

## Renewed Interest in Cholera Control

Sujit K. Bhattacharya<sup>1\*</sup>, G. Balakrish Nair<sup>2</sup> and Yoshifumi Takeda<sup>3</sup>

<sup>1</sup>Department of Internal Medicine, Bengal Faith Hospital, Burdwan, West Bengal, India

<sup>2</sup>Ex-Director, National Institute of Cholera and Enteric Diseases, Kolkata, India

<sup>3</sup>National Institute of Infectious Disease, Tokyo, Japan

### ABSTRACT

Cholera is an ancient disease of significant public health importance accounting for approximately 1.3-4 million cases worldwide and about 21000–143,000 deaths. Cholera is endemic in many developing countries where sanitation is poor and lack in safe water. The disease has the potential to cause large-scale epidemics and pandemics. The ongoing seventh pandemic has spread to more than 100 countries since its origin in 1961 in Indonesia. Travellers from developed countries travelling to cholera endemic areas are at higher risk of getting cholera. Oral rehydration therapy (ORT) has revolutionized the treatment of cholera and causes reduction of mortality. ORT has saved the lives of millions of children all over the world and is considered the single most significant discovery in medicine of the century. Effective oral cholera vaccines have been developed and are being used but not to its full potential to control cholera. Since the disease burden due to cholera is huge and we have the tools to combat cholera, particularly reduce mortality, it is imperative that the global communities should embark on cholera control as an urgent priority of human health. Cholera control should be viewed as a poverty alleviation programme for the marginalised population. The current pandemic of COVID-19 overwhelmed the economy and healthcare systems so much so that the health authorities undermined the cholera control measures even during ongoing epidemics of cholera. The World Health Organization (WHO) has reframed the strategy with renewed interest on cholera control with a target of reducing the mortality from cholera by 90 percent by 2030. Member countries should mobilize enough funds for the programme and actively implement it. Improvement of sanitation and safe water for all should continue as long-term solution for combating the menace of cholera.

### \*Corresponding author

Sujit K. Bhattacharya, Department of Internal Medicine, Bengal Faith Hospital, Burdwan, West Bengal, India. Ph: +91-8697462003; E-mail: sujitkbhattacharya@yahoo.com

**Received:** March 09, 2022; **Accepted:** March 14, 2022; **Published:** March 21, 2022

**Keywords:** Cholera, Control, Sanitation, Safe Water, Vaccines, Management, Public Health

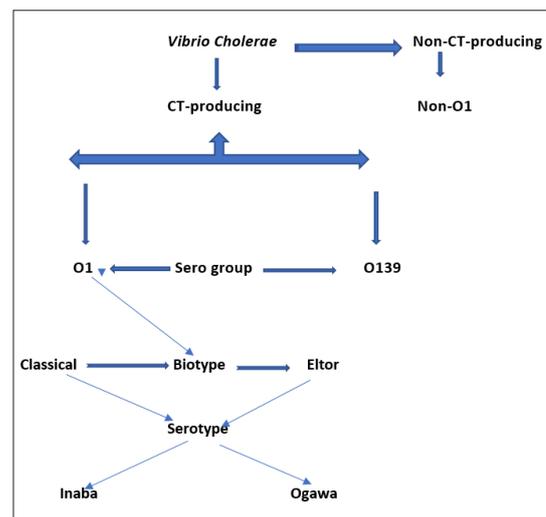
### History

Cholera is an epidemic prone disease and known to mankind from ancient times. A severe acute diarrhea occurred in Alexandria, Egypt in 1883. Two teams, namely-German team led by Robert Koch and French team led by Louis Pasteur simultaneously proceeded to Alexandria to investigate the outbreak. One member of the team led by Louis Pasteur died from cholera and the team retreated back, while the other team continued to proceed towards Alexandria. Robert Koch found that the diarrhea cases that died showed the presence of a bacterium in their intestinal mucosa which he could not identify. He then moved to Calcutta, India and identified the bacterium as *Vibrio cholera* in 1883 [1]. Among his other significant researches, he was awarded the Nobel Prize in Medicine and Physiology. S N De described the cholera toxin (CT) elaborated by *Vibrio cholerae* O1 in rabbit ileal loop model in Calcutta [2].

### Bacteriology

Cholera is caused by *Vibrio cholera*. *V. cholera* is a highly, motile, comma-shaped, gram-negative bacillus. The Judicial Commission of the International Committee on Bacteriological Nomenclature in 1965 and the International Association of Microbiological Societies in 1966 accepted the name of *Vibrio cholera* [3,4]. It has two biotypes---classical and eltor. Each has two serotypes-inaba and ogawa. Both *Vibrio cholerae* O1 and O139 are CT-producing

(Figure) and cause similar clinical pictures. A flagellum is present in one pole of the bacterium; several pili are seen on the surface of the bacterium [5]. Of the two circular DNA present in the bacterium, one is responsible for elaborating CT [6]. Integrated into the *V. cholerae* genome, CTX phages are found on the two chromosomes of the bacterium. CTX $\phi$  encodes for the genes for cholera toxin. The usefulness of phage therapy for prevention and treatment of cholera is controversial and needs careful research to document its role [7].



**Figure:** Classification of *Vibrio cholerae*

## Disease Burden

Cholera is characterized by acute onset of loose (watery) stools mixed with mucus, vomiting and dehydration. Cholera is an important cause of morbidity and mortality, particularly in areas where sanitation is poor and safe water is not available. Cholera accounts for approximately 1.3-4 million cases worldwide and about 21000-143,000 deaths [8]. Cholera is well known to cause epidemics and even pandemics and is endemic in the developing countries. Cholera affects people in overcrowded areas, the refugee camps, and during flood and famine. In cholera endemic areas, sporadic outbreaks are seen. The global impact of COVID-19 pandemic has been tremendous on the economy, and the healthcare system was overwhelmed by mere rush of patients [9]. It has been observed that during the current COVID-19 pandemic, most countries where cholera is endemic with many outbreaks every year, for example-Ethiopia and Sudan, have undermined the responses to the ongoing cholera epidemic [10]. A study conducted in Bangladesh found that by preventing one episode of cholera of average 3 days duration, a total cost of US\$30.40 per household is averted [11].

## Epidemiology

John Snow, a London Physician, in 1854 made the classical observation that those who drank water from a pump in the Broad Street in London did develop cholera as compared to those who did not [12,13]. When the pump was sealed, the cholera cases came down. This simple classical experiment elucidated that cholera is transmitted by faecal-oral-route. His findings proved beyond doubt that cholera is caused by this observation by John Snow is considered a hallmark in the epidemiology of infectious diseases. Cholera occurs as sporadic cases, causes epidemics, pandemics and is endemic in many countries in the developing world where sanitation is poor and safe water is not available. Epidemics have recently been reported from Haiti, Peru, Rwanda, Mozambique, Brundi, Cameroon, Mali, Nigeria, DR Congo, Ethiopia, Kenya, Ethiopia, Dominican Republic, Bangladesh, India, Nepal, Afghanistan and Malaysia. The Gangetic delta is a hotspot of origin of cholera outbreaks, and Bangladesh and India bear the major brunt of cholera epidemics occurring every year. People of low socio-economic condition that is associated with poor sanitation, malnutrition, poor housing, access to safe water and healthcare make them vulnerable to infectious diseases including cholera.

There have been seven pandemics of cholera. The first cholera pandemic (1817-1824), second pandemic (1826 -1837), third pandemic (1846- 1860), fourth pandemic (1863 to 1875) fifth pandemic (1881-1896) and the sixth (1899-1923) have been reported. The ongoing seventh pandemic originated in the Celebes Island in Indonesia in 1961 and has spread across the globe travelling through the Asia, Indian Sub-continent, Middle east and reached Europe and finally spread to North America. The first four pandemics were caused by classical biotype, and the seventh pandemic is caused by biotype eltor. As early as 5<sup>th</sup> century BC, reference of cholera has been noted in the Sanskrit literature. Although it is generally considered that Eltor *Vibrio* has completely displaced classical strains, but classical biotypes have been encountered in Bangladesh (1961-1968; 1982-1992), Mexico (1991-1997) and Thailand (2000) [14].

In 1971, an unprecedented happening occurred in the epidemiology of cholera when severe outbreaks of acute diarrhoea were encountered simultaneously in Kolkata (India) and Dhaka (Bangladesh). The diarrhoea cases had similar clinical features of O1 cholera and the stains of *Vibrio cholerae* elaborated an exotoxin akin the

cholera toxin (CT) [15-17]. The new stain was designated as *Vibrio cholerae* O139 Bengal as it was first isolated from the Gangetic delta of Bengal [18]. *Vibrio cholerae* O139 spread to the countries in Asia, Middle East and even cases were reported from developed countries (Netherland, Japan, Germany and UK). The cases were imported in the developed countries by tourists visiting the affected areas. The scientists engaged in Cholera research apprehended that probably this was the beginning of the eighth pandemic of cholera which fortunately did not happen. However, the disease became endemic in many areas in the developing of countries.

Some of the cholera cases upon recovery continues to excrete *Vibrios* in their stool. 21.7% of household contacts of cholera patients were found to be carriers for about 5-19 days as observed in a study from the Philippines. Long-term cholera carriers, though rare, have been reported [19].

## Pathogenesis

It has been demonstrated by S N De2 in Calcutta (now Kolkata) in 1959 in rabbit ileal loop model that *Vibrio cholerae* produces an exotoxin (the ligated ileal loops became distended when the culture filtrate of *Vibrio cholerae* O1 was inoculated inside the ileal loops)7 which is responsible for the pathogenesis of cholera. The cholera toxin (CT) produced in the small intestine attaches to GM1 gangliocytes in the gut mucosa with the help of the B-binding part of the toxin molecule assisted by the toxin-regulated pilus (T<sub>cp</sub>). The other, A-part of the molecule, enters the epithelial cells of the intestine and activates the adenylate cyclase which helps in production of Cyclic-AMP. The net result is outpouring of fluid rich in electrolytes (sodium and potassium). The fluid reaches the large intestine and when the volume of the fluid exceeds the capacity of the colon to reabsorb, diarrhoea ensues. The resultant effect is dehydration. There are no structural changes in the gut mucosa. The new diarrhoea cases caused by *Vibrio Cholerae* O139 had similar clinical features as that of O1 cholera and the stains of *Vibrio cholerae* elaborated an exotoxin akin the cholera toxin (CT). In cholera endemic areas, all patients presenting with acute diarrhoea should be screened for HIV. Cholera is more common in HIV individuals than in non-HIV individuals [20].

## Clinical features

Cholera has an incubation period of <1-5 days. The infective dose is as low as 108 organisms and therefore easily infects others and spread rapidly. Patients who have undergone gastrectomy or are receiving anti-acid drugs (e.g., pantoprazole, omeprazole, antacids) are more prone to acquire cholera as their lower acid level in the stomach permits the vibrio. Blood group of 'O' individuals are more prone to cholera [21]. The spectrum of the disease ranges from asymptomatic infection to severe life-threatening diarrhoea and dehydration which may kill the patient if not treated promptly and adequately. Classically, the liquid stools are mixed with flecks of mucus which are suspended and giving a fishy smell. This is known as "rice water" stool. Signs of dehydration include thirst, sunken eyes, loss of tears, reduced skin turgidity, reduced urine output, low volume or thready pulse, hypotension, depressed fontanelle (new-borns) and impaired level of consciousness or even coma. Hypovolemia and hypotension may lead to acute tubular necrosis and ultimately acute kidney injury. All cholera cases will not have all the signs and symptoms mentioned here. Dehydration is usually classified into NO dehydration, mild, moderate and severe dehydration. Severe dehydration is often life-threatening and presents with frequent passage of profuse watery stools, repeated vomiting, thready or absent pulse, hypotension, oliguria or anuria and coma. Practitioners often use antiemetics (e.g., metoclopramide) to stop vomiting in cholera patients. This

is not only irrational and also secedes the child, which may be confused with coma. Thirst may be the only feature of mild dehydration, while moderate dehydrated child will exhibit more severe signs, e.g., deeply sunken eyes and very deduced skin turgidity (usually elicited over the abdominal muscles. Mild to moderate dehydration together are synonymous with “some” dehydration. Cholera in pregnancy may result in foetal death [22].

### Management

Treatment of cholera is essentially replacement of fluid already lost and maintenance for ongoing losses. Since there was no structural damage to the intestinal mucosa and the absorptive capacity of the small intestine remained intact, it is possible to replenish fluid by the oral route. It was also demonstrated that glucose can help in the absorption of sodium from the small intestine. This led to the development of oral rehydration therapy (ORT) using oral rehydration salt solution containing glucose and sodium. As there is also loss of potassium, potassium was added to the solution. Oral Rehydration Salt Solution (ORS) or intravenous fluid or both are required depending upon the severity of dehydration.

The World Health Organization (WHO)/UNICEF recommend that Oral Rehydration Therapy (ORT) should be able to correct mild and moderately dehydrated diarrhea cases. The composition of the ORS (Table) recommended is Glucose 20 gm, Sodium chloride 2.5 gm, Potassium chloride 1.5 gm and Sodium bicarbonate 2.5 gm (or trisodium citrate, dihydrate 2.9 gm) dissolved in one glass of water. The solution should be given spoon by spoon to the child by the mother, while adults can drink as much fluid as possible. Since the concern that this fluid is hyperosmolar and potential to cause hypernatremia in young children with non-cholera diarrhea, a revised formula where glucose and sodium chloride concentrations were reduced, has been recommended. This hypoosmolar solution when given to adults with cholera, unscheduled intravenous fluid may be required in cases of profuse ongoing purging [23,24]. Severely dehydrated cholera cases should be rehydrated initially by intravenous Ringer’s lactate or normal saline. When vomiting stops, the patient should be given ORS for maintenance of hydration and combat with the ongoing diarrheal fluid loss. The treatment outcome of cholera with emphasis on ORT is so gratifying to see that a child of cholera prostrated with severe dehydration can leave the hospital on his own after several hours of rehydration. The tendency of combining metronidazole with an antibiotic for treatment of cholera and other acute diarrheas is highly discouraged and marketing such formulations should be prohibited.

**Table: Composition of Oral Rehydration Salt Solution (ORS)**

Ingredient (mmol/L)	Standard WHO/ORS	Low Osmolarity WHO/ORS
Glucose	111	75
Sodium	90	75
Potassium	20	20
Chloride	80	65
Citrate	10	10
Total Osmolarity	311	245

ORS has saved the lives of millions of children worldwide so much so that it has been acclaimed in an Editorial in the Lancet as “potentially the most important medical advance this century” (Anonymous. Water with sugar and salt (Editorial) Lancet 1978; ii: 300–01). As many paediatricians were sceptical about the usefulness of the oral therapy in diarrhoea, WHO conducted

training of paediatricians and other practitioners on the usefulness of ORT. In the hospitals where diarrhoea cases are treated, ORT corners were set up so that the mother of the child can give ORS as an outpatient as well as understand the rehydration procedure by using ORS for future similar diarrhoea case in the family and also help the neighbourhood. However, it is painful to note that many physicians even today do not treat children, who do not require intravenous fluid, with ORS and indiscriminately using antibiotics. Such practice is not rational and adds to cost of treatment and facilitates development of drug resistance.

It is gratifying to witness how severely dehydrated cholera cases respond to rehydration treatment with emphasis on ORT. Severe dehydration initially requires intravenous normal saline or Ringer’s lactate as fast as possible and may even be given in two sites. After sometime, the pulse becomes palpable, the blood pressure becomes recordable and the patient opens the eyes taking interest in the environment. By this time generally, acidosis is corrected and vomiting stops permitting oral rehydration with ORS. ORT is started. There will be a stage when the patient gets both intravenous fluid and ORS. As the correction of dehydration progresses, the intravenous fluid may be withdrawn and ORS alone continued. Progress of rehydration is clinically judged and monitored by pulse volume, blood pressure, level of consciousness (if unconscious) and urine output. Maintenance should be done with ORS. It is also important to recognise that some cases that are being rehydrated as above may again develop severe dehydration due to continuing severe purging. Obviously, these patients will require intravenous fluid again. Early feeding is encouraged to prevent malnutrition.

Laboratory investigations are not usually required. Blood count, estimations of serum electrolytes, particularly sodium, potassium, and bicarbonate, and urea and creatinine, and ABG may be required in case-to-case basis. Clinical judgement is enough to successfully treat cholera cases in resource poor settings. It is even possible to successfully treat cholera cases in refugee camps, where no laboratory facilities are available, by the trained health workers and nurses with emphasis on Oral Rehydration Therapy.

Antimicrobial resistance: Antibiotics (tetracycline, doxycycline, fluoroquinolones) are the main stay of the antibiotic treatment of severe cholera as an adjunct to rehydration therapy [25]. Antibiotics have been shown to reduce the stool volume and as a result the fluid requirement is minimised. Single dose of doxycycline is also recommended [26]. Antibiotic should be given orally as soon as vomiting stops and should be given orally as soon as vomiting stops. It has been documented that the *vibrio cholerae* can develop resistance to tetracycline limiting its role in the treatment of severe cholera cases. Furazolidone is no longer used because of rampant drug resistance. Chemoprophylaxis with tetracycline is strongly discouraged. Pectin, Kaolin and charcoal are not useful. WHO has recommended Zinc supplementation for cholera cases in children aged between 6 months to 5 years [27]. Such supplementation in a dose of 20 mg has been found to reduce stool volume by 10%. Zinc is delivered together with ORS. There has been a positive impact in cholera patients when Zinc was given with oral cholera vaccine and ORS. Malnourished children should be supplemented with oral Vitamin A [28]. The role of Probiotic for cholera remains in the research domain [29].

### Prevention

Cholera is transmitted mainly through facially contaminated water carrying *Vibrio Cholerae*. Interruption of transmission

of the bacteria can be achieved by safe drinking water and handwashing. Improved sanitation is required for long term solution of the control of the disease. Vaccination is an attractive disease prevention strategy. Currently there are three WHO pre-qualified oral cholera vaccines (OCV): Dukoral®, Shanchol™, and Euvichol-Plus®. All three vaccines require two doses for full protection. A bivalent heat-killed oral cholera vaccine has been evaluated in Kolkata, and during five-year follow-up, it has been shown that it can prevent cholera in 65% of vaccinees. In addition to improvement of sanitation and safe water, cholera vaccination can be undertaken in cholera-endemic areas before the cholera season begins [30]. Reactive oral cholera vaccination may be useful in cholera epidemics area. Since the actual disease burden of cholera is undermined by the health authorities in the affected countries, the acceptance and implementation of the vaccine have not been done in all those situations where it is needed. Advocacy under the umbrella of WHO is expected to motivate them to implement the effective vaccine along with safe water and sanitation.

### Control and future perspective:

The WHO formulated the Control of Diarrheal Diseases (CDD) Programme and encouraged the member countries to adopt and implement the control programmes with emphasis on ORT. Although the initial response was highly encouraging, the interest on diarrheal diseases including cholera control research became drastically lost. Diarrhea was no longer a priority. Cholera continued to invade many countries and added to the misery of the children. Recently, the renewed interest created the WHO vision of “The Global Roadmap to 2030 is that the world is free of cholera and is no longer an active threat to public health”. The renewed strategy envisages reducing the mortality from cholera by 90 percent by 2030 [31].

### References

1. Robert, Koch (1884) Sechster Bericht der deutschen wissenschaftlichen Commission zur Erforschung der Cholera. Deutsche Medizinische Wochenschrift 10: 191-192.
2. De SN (1959) Enterotoxicity of bacteria-free culture filtrate of *Vibrio cholerae*. Nature 183: 1533-1534.
3. Judicial Commission of the International Committee on Bacteriological Nomenclature (1965) Opinion 31. Conservation of *Vibrio* Pacini 1854 as a Bacterial Generic Name, Conservation of *Vibrio Cholerae* Pacini 1854 as the Nomenclatural Type Species of the Bacterial Genus *Vibrio*, and Designation of Neotype Strain of *Vibrio Cholerae* Pacini. International Bulletin of Bacteriological Nomenclature and Taxonomy 15: 185-186.
4. Feeley JC (1966) Minutes of IAMS Subcommittee on Taxonomy of *Vibrios*. International Journal of Systematic Bacteriology 16: 135-142.
5. Davis Brigid M, Waldor Matthew K (2003) Filamentous phages linked to virulence of *Vibrio cholera*. Current Opinion in Microbiology 6: 35-42.
6. John F Heidelberg, Jonathan A Eisen, William C Nelson, Rebecca A Clayton, Michelle L Gwinn, et al. (2000) DNA sequence of both chromosomes of the cholera pathogen *Vibrio cholera* 406: 477-483.
7. Bhandare Sudhakar, Joan Colom, Abiyad Baig, Jenny M Ritchie, Habib Bukhari, et al. (2019) Reviving phage therapy for the treatment of cholera. The Journal of infectious diseases 219: 786-794.
8. Ali M, Nelson AR, Lopez AL, Sack D (2015) Updated global burden of cholera in endemic countries. PLoS Neg Trop Dis 4: 9 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4455997/>.
9. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, et al. (March 2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579: 270-273.
10. Oloche Owoicho, Priscilla Abechi, Charles Ochieng Olwal (2021) Cholera in the Era of COVID-19 Pandemic: A Worrying Trend in Africa? Int J Public Health 66: 1604030.
11. Sarker AR, Islam Z, Khan IA, Amit Saha, Fahima Chowdhury et al. (2013) Cost of illness for cholera in a high-risk urban area in Bangladesh: an analysis from household perspective. BMC Infect Dis 13: 518.
12. John Snow (2018) Encyclopædia Britannica. 8 March 2018. Retrieved 12 March 2018.
13. Ball Laura (2009) Cholera and the Pump on Broad Street: The Life and Legacy of John Snow. The History Teacher. 43: 105-119.
14. Faruque SM, Abdul Alim AR, Rahman MM, Siddique AK, Sack RB, et al. (1993) Clonal relationships among classical *Vibrio cholerae* O1 strains isolated between 1961 and 1992 in Bangladesh J Clin Microbiol 31: 2513-2516.
15. Ramamurthy T, S Garg, R Sharma, SK Bhattacharya, GB Nair, et al. (1993) Emergence of novel strain of *Vibrio cholerae* with epidemic potential in southern and eastern India. Lancet 341: 703-704. 51.
16. Albert MJ, AK Siddique, MS Islam, AS G Faruque, M Ansaruzzaman, et al. (1993) Large outbreak of clinical cholera due to *Vibrio cholerae* non-01 in Bangladesh. Lancet 341:704. 9. Barua, D. 1992. History of cholera 1-36.
17. Bhattacharya SK, MK Bhattacharya, GB Nair, D Dutta, A Deb, et al. (1993) Clinical profile of acute diarrhoea cases infected with the new epidemic strain of *Vibrio cholerae* 0139: designation of the disease as cholera. J. Infect 27: 11-15.
18. Shimada T, GB Nair, BC Deb, MJ Albert, RB Sack (1993) Outbreak of *Vibrio cholerae* non-01 in India and Bangladesh. Lancet 341:1347- 1358.
19. Sinha Renuka Deb, BC De SP, Abou-Gareeb AH, Shrivastava DL (1967) Cholera carrier studies in Calcutta in 1966-67\*. Bulletin of the World Health Organization 37: 89-100 <https://apps.who.int/iris/handle/10665/266313>.
20. Lorenz von Seidlein, Xuan-Yi Wang, Arminda Macuamule, Catarina Mondlane, Mahesh Puri, et al. (2008) Is HIV infection associated with an increased risk for cholera? Findings from a case-control study in Mozambique Tropical Medicine and International Health 13: 683-688.
21. Roger I, Glass JH, Charles EH, Khan HMN, Annmari S, et al. (1985) Predisposition for cholera of individuals with O blood group possible evolutionary significance. American Journal of Epidemiology 121: 791-796.
22. Iza Ciglenecki, Mathieu Bichet, Javier Tena, Erneau Mondesir, Mathieu Bastard, et al. (2013) Cholera in Pregnancy: Outcomes from a Specialized Cholera Treatment Unit for Pregnant Women in Léogâne, Haiti 7: e2368.
23. Hahn S, Kim Y, Garner P (2001) Reduced osmolality oral rehydration solution for treating dehydration due to diarrhoea in children: systematic review. BMJ 323: 81-85
24. International Study Group on Reduced-osmolality ORS solutions (1995) Multicentric evaluation of reduced-osmolality oral rehydration salt solution.
25. Koel Bhattacharya, Suman Kanungo, Dipika Sur, Banwari Lal Sarkar, Byomkesh Manna, et al. (2011) Anna Lena Lopez, Manjira Bhattacharya, Suman Nandy, and Swapan Kumar Niyogi. Tetracycline-Resistant *Vibrio cholerae* O1, Kolkata, India. Emerg Infect Dis 17: 568-569.
26. Alam AN, Alam NH, Ahmed T, Sack DA (1990) Randomised

- double blind trial of single dose doxycycline treating cholera in adults *Jun 23*: 1619-1621.
27. M Imran Qadir, Arfa Arshad, Bashir Ahmad (2013) Zinc: Role in the management of diarrhea and cholera. *World J Clin Cases 1*: 140-142.
28. Danny V (2013) Colombara, Karen D. Cowgill, Abu S. G. Faruque. Risk Factors for Severe Cholera among Children under Five in Rural and Urban Bangladesh, 2000-2008: A Hospital-Based Surveillance Study.
29. Jari E Heikkilä, Sonja MK Nybom, Seppo J Salminen, Jussi AO Meriluoto (2012) Removal of Cholera Toxin from Aqueous Solution by Probiotic Bacteria. *5*: 665-673.
30. Sujit K Bhattacharya, Dipika Sur, Mohammad Ali, Suman Kanungo, Young Ae You, et al. (2013) 5 year efficacy of a bivalent killed whole-cell oral cholera vaccine in Kolkata, India: a cluster-randomised, double-blind, placebo-controlled trial. *Lancet Infect Dis 13*: 1050-6.
31. WHO. Cholera. Partners commit to reduce cholera deaths by 90% by 2030. The Global Task. WHO. Safe water essential to prevent cholera.

**Copyright:** ©2022 Sujit K. Bhattacharya, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.