International Journal of Multidisciplinary Research and Development
Online ISSN: 2349-4182, Print ISSN: 2349-5979; Impact Factor: RJIF 5.72
Received: 13-07-2019; Accepted: 15-08-2019
www.allsubjectjournal.com
Volume 6; Issue 10; October 2019; Page No. 77-81

Cholera Disease and its challenges with a focus on vaccine scenario: A Review

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Abstract
Cholera is a potentially epidemic and clinically indistinguishable from other causes of watery diarrheal illness characterized by the profound and rapid loss of fluid and electrolytes, abdominal discomfort and vomiting. The causative agent belongs to the members of the species Vibrio cholerae which are found in water or food contaminated with faeces. In developing countries, where the population is high, cholera is the main cause of epidemic diarrhoea. In India, cholera is endemic in the Ganges and Brahmaputra deltas of Indian subcontinent. Cholera continued to be a major global problem during the years 2010–2017, with large epidemics affecting people in Haiti and Yemen, and surges in endemic disease in areas of sub-Saharan Africa and Asia. Prospective population-based cholera surveillance in an African sentinel network showed an incidence of 0.3/10 000 in endemic settings that increased to <20/10 000 during epidemics. The incidences of cholera disease were mostly recorded in Africa and southern Asia, with about 99% of all cases occurring in these regions. Approximately 1.3 billion people are at risk of cholera in endemic countries. An estimated 2.86 million cholera cases occurs annually in endemic countries. Among these cases, there are an estimated 95,000 deaths (uncertainty range: 21 000 – 143 000). As per WHO the incidence rates are 2–4 times higher than those of the overall population, with children aged <2 years having by far the highest incidence rates (8.6/1000 in Kolkata and 3.2/1000 in North Jakarta). Preventive measures include a clean water supply and appropriate sanitation. Oral cholera vaccines elicit immune response of a longer shelf life and good memory. These vaccines may be particularly useful as part of cholera prevention programs in endemic or epidemic areas. The primary treatment of cholera includes intravenous rehydration and oral rehydration. Antibiotics play a secondary role in the treatment of cholera by shortening the length of cholera diarrhoea. Cholera outbreaks are influenced by environmental factors and geographical frames as it influences the Vibrio cholerae dynamics. Population density, urbanization and overcrowding also influence cholera transmission. It is also closely associated with the social and behavioral aspects of individuals as well as communities. Each year, many cholera outbreaks are reported from different regions of the world. These outbreaks have negative impact on social and economic conditions of the affected countries.

Keywords: Vibrio Cholerae, Cholera Disease, O1/O139, Oral Cholera Vaccine (OCV), Cholera Toxin (CT)

1. Introduction
Vibrio cholerae is a Gram-Negative Comma-Shaped Bacterium that causes Cholera, a harmful bacterial disease. Ingestion of contaminated water and food is the primary cause of the disease. It is believed that the natural reservoir for the bacterium is human, but some new evidence suggests that it is the aquatic environment [1]. Without treatment, this bacterial infection may become fatal. WHO position paper on Cholera vaccines published in August 2017 suggested that a total of 172 454 cholera cases and 1304 deaths were reported to WHO by 42 countries in the year 2015. However, this indicates that the actual number of cholera cases that were occurring may vary from reported cases. This contradiction in the reporting of results can be attributed to lack of diagnostic facilities, inadequate disease surveillance and reporting and fear of the economic impact on trade and tourism. The estimated actual burden of cholera is in the vicinity of 3 to 5 million cases and 100,000 to 130,000 deaths per year [2].
The disease is endemic to parts of Africa, Asia, the Middle East, and South America. African and South Asian regions are mostly under the burden of cholera disease which accounts for almost 99% of all cases which were occurring. The Cholera toxin secreted by the Vibrio cholerae acts on the mucosal epithelium of the human and causes the characteristic diarrhoea symptom of the disease. A healthy person infected with the bacteria may show signs of disease after an incubation period of 24 hours to 5 days. The characteristic symptom of cholera is watery diarrhoea which causes loss of fluids resulting in dehydration and then death [18]. *Vibrio cholerae* was first described in 1854 in Italy by Pacini as large number of curved bacteria in the intestine of cholera victims. In 1883, Robert Koch studied that cholera was caused by a comma shaped organism named Kommabazillen. Subsequently, the name was changed to *Vibrio cholerae* [3]. There are many serotypes of *V. cholerae* in addition to O1 and O139. These bacteria may cause diarrheal illness, but the resulting infections are not associated with epidemic disease. The serogroup O1 *V. cholerae*, have two serotypes, Ogawa and Inaba and these can be identified by agglutination with specific antisera. A third serotype, Hikojima has the ability to agglutinate with both the Ogawa and the Inaba antisera. The serotype is useful as a marker of the epidemic strain. The serogroup O1 has two major biotypes known as classical and El Tor [4]. The major surface antigen on *V. cholerae* is based on the O-antigen variation. *V. Cholerae* is classified into 206 O serogroups [5], toxigenic *V. cholerae* belonging to the O1/139 serogroups are the causative agents of cholera and acute dehydrating diarrhoea that occurs in epidemic form.

There are now two serogroups O1 and O139 that have been associated with epidemics of cholera [6].

2. Epidemiology

In 1817, first pandemic of Cholera occurred from traditional Ganges region of Asia [7, 8]. But it has spread worldwide and mostly affected developing countries. The second pandemics originated in Bengal in 1826 and reached Punjab after affecting UP and Delhi in 1827. The third pandemic, following a recrudescence in India, was conspicuous for its spread to countries that were till then not seriously affected by the disease. The fourth pandemic was a major epidemic in Mecca in 1865. The fifth cholera pandemic caused considerably less havoc than the previous four pandemics. In sixth pandemic, cholera cases in India had begun rising since 1899 and there were major outbreaks in Calcutta and Bombay in 1990. High mortality rates made regions of Bengal, coastal Orissa and some districts of Assam and Bihar, the endemic home of classical cholera. The seventh pandemic, in 1965, E1 tor cholera was reported from Delhi, Gurgaon, Surat and Madras. West Africa and Ghana were also affected by cholera during the seventh pandemic. Between 1841 and 1865, the annual reported deaths due to cholera in Calcutta ranged from 2,500 to 7,500. Incidence of El tor cholera during 1962 was 13,393 cases with 1,977 deaths [9].

The cholera cases and deaths in India were reported to WHO regularly from 1997 to 2006 and over the 10-year period, the average number of cases reported annually was 3631. The case fatality rate showed a somewhat decreasing trend (range: 0.57–0.07) [10].

Each year cholera epidemics spurt out simultaneously in many places in different countries round the world. In endemic regions, the majority of cases occur among children less than 5 years of age and in reproductive-age women. Malnourished children and people with low immunity, such as HIV cases, have a higher mortality risk from cholera infection as compared to the normal population. Recurrence of epidemic cholera has also been related to climatic factors [8].

The documented evidences also reported cholera outbreaks after cyclones in regions such as West Bengal and Odisha. The large number of human gatherings such as in "Kumbh Mela" has given history of cholera outbreaks. In recent years, with development of effective cholera vaccines that are easily delivered orally, these events serve as an opportunity to intervene with vaccines [11].

3. Symptoms

The symptoms of the cholera disease usually exhibits 1–3 days after ingestion of contaminated food or water and can be mild to moderate, but in 20% of cases, severe life-threatening fatal conditions appear. It has been estimated that classical strains are more virulent than El Tor strains. The incubation period of cholera is dependent on inoculum size and ranges from several hours to 5 days. The onset of the clinical manifestation may be sudden profuse watery diarrhea followed by anorexia and abdominal discomfort in some cases. Initially the stool will be dark brown with solid nature; gradually it turns to whitish watery stool giving a rice water appearance [12]. This is the characteristic feature of cholera which is useful in diagnosis of cholera and differentiates it from other gastrointestinal infections. The fluid loss via vomiting and excessive diarrhoea is due to the action of enterotoxins produced by the *V. cholera,* which is cytotoxic and have the ability to alter the permeability of the intestinal epithelial cells by creating pores. Due to which the process of osmosis takes place and water and other fluid substances flow out of the body leading to massive diarrhoea and dehydration. In cholera gravis the rate of diarrhoea reaches a maximum to 600–1000 ml/h leading to hypotension, tachycardia and vascular collapse [12].

4. Pathogenesis

In the epidemic cases the feces of diseased person acts as a source of infection. Identification of source of infection is necessary for appropriate and effective prophylaxis of the disease. Invasion begins as soon as the bacterium colonizes in epithelial layer of the small intestine by penetrating the mucous. Mucolytic enzymes help in penetration of the mucous and destroy the mucous integrity, and also the long tail of the invading organism allows it to propel itself through the thick mucosal layer. Pili help the bacterium to attach onto the microvilli of the small intestine. An endotoxin produced by the bacteria is called Cholera toxin (CT) plays a major role in virulence mechanism. So it is proved that only strains that produce CT are able to cause cholera [13].

The CT is comprised of six protein subunits: one A subunit and five copies of B subunits, generally denoted as AB5. B subunit is known as the binding factor as it binds to the GM1 ganglioside receptor of the epithelial cells of the small intestine. Once bound with the target cells, it forms a toxin complex which is then endocytosed by the cell. After the process of endocytosis, the enzymatic activation of A subunit occurs leading to increased adenylate cyclase activity, which increases the concentration of cAMP to >120-folds. This in turns leads to increased permeability of the chloride channels subsequently mediating the efflux of more ATP-mediated chloride ions and secretion of mere H_2O, Na+, K+ and HCO_3 − into the lumen of the intestine [14, 15, 16]. The increased absorption of water as well as electrolytes is responsible for the massive dehydration leading to the clinical symptoms of cholera.

5. Diagnosis

It is difficult to distinguish between a single patient with cholera and patient infected by another pathogen that causes acute watery diarrhea without testing a stool sample. Most cases of cholera are presumptively diagnosed based on clinical suspicion in patients with severe acute watery diarrhoea. The diagnosis can be confirmed by isolation of *V. cholerae* bacteria from faecal samples and culturing on selective media. Rapid tests such as stool dipsticks or darkfield microscopy can support the diagnosis in settings where stool culture is not readily available. According to the World Health Organization, cholera should always be suspected when a patient five years or older develops severe volume depletion from acute watery diarrhoea, even in an area where cholera is not known to be endemic [17]. Isolation and identification of *Vibrio cholerae* serogroup O1 or O139 by culture of a stool specimen is the gold standard for the laboratory diagnosis of cholera. Stool samples can be transported in Cary Blair media and isolation and identification can be performed on the selective thiosulfate citrate bile salts agar media. More advance and accurate techniques such as polymerase chain reaction (PCR) methods are also available for disease confirmation, but it

requires enhanced laboratory capacity [18]. Some Rapid test kits for the confirmation of cholera are also available in the market. SD BIOLINE Cholera Ag O1/O139 kit is based on a rapid immunochromatographic assay for qualitative detection of *Vibrio cholera* O1/O139 in human faecal. Crystal VC Rapid Diagnostic Test (RDT) Procedure kit is used to detect O1/O139 Ag and based on dipstick method.

6. Treatment

Most people infected with the cholera bacterium have mild diarrhoea or no symptoms at all. Only about 5-10% of persons infected with *Vibrio cholerae* O1 may have illness requiring treatment at a hospital [19]. The majority of people can be treated by quick administration of oral rehydration solution (ORS). Rapid administrations of intravenous fluids were required in case of severely dehydrated patients. Mass administration of antibiotics is not recommended, as it has no proven effect on the spread of cholera may contribute to antimicrobial resistance. Zinc is an important adjunctive therapy for children under 5, which also reduces the duration of diarrhoea and may prevent future episodes of other causes of acute watery diarrhoea.

Doxycycline is the recommended first choice for treatment of all patients including adults, children and pregnant women. Ciprofloxacin or azithromycin are alternatives in situations where there is doxycycline resistance. Antibiotic sensitivity testing should be performed on a representative sample of isolate to guide treatment during an outbreak, but is not required for individual cases. Resistance to first-line antibiotics and multidrug resistance occur frequently and have been associated with more severe illness and higher rates of secondary infection. Drug resistance is a frequent occurrence in cholera-endemic areas and can complicate the treatment of cholera and increase treatment costs [18].

7. Prevention and Control

A multifaceted approach is the key to control cholera, and to reduce deaths. To prevent the disease from infecting the peoples it is necessary to provide basic amenities such as portable drinking water, awareness about the hygienic conditions and sanitation, surveillance of affected areas, social mobilisation, treatment, and oral cholera vaccination. A clean water supply and appropriate sanitation are the important aspects of cholera prevention. An estimated 760 million people lack access to clean water sources and are thus at risk for waterborne diseases such as cholera [20].

For cholera prevention the establishment and enforcement of standard sanitation laws for food industries, including food vendors and interventions to promote hand washing with soap and safe food handling are also important. Cholera vaccination is a secondary preventive tool to control the disease, but the government agencies need to focus on primary facilities such as supplying safe water and sanitation [18].

8. Current scenario of Oral Cholera Vaccines:

For residents in endemic areas, WHO recommends the inclusion of oral cholera vaccines in cholera control programs in endemic areas, in conjunction with other prevention and control strategies [21]. WHO also recommends that oral cholera vaccines to be considered as part of an integrated control program in areas at risk for a cholera outbreak [22]. Observational data suggest that vaccination following the onset of an epidemic is effective in reducing the risk of cholera [23], even if only a single dose can be given [24].

Cholera is an acute diarrhoeal illness caused by toxigenic strains of *Vibrio cholerae* serogroups O1 and O139. Presently, *V. cholerae* O1 belonging to the El Tor biotype is the most common serogroup in India, while the frequency of serogroup O139 has declined considerably over the past few years [25]. Acknowledging that cholera is a significant public health threat in south-eastern Asia will allow policy-makers to target control interventions in high-risk areas. Vaccines may be another preventive strategy that can be more feasible in cholera-endemic countries. They may be used in addition to other traditional cholera control strategies, along with improved access to safe water and adequate sanitation [26].

Given the availability of two OCVs (one prequalified and the other pending prequalification by WHO) and new data on their efficacy, field effectiveness, feasibility and acceptance in cholera-affected populations, these vaccines should be used in areas where cholera is endemic, particularly in those at risk of outbreaks, in conjunction with other prevention and control strategies [26]. Of the two OCVs, the low-cost bivalent inactivated whole-cell OCV known as Shanchol® (Shantha Biotechnics Ltd., Hyderabad, AP, India) is now licensed in India following clinical trials in Viet Nam [27] and in the city of Kolkata [28, 29].

A safe, inexpensive and efficacious cholera vaccine has thus become available in India after almost three decades of non-availability of any cholera vaccine in India. Shanchol® traces its lineage to the original bivalent ORC-Vax® (VaBiotech, Hanoi, Viet Nam) that was licensed in Vietnam in 1997. In collaboration with the manufacturer, the International Vaccine Institute (IVI) modified the ORC-Vax® by altering the cocktail of immunizing strains, which resulted in an increase in the lipopolysaccharide content [30].

Another live oral attenuated cholera vaccine known as VA1.4, created in India and manufactured by Shantha Biotechnics, Ltd., will shortly undergo phase III field trials in Kolkata [31]. Hilleman Laboratories, a vaccine developer, has entered into a collaboration with Bharat Biotech in India for further development, manufacturing and commercialisation of Hillchol, its next generation oral cholera vaccine. HillChol, will be taken into phase three of clinical trial by Bharat Biotech.

The World Health Organisation (WHO) has pre-qualified three oral vaccines—Dukoral, developed by Swedish company Valneva, Shanchol, developed by Shanta Biotech (now owned by French vaccine maker Sanofi, and Euvichol, manufactured by South Korea's Eubiologics Dukoral is administered with a buffer solution that, for adults, requires 150 ml of clean water. Dukoral vaccine can be given to all individuals over the age of 2 years and the gap between the 2 doses should not be more than 6 weeks, Children aged 2 - 5 years require a third dose of Dukoral vaccine. Shanchol and Euvichol-Plus are liquid vaccines produced by two different manufacturers. They are given to all individuals over the age of one year. There must be a minimum of two weeks delay between each dose of these two vaccines. Two doses of Shanchol and Euvichol-Plus provide protection against cholera for three years, while one dose provides short term protection [32].

9. Conclusion

Rapid urbanization and population growth present increasing and competing demands for water and it is

evident that the risk for cholera would increase without timely intervention. The foundation for any effective control or response measure for cholera largely depends on availability of reliable epidemiological data [33]. Although mortality due to cholera has reduced significantly in India, the number of cases due to the disease remains very high. The Global Task Force on Cholera Control of WHO has also been revitalized and has launched a Global Roadmap to end cholera by 2030. India has an opportunity to work with global partners to improve detection, mobilize resources and act against cholera. With the Swachh Bharat Abhiyan, a program led by the Prime minister's office, there is already an emphasis on improving access to improved sanitation and toilets.

Despite the emergence of improved sanitation, antimicrobial therapy and vaccine development, cholera still remains a global threat. The current control strategies have an infinite no. of challenges and are not effective in the areas with high burden of cholera. With political instability, increasingly displaced populations from wars, global warming, emerging variant of cholera strains; cholera control has again become a WHO priority. Ending Cholera-A Global Roadmap to 2030 was implemented. Access and distribution of the OCV stockpiles should be readily available to population at risk and should follow the stockpile management mechanisms [34]. Identifying the areas with high burden of cholera disease and target vaccination will be cost effective in controlling outbreaks in endemic areas. The development of new generations of OCVs, cost-effectiveness of Vaccine campaigns, new vaccine distribution strategies and Public awareness will enhance cholera control efforts [34].

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