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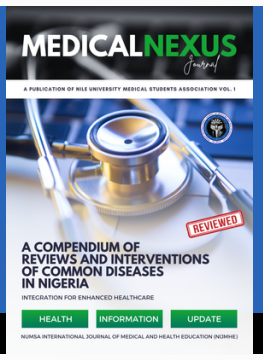

Cholera: A Review

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Abstract

Cholera is an acute diarrheal disease caused by Vibrio cholerae, transmitted primarily through contaminated water and food. This review provides a comprehensive overview of cholera, tracing its historical pandemics, epidemiology, pathophysiology, and clinical manifestations. It highlights the global and local burden of cholera, with emphasis on recurrent outbreaks in Nigeria, where poor sanitation, flooding, and limited healthcare infrastructure exacerbate transmission and mortality. The discussion explores diagnostic methods, treatment strategies such as oral rehydration therapy, intravenous fluids, and antibiotics, alongside preventive measures including vaccination, improved water, sanitation, and hygiene practices. The paper further examines global efforts to combat cholera, notably the WHO's "Ending Cholera: A Global Roadmap to 2030," and outlines challenges such as climate change, vaccine shortages, and weak healthcare systems. Despite advances in treatment and prevention, cholera remains a major public health threat, necessitating coordinated interventions, strengthened surveillance, and sustained global commitment to reduce mortality and achieve long-term control.

Keywords: *Vibrio cholerae, diarrheal disease, Nigeria; water and sanitation; oral rehydration therapy, vaccination, public health challenges*

INTRODUCTION

Cholera is an acute diarrheal infection caused by ingesting food or water contaminated with the bacterium Vibrio cholerae (1). Cholera is a disease that has shaped the course of human history and challenged the fabric of society. Despite efforts to eradicate it, cholera continues to remain endemic in various communities, its eradication an ongoing battle. This review discusses the history of cholera, its biological and clinical features, measures taken, and the challenges faced in its eradication.

CHOLERA PANDEMICS

The origins of cholera are believed to be in the Ganges River Delta in India, where the bacterium naturally occurs (2). The first recorded instances of cholera-like illness date back to texts from ancient India and Greek medicine (3,4). However, the global spread of cholera did not begin until modern times.

The first cholera pandemic occurred in the Bengal region of India, from 1817 through 1824. It spread across Asia to Southeast Asia, the Middle East, Africa, and the Mediterranean. This spread was propagated through trade routes (5). The second cholera pandemic began in 1829 and spread to Europe and the Americas. This pandemic led to the first significant public health reforms, especially in Europe. The third pandemic began in 1852 and lasted till 1860, and is said to have erupted in India. This was considered the most virulent and deadly. It quickly spread to all continents, with Africa being the most affected (6). The third pandemic is known for the 1854 outbreak in London, where Dr. John Snow's pioneering epidemiological work demonstrated that cholera was spread through contaminated water, not air (miasma theory), marking a major advance in public health science (7).

The fourth and fifth pandemics began in 1863 and 1881 respectively and are said to be less severe than the previous pandemics (6). Scientific advancements, including the development of the cholera vaccine by Waldemar Haffkine in 1892, began to reduce the impact of cholera in Europe. (8)

The sixth pandemic lasted from 1899 to 1923 and was especially lethal in India, in Arabia, and along the North African coast. During this period, Europe and North America experienced fewer outbreaks due to improvements in water treatment and sanitation. (6)

The seventh and currently ongoing pandemic began in 1991 in South Asia and spread to Africa in 1971 and America in 1991. The WHO also noted that cholera has become endemic in many countries. In 2017, the WHO announced a global strategy, Ending Cholera: A Global Roadmap to 2030. It was aimed at reducing cholera deaths by 90% by 2030. (1)

Cholera has a notable history in Nigeria, marked by periodic outbreaks and ongoing public health challenges. The disease first appeared in Nigeria during the second cholera pandemic, affecting coastal cities like Lagos. Major outbreaks occurred in the 1970s and 1990s, with the 2009 outbreak in northern regions highlighting the need for improved sanitation and public health infrastructure. Cholera continued to be endemic, with significant outbreaks in 2010 and 2018, driven by poor sanitation and access to clean water. (9)

From 2021 to 2022, Nigeria faced severe outbreaks, exacerbated by flooding and conflicts, prompting government and international responses, including vaccination campaigns.

In 2024, Nigeria experienced a severe cholera outbreak with cases rising by 220% compared to the previous year. As of October 2024, the Nigeria Centre for Disease Control (NCDC) reported over 10,800 suspected cases and 359 deaths, significantly higher than in 2023. Lagos state has been particularly affected, contributing 43% of the national total, while Adamawa, Jigawa, Kano, Borno, and Katsina states have also reported high case numbers. (10)

EPIDEMIOLOGY

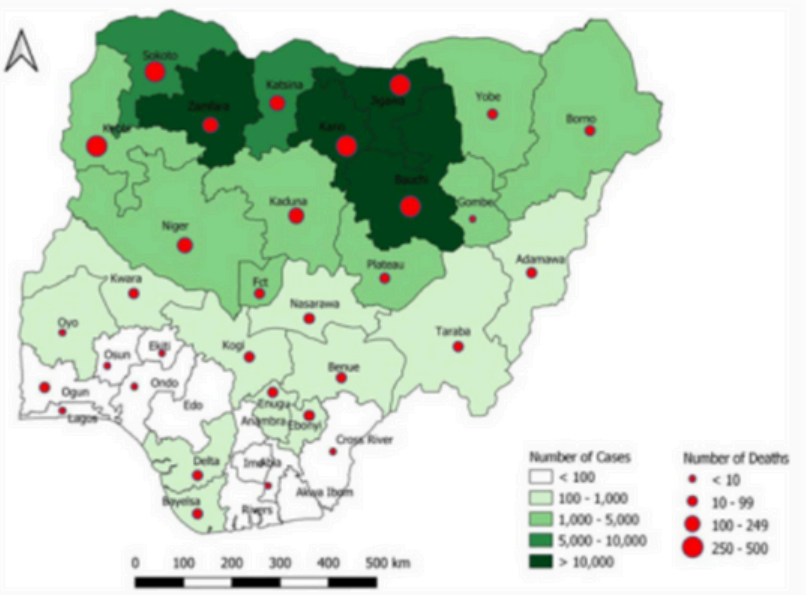
Vibrio cholerae is estimated to be the cause of 3 million instances of diarrheal disease and 100,000 fatalities globally each year. However, accurate estimates of the morbidity and death attributed to cholera are lacking due to the disease being largely underreported.

Cholera mostly affects areas with poor access to sanitary facilities and clean water; it can spread both endemically and epidemically. Approximately 50 countries, primarily in Asia and Africa, have recorded cholera cases in the last five years, making them endemic.

V. Cholera-related epidemics have spread to South and Central America, Africa, Asia, the Middle East, and the Caribbean. Epidemics can occur over a large geographic region; for instance, the strain implicated in the 2010 outbreak in Haiti was subsequently associated with outbreaks in the neighboring countries of the Dominican Republic, Cuba, and Mexico. (11)

Nigeria reported 2102 cases and 63 deaths with a Case Fatality Rate (CFR) of 3% across 33 states since January 2024. In 2024, Nigeria reported 1094 new cases of cholera and 41 related fatalities, yielding a CFR of 3.7%. Compared to the preceding month, there has been an 1143% increase in cases and a 1950% increase in deaths. The spike in cases in June was especially concerning, especially because almost half of all cases reported in the nation this year have occurred in Lagos state. (12)

Below is a map showing the distribution of cholera in Nigeria. (13)



TRANSMISSION

Cholera is primarily transmitted through the consumption of water or food contaminated with the bacterium Vibrio cholerae. The main routes of transmission include:

- **Contaminated Water**: The most common means of transmission is drinking water contaminated with Vibrio cholerae, often due to poor sanitation systems.
- **Contaminated Food**: Food exposed to unsanitary conditions or contaminated water can harbor cholera bacteria.
- **Person-to-Person Contact**: Direct contact with an infected person's feces or vomit can transmit cholera.
- **Fecal-Oral Transmission**: The bacteria spread when fecal matter contaminates food or water, common in areas with poor sanitation.
- **Environmental Reservoirs**: The bacteria can survive in brackish waters and within aquatic organisms, acting as sources for human outbreaks.

AETIOLOGY

The development of the diarrheal disease cholera is attributed to the consumption of food or water contaminated by the toxigenic strains of microorganisms, *Vibrio cholerae*, and subsequent intestinal colonization. The intestinal colonization by the microorganism is initiated by feco-oral ingestion of the organism, directly insinuating a compromise in water integrity, contamination via fomites (hand to mouth), or exposure of food to the action of mechanical vectors of the bacteria. Freshly shed feces are highly infectious 24 hours after release into the environment and can survive for long periods outside the body, greatly increasing the rate of infection. These forms of transmission are more common in developing countries and countries ravaged by war or famine (14).

FACTORS THAT PLAY A ROLE IN THE SPREAD OF CHOLERA

- **Environmental Factors**: V. cholerae has two major reservoirs: humans and water.
- **Host Factors:** Malnutrition increases susceptibility to cholera (15). Blood type O also has twice the incidence rate, but the cause is unknown (15).

Infection rates are lower in regions where the disease is endemic. Large outbreaks of the disease are linked to contamination of the communal water supply with the feces of an infected host.

PATHOPHYSIOLOGY

Due to the intestinal tropic nature of the organism, the organism must pass through the upper GI tract and the stomach, surviving the low pH of the gastric secretions to perform its pathogenic effects. However, the organism is not resistant to the acidic nature of the stomach and requires a large inoculum size to survive (15).

the infectious dose of V. cholerae required to exert pathophysiological effects may vary depending on the method of contamination.

Via Water: 10^3 – 10^6 organisms [15]

Via Food: 10^2 – 10^4 organisms [15]

The gastric susceptibility to V. cholerae can be greatly increased by the regular use of antacids, histamine receptor blockers, and proton pump inhibitors.

Toxic strains of the organisms elicit clinical disease by releasing enterotoxins that promote the secretion of fluids and electrolytes into the lumen of the small intestine.

Enterotoxin comprises an A1 subunit that activates adenylate cyclase to increase cAMP. cAMP then inhibits the absorption of sodium and chloride from the microvilli, increasing the secretion of chloride and water from the crypt cells.

The result is watery diarrhea with isotonic electrolyte concentrations to those of plasma, leading to severe dehydration and probable death. (14-18)

CLINICAL PRESENTATION

Cholera is characterized by three cardinal signs: Diarrhoea, Vomiting, and Dehydration

- **Diarrhea**: Profuse watery diarrhea is a hallmark of cholera. Cholera should be suspected if a patient above 5 years develops severe dehydration (14). Patients with severe disease may have a stool volume of more than 250mL/kg body weight per day (19), producing a rice water-like stool in appearance.
- **Vomiting**: Vomiting may be caused by associated symptoms of cholera, such as acidaemia (19), or may not be present at all.
- **Dehydration**: If left untreated, diarrhea and vomiting lead to isotonic dehydration, which can lead to acute tubular necrosis and renal failure (19). The dehydration ensuing from the disease therefore produces a water loss proportional among the three fluid compartments of the body. (19)

DIAGNOSIS OF CHOLERA

Diagnosing cholera requires a combination of clinical suspicion, especially in regions where cholera is endemic or during outbreaks, and laboratory confirmation to establish the presence of Vibrio cholerae.

When to Suspect Cholera?
Cholera should be considered in any patient presenting with acute watery diarrhea, particularly if rapid and severe dehydration occurs. The World Health Organization (WHO) provides specific guidelines for cholera diagnosis based on the geographical context and outbreak status:

- **In areas where cholera has not been declared:**

For patients aged 2 years and older, cholera should be suspected if they present with acute watery diarrhea (defined as 3 or more loose stools per day, lasting no longer than 14 days) accompanied by severe dehydration or in cases where they die from acute watery diarrhea with no other plausible cause.

A confirmed case of cholera is defined as any person infected with Vibrio cholerae O1 or O139, confirmed by stool culture, serological agglutination, or polymerase chain reaction (PCR).

- In areas where a cholera outbreak has been declared:

Any person presenting with acute watery diarrhea, or who has died from acute watery diarrhea should be suspected of cholera.

OUTBREAK DEFINITIONS

- **A suspected cholera outbreak** is identified when two or more suspected cholera cases, or one suspected cholera case with a positive rapid diagnostic test (RDT), are reported within the same surveillance unit within 7 days.
- **A probable diagnosis** is made when the number of suspected cholera cases with a positive RDT result surpasses a pre-defined threshold, taking into account the number of suspected cases tested.
- **A confirmed cholera outbreak** is established when at least one locally acquired case of cholera is confirmed within a surveillance unit.

CLINICAL DIAGNOSIS

Cholera presents with characteristic symptoms, and a high index of suspicion is critical, particularly during outbreaks or in endemic regions. The hallmark features of cholera include:

- Profuse watery diarrhea (often described as "rice water stool" due to its pale, milky appearance).
- Vomiting, frequently without nausea.
    - Signs of severe dehydration, including:

- Dry mouth and tongue
- Low blood pressure
- Rapid pulse
- Loss of skin turgor
- Intense thirst

LABORATORY DIAGNOSIS

Laboratory confirmation plays a crucial role in the definitive diagnosis of cholera. Several methods can be used:

- **Stool Culture:** The gold standard for cholera diagnosis, stool culture involves isolating Vibrio cholerae using selective media, such as Thiosulfate Citrate Bile Salts Sucrose (TCBS) agar. Alternative media, such as Tellurite Taurocholate Gelatin Agar (TTGA), can also be used. Once cultured, further identification can be performed using biochemical tests or serotyping to determine the specific strain (O1 or O139).
- **Dark-Field Microscopy**: This method detects the motility of Vibrio cholerae and can provide a preliminary diagnosis. However, it is not commonly used due to its lower sensitivity and specificity.
- **Polymerase Chain Reaction (PCR)**: PCR is a highly sensitive and specific method for detecting Vibrio cholerae DNA in stool samples. Despite its accuracy, it requires specialized equipment, which limits its use in resource-poor settings.
- **Rapid Diagnostic Tests (RDTs)**: When laboratory facilities are unavailable or limited, the Crystal VC RDT can be used to screen stool samples for Vibrio cholerae O1 or O139. A dipstick is employed to detect the presence of the cholera pathogen. However, like dark-field microscopy, RDTs lack sensitivity and specificity, and a positive result should be confirmed by stool culture for definitive diagnosis.

DIFFERENTIAL DIAGNOSIS

Symptoms such as watery diarrhea and dehydration are not unique to cholera and can be found in a wide range of diseases, such as rotavirus infection, enterotoxigenic E coli infection, giardiasis, and norovirus infections, all present with acute diarrheal diseases. It is important to distinguish cholera by carrying out efficient laboratory testing [21]

TREATMENT

The treatment of cholera should be immediate

due to the presence of severe dehydration that can lead to shock and ultimately death within hours. The main goal of treatment focuses on rapid rehydration to replace the extensive loss of body fluids and electrolytes.

REHYDRATION THERAPY

- **Oral rehydration salts**- it is a fluid mixture made of glucose, sodium, potassium, and chloride. The WHO/UNICEF standard sachet is to be dissolved in 1 liter of clean water, although adults may need about 6 liters to treat moderate dehydration on day 1 of treatment. The WHO recommends using low-osmolality ORT, and it should be administered in small, frequent sips, regardless of whether vomiting is present or not. [23]
- **Intravenous fluids**- Recommended in cases of severe dehydration or shock where a patient can't drink enough ORS. Ringer's lactate is the preferred solution because it contains more vitamin K and bicarbonate[24]
- **Antibiotics** –This is only required in severe cases/endemic areas. It is given to shorten the duration of diarrhoea and reduce the volume of rehydration fluid required. Common drugs such as azithromycin, doxycycline, and ciprofloxacin. Antibiotics should serve as an adjunct to, rather than a replacement for, rehydration therapy. [24]
- **Zinc supplementation in children**—zinc decreases the duration and severity of diarrhoea in children, and it also serves as an adjunctive therapy.[23]
- **Nutrition**- patients should start feeding with clean, safe, and healthy foods as soon as it is possible to do so; breastfeeding should continue.[23]

PREVENTION AND CONTROL

Prevention and control focus on reducing the transmission of V. cholerae; emphasis should be made on improving water quality, hygiene, environmental sanitation, and vaccination.

- **Water supply** – effective water treatment is essential to prevent the outbreak of cholera. Measures such as boiling, filtration, chlorination, and safe storage should be carried out.[25]
- **Hand hygiene**- Washing of hands with soap and water and using an alcohol-based hand sanitizer should be done after toilet use, before and after eating, and before and after food preparation. [25]
- **Food hygiene**- raw, undercooked food, mostly seafood (especially shellfish) should be avoided, and fruits and vegetables should be peeled before eating.[25]
- **Environmental sanitation**-- Proper sewage disposal in clean and functional latrines/toilets tends to reduce transmission; pit latrines should be dug away from water bodies (wells included). Open defecation should be abolished in communities.[25]
- **Surveillance and early detection**- cholera surveillance systems are necessary in high-risk regions to monitor the outbreak of cholera and efficiently detect cases so that rapid response can be initiated to limit the spread. (23)
- **Community awareness programs** - The people should have extensive knowledge of cholera and its preventive measures. Campaigns should be organized using radio, social media, posters, community meetings, and school programs to educate people on cholera prevention and actions to take during an outbreak. [23]

ORAL CHOLERA VACCINES (OCVS)

Currently, there are three WHO-prequalified oral cholera vaccines:

- **Dukoral**: This vaccine is a killed whole-cell vaccine that includes the cholera toxin B subunit. It requires administration with a buffer solution (sodium bicarbonate) to enhance its efficacy. Dukoral is recommended for individuals aged 2 years and older, and it requires two doses for optimal protection, with the second dose administered at least one week after the first.
- **Shanchol**: A bivalent vaccine containing killed cells of Vibrio cholerae serogroups O1 and O139. It does not require a buffer for administration, making it easier to deploy in resource-limited settings. Shanchol is also administered in two doses, with the second dose recommended at least two weeks after the first. This vaccine is safe for all age groups, including infants as young as one year.
- **Euvichol-Plus**: Similar to Shanchol, Euvichol-Plus is a bivalent vaccine that protects against both O1 and O139 serogroups. It also does not require a buffer for administration and requires two doses for optimal protection. Clinical studies have demonstrated its safety and efficacy.

Efficacy and Duration of Protection: The protective efficacy of OCVs typically ranges from 65% to 85% in the first six months post-vaccination, gradually declining over time. Booster doses may be necessary to maintain immunity, particularly in high-risk populations or areas with ongoing cholera transmission.

Recommendations for Use: OCVs are recommended for individuals living in or traveling to endemic areas, especially during outbreaks. They are particularly beneficial for high-risk groups, including children under five, individuals with compromised immune systems, and populations residing in cholera-prone regions. The integration of vaccination with other cholera prevention strategies, such as improved water, sanitation, and hygiene (WASH) interventions, is crucial for effectively reducing cholera incidence.

INJECTABLE CHOLERA VACCINES (ICVS)

In addition to oral vaccines, there are also injectable cholera vaccines, which are typically less commonly used due to their limitations in terms of accessibility and acceptability.

- **Whole-Cell Vaccines:** These vaccines consist of killed whole cells of Vibrio cholerae. Historically, they were used in some countries but have largely been replaced by oral vaccines due to the lower acceptance of injections in many populations. The protective efficacy of injectable whole-cell vaccines is variable and often requires multiple doses.
- **Subunit Vaccines**: Research into subunit vaccines, which target specific components of the cholera toxin, is ongoing. These vaccines aim to elicit a strong immune response with fewer side effects. However, as of now, there are no WHO prequalified injectable subunit cholera vaccines available for public use.

Limitations of Injectable Vaccines: ICVs may be less desirable in endemic regions due to the need for healthcare infrastructure to administer injections and the potential for increased pain and discomfort compared to oral vaccines. They may also require multiple doses to achieve effective immunity, which can be logistically challenging in outbreak settings.

CHALLENGES IN MANAGING CHOLERA

- **Climate Change**: the rising global temperatures and extreme weather events such as floods and droughts have exacerbated the epidemics of cholera by increasing water contamination and limiting clean water access. In the prelude to the 2022 United Nations Climate Change Conference (COP27), it was noted that floods and rising sea levels have affected environmental hygiene, leading to waterborne and diarrhoeal diseases, with extreme weather conditions negatively impacting water supply. [28] [31]
- **Inadequate access to clean water, sanitation, and hygiene (WASH):** This particularly occurs in rural areas, overcrowded environments, camps for refugees and internally displaced people, and conflict-affected areas. These regions are exposed to open defecation, poor hygiene, and the use of unsafe water sources. [29][31]
- **Shortage of cholera vaccines**: The cholera vaccine shortage in Nigeria in 2024 is driven by both global and local challenges. On a global scale, the supply of oral cholera vaccines (OCVs) has not kept pace with rising demand, as countries around the world face increasing outbreaks. This global supply constraint severely affects Nigeria's ability to secure enough vaccines for its population. Logistical challenges within Nigeria, such as inadequate cold chain infrastructure and difficulties reaching remote or conflict-affected areas, further complicate vaccine distribution. Additionally, with the surge in cases, the demand for vaccines has exceeded supply, forcing health authorities to prioritize hotspots, leaving other regions vulnerable. Financial and political constraints also play a role, as limited resources and inconsistent government support have delayed and disrupted vaccination efforts. [29]
- **Inadequate healthcare infrastructure**: this includes limited access to healthcare facilities, a shortage of trained healthcare workers, and an inadequate surveillance and response system. These factors combined make it difficult to detect and respond to a cholera outbreak promptly. The Nigeria Centre for Disease Control (NCDC) has reported that out of Nigeria's over 700 local government areas, many do not have functioning health facilities capable of providing timely treatment for cholera. [29]

GLOBAL EFFORT AND FUTURE DIRECTIONS

Global Task Force on Cholera Control (GTFCC) is a network of governmental and non-governmental organizations, UN agencies, and scientific partner institutions that helps coordinate activities for cholera control. This initiative, led by the WHO, is a coalition of organizations working to reduce cholera deaths by 90% by 2030 through targeted vaccination campaigns, improving healthcare, and long-term preventive strategies. [26] In October 2017, GTFCC partners launched a strategy for cholera control: Ending Cholera: A Road Map to 2030. The global road map focuses on three strategies:

- **Early detection and quick response to contain outbreaks**: this strategy focuses on containing outbreaks, through early detection and rapid multisectoral response, including community engagement, strengthening surveillance and laboratory capacity, health systems and supply readiness, and supporting rapid response teams.
- **A targeted approach to improve prevention**: this involves multi-sectoral cooperation of partners and countries to focus on specific geographic areas that experience a high incidence or prevalence of cholera cases. Cholera transmission can be stopped in these areas through measures including improved WASH and the use of oral cholera vaccines.
- **Coordination of human, technical, and financial resources**: the processes of coordination and partnership occur at local and global levels. This provides a strong framework to support countries and intensify efforts to control cholera, building upon country-led cross-sectoral cholera control programs and supporting them with human, technical and financial resources.[26] [27] With the commitment of countries, partners, and donors, the GTFCC is working to achieve the goals in the global roadmap.
- **Future Vaccine Strategies**: A single dose of an OCV induces a vibriocidal response among exposed populations, as observed in previous clinical trials. A single dose of an OCV was shown to be efficacious (57%) among those above 5 years of age, however, no protective efficacy was observed for those below 5 years of age. Studies on the use of booster doses of OCVs have been conducted in Bangladesh, which showed that children who received a single dose of an OCV 3 years earlier showed significantly increased vibriocidal antibody responses after receiving one booster dose of an OCV compared to those who did not receive an OCV earlier. These results suggest that boosting with one dose of an OCV augmented the immune responses in children. [32]

Large campaigns of two doses of an OCV were conducted in 2017 among the Rohingya population in Bangladesh. The study revealed a significant increase in vibriocidal antibody titers 14 days following the first dose of the OCV. Similarly, another study

conducted during a humanitarian crisis in South Sudan showed that only one dose of an OCV was immunogenic and induced short-term antibodies. [32]

CONCLUSION

Vibrio cholerae causes periodic cholera epidemics in several regions around the globe. The disease requires immediate treatment as it can lead to death within hours in patients with moderate to severe cholera. With the development of i.v. fluids, ORS, and Zinc therapy, progression to severe dehydration and mortality. [32]

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