant strains. Cholera disease is a sign of poor hygiene and sanitation, as well as a lack of access to safe water. Improvements in hygiene practices, such as handwashing and the availability of safe water, will help to prevent cholera outbreaks. Massive public awareness by governmental and non-governmental organizations would help to reduce unnecessary use of antibiotics without proper medical prescription. This can be done through media communication (such as radio, television, and social media) and face-to-face awareness. Disease control centres should implement the use of artificial intelligence in epidemiologic surveillance. Several factors, such as bad roads, also contribute to AMR. The provision of good roads gives people from rural communities quick access to professional health personnel to avoid un-prescribed and misuse of antibiotics. Clinical approaches such as development of vaccines, probiotics, use of phage therapy, and rapid diagnostic tools will help to reduce unnecessary use of antibiotics by strengthening the previous and developing new antimicrobials and molecular techniques in characterization of the agent. Infectious disease researchers, such as doctors, pharmacists, microbiologists, and others, should be given extra-rewards and grants to conduct research.

Authors' Contributions

All authors contributed in all parts of the study and approved the final version of this article.

Conflict of Interest Disclosures

Both authors declare that they have no conflict of interest.

Ethical Approval

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Review Highlights

What Is Already Known?

Nigeria is a major cholera hotspot, with the highest cholera case fatalities in West Africa in 2021. When left untreated, the disease is fatal. Although many serotypes have been identified, only the O1 and 0139 serogroups are responsible for the majority of cholera outbreaks. Antimicrobial therapy combined with oral dehydration therapy is recommended for the treatment of cholera cases, and the etiological agent is developing AMR.

What Does This Study Add?

This study clearly adds some new findings, such as the efficacy of phage therapy, probiotics, and vaccination, as well as some non-clinical approaches for cholera and AMR control.

References

1. Marin MA, Thompson CC, Freitas FS, et al. Cholera outbreaks in Nigeria are associated with multidrug resistant atypical El Tor and non-O1/non-O139 *Vibrio cholerae*. PLoS Negl Trop Dis. 2013;7(2):e2049. doi:10.1371/journal.pntd.0002049.
2. Mohammed Y, Aboderin AO, Okeke IN, Olayinka AT. Antimicrobial resistance of *Vibrio cholerae* from sub-Saharan Africa: a systematic review. Afr J Lab Med. 2018;7(2):778. doi:10.4102/ajlm.v7i2.778.
3. Garbati MA, Baba AS, Mursal A, Gadzama GB. Circulating serotypes and antimicrobial susceptibility pattern of *Vibrio cholerae* isolates from insurgency-stricken Maiduguri, northeastern Nigeria. Sub-Saharan Afr J Med. 2019;6(1):21-26. doi:10.4103/ssajm.ssajm_12_19.
4. Kamuriwo AT, Gundidza M, Manyuchi P. A retrospective study of antimicrobial resistance of *Vibrio cholerae* O1 serotype Ogawa in the 2018 cholera outbreak in Harare. Pharm Med Sci J. 2021;1:1-8.
5. Deen J, Mengel MA, Clemens JD. Epidemiology of cholera. Vaccine. 2020;38 Suppl 1:A31-A40. doi:10.1016/j.vaccine.2019.07.078.
6. Baine WB, Mazzotti M, Greco D, et al. Epidemiology of cholera in Italy in 1973. Lancet. 1974;2(7893):1370-1374. doi:10.1016/s0140-6736(74)92233-8.
7. Adagbada AO, Adesida SA, Nwaokorie FO, Niemogha MT, Coker AO. Cholera epidemiology in Nigeria: an overview. Pan Afr Med J. 2012;12:59. doi:10.11604/pamj/2012.12.59.1627.
8. Huq A, Yunus M, Sohel SS, et al. Simple sari cloth filtration of water is sustainable and continues to protect villagers from cholera in Matlab, Bangladesh. mBio. 2010;1(1):e00034-10. doi:10.1128/mBio.00034-10.
9. Brown J, Cairncross S, Ensink JH. Water, sanitation, hygiene and enteric infections in children. Arch Dis Child. 2013;98(8):629-634. doi:10.1136/archdischild-2011-301528.
10. Richterman A, Sainvilien DR, Eberly L, Ivers LC. Individual and household risk factors for symptomatic cholera infection: a systematic review and meta-analysis. J Infect Dis. 2018;218(Suppl 3):S154-S164. doi:10.1093/infdis/jiy444.
11. Weil AA, Becker RL, Harris JB. *Vibrio cholerae* at the intersection of immunity and the microbiome. mSphere. 2019;4(6):e00597-19. doi:10.1128/mSphere.00597-19.
12. NCDC attributes 3,604 Cholera's deaths in 2021 to state's denial. The Guardian; 17 February 2022. https://guardian.ng/news/ncdc-attributes-3604-choleras-deaths-in-2021-to-states-denial. Accessed July 25, 2022.
13. Kitaoka M, Miyata ST, Unterweger D, Pukatzki S. Antibiotic resistance mechanisms of *Vibrio cholerae*. J Med Microbiol. 2011;60(Pt 4):397-407. doi:10.1099/jmm.0.023051-0.

14. Ghose AC. Lessons from cholera & *Vibrio cholerae*. Indian J Med Res. 2011;133(2):164-170.
15. Davies HG, Bowman C, Luby SP. Cholera - management and prevention. J Infect. 2017;74 Suppl 1:S66-S73. doi:10.1016/s0163-4453(17)30194-9.
16. World Health Organization (WHO). Cholera fact sheet; 30 March, 2022. https://www.who.int/news-room/fact-sheets/detail/cholera. Accessed May 1, 2021.
17. Sodjinou VD, Talisuna A, Braka F, et al. The 2021 cholera outbreak in West Africa: epidemiology and public health implications. Arch Clin Biomed Res. 2022;6(2):296-307. doi:10.26502/acbr.50170245 .
18. Taraba, Cross River lead as NCDC records over 3,000 suspected cholera cases in 7 months. TheCable; 23 August, 2022. https://www.thecable.ng/taraba-cross-river-lead-as-ncdc-records-over-3000-suspected-cholera-cases-in-7-months/amp. Accessed August 25, 2022.
19. Musa SS, Gyeltshen D, Manirambona E, et al. Dual tension as Nigeria battles cholera during the COVID-19 pandemic. Clin Epidemiol Glob Health. 2021;12:100913. doi:10.1016/j.cegh.2021.100913.
20. Idris I, Adesola RO. Vaccine as a remedy for antimicrobial resistance; what are the Pros and Cons? World News Nat Sciences. 2022;42:76-84.
21. Hsueh BY, Waters CM. Combating cholera. F1000Res. 2019;8:F1000 Faculty Rev-589. doi:10.12688/f1000research.18093.1.
22. Ahmadi MH. Global status of tetracycline resistance among clinical isolates of *Vibrio cholerae*: a systematic review and meta-analysis. Antimicrob Resist Infect Control. 2021;10(1):115. doi:10.1186/s13756-021-00985-w.
23. Mandal S, Mandal MD, Pal NK. Cholera: a great global concern. Asian Pac J Trop Med. 2011;4(7):573-580. doi:10.1016/S1995-7645(11)60149-1.
24. World Health Organization. Antimicrobial resistance. October, 2020. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance. Accessed April 2, 2022.
25. Strathdee SA, Davies SC, Marcelin JR. Confronting antimicrobial resistance beyond the COVID-19 pandemic and the 2020 US election. Lancet. 2020;396(10257):1050-1053. doi:10.1016/s0140-6736(20)32063-8.
26. Garbern SC, Chu TC, Yang P, et al. Clinical and socio-environmental determinants of multidrug-resistant *Vibrio cholerae* 01 in older children and adults in Bangladesh. Int J Infect Dis. 2021;105:436-441. doi:10.1016/j.ijid.2021.02.102.
27. Centre for Disease Control and Prevention. Recommendations for the Use of Antibiotics for the Treatment of Cholera. https://www.cdc.gov/cholera/treatment/antibiotic-treatment.html. Accessed August 26, 2022.
28. World Health Organization. Cholera. October, 2020. https://www.who.int/news-room/fact-sheets/detail/cholera. Accessed April 24, 2022.
29. Hay AJ, Zhu J. Microbiota talks cholera out of the gut. Cell Host Microbe. 2014;16(5):549-550. doi:10.1016/j.chom.2014.10.011.
30. Lin DM, Koskella B, Lin HC. Phage therapy: An alternative to antibiotics in the age of multi-drug resistance. World J Gastrointest Pharmacol Ther. 2017;8(3):162-173. doi:10.4292/wjgpt.v8.i3.162.
31. Adesola RO, Moses OO. Common genetic mechanisms implicated in Antibiotic Resistance. Genetics & Applications. 2022;6(1):1-10. doi:10.31383/ga.vol6iss1pp1-10.
32. Ezemokwe CG, Agwom FM, Okoliegbe I, et al. Complete genome sequence of pseudomonas phage Zikora. Microbiol Resour Announc. 2021;10(30):e0048921. doi:10.1128/mra.00489-21.
33. Delbrück M. The growth of bacteriophage and lysis of the host. J Gen Physiol. 1940;23(5):643-660. doi:10.1085/jgp.23.5.643.
34. Ohnishi M, Kurokawa K, Hayashi T. Diversification of Escherichia coli genomes: are bacteriophages the major contributors? Trends Microbiol. 2001;9(10):481-485. doi:10.1016/s0966-842x(01)02173-4.
35. Chanishvili N. Phage therapy--history from Twort and d'Herelle through Soviet experience to current approaches. Adv Virus Res. 2012;83:3-40. doi:10.1016/b978-0-12-394438-2.00001-3.
36. Jun JW, Shin TH, Kim JH, et al. Bacteriophage therapy of a *Vibrio parahaemolyticus* infection caused by a multiple-antibiotic-resistant O3:K6 pandemic clinical strain. *J Infect Dis.* 2014;210(1):72-78. doi:10.1093/infdis/jiu059.
37. Makumi A, Mhone AL, Odaba J, Guantai L, Svitek N. Phages for Africa: the potential benefit and challenges of phage therapy for the livestock sector in sub-Saharan Africa. Antibiotics (Basel). 2021;10(9):1085. doi:10.3390/antibiotics10091085.
38. Granowitz EV, Brown RB. Antibiotic adverse reactions and drug interactions. Crit Care Clin. 2008;24(2):421-442. doi:10.1016/j.ccc.2007.12.011.
39. Bornside GH. Waldemar Haffkine's cholera vaccines and the Ferran-Haffkine priority dispute. J Hist Med Allied Sci. 1982;37(4):399-422. doi:10.1093/jhmas/xxxvii.4.399.
40. Harris JB. Cholera: immunity and prospects in vaccine development. J Infect Dis. 2018;218(Suppl 3):S141-S146. doi:10.1093/infdis/jiy414.
41. Wierzba TF. Oral cholera vaccines and their impact on the global burden of disease. Hum Vaccin Immunother. 2019;15(6):1294-1301. doi:10.1080/21645515.2018.1504155.
42. Chen WH, Cohen MB, Kirkpatrick BD, et al. Single-dose live oral cholera vaccine CVD 103-HgR protects against human experimental infection with *Vibrio cholerae* O1 El Tor. Clin Infect Dis. 2016;62(11):1329-1335. doi:10.1093/cid/ciw145.