Cholera

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Lancet 2012; 379: 2466–76

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Cholera is an acute, secretory diarrhoea caused by infection with *Vibrio cholerae* of the O1 or O139 serogroup. It is endemic in more than 50 countries and also causes large epidemics. Since 1817, seven cholera pandemics have spread from Asia to much of the world. The seventh pandemic began in 1961 and affects 3–5 million people each year, killing 120 000. Although mild cholera can be indistinguishable from other diarrhoeal illnesses, the presentation of severe cholera is distinct, with pronounced diarrhoeal purging. Management of patients with cholera involves aggressive fluid replacement; effective therapy can decrease mortality from more than 50% to less than 0·2%. Antibiotic treatment decreases volume and duration of diarrhoea by 50% and is recommended for patients with moderate to severe dehydration. Prevention of cholera depends on access to safe water and sanitation. Two oral cholera vaccines are available and the most effective use of these in integrated prevention programmes is being actively assessed.

Introduction and history

Cholera is an acute secretory diarrhoea caused by the Gram-negative bacterium *Vibrio cholerae*.[1–4] Cholera epidemics have been increasing in intensity, duration, and frequency, showing the need for more effective approaches to prevention and control.

Descriptions of a disease thought to be cholera are found in Sanskrit back to the 5th century BC, and the disease has existed on the Indian subcontinent for centuries. In 1817, cholera spread beyond the Indian subcontinent, and six worldwide cholera pandemics occurred between 1817 and 1923. Between 1849 and 1854, London physician John Snow proposed that cholera was a communicable disease and that stool contained infectious material. He suggested that this infectious material could contaminate drinking water supplies, resulting in transmission of cholera. Filippo Pacini, working independently in Italy in 1854, first observed comma-shaped forms under a microscope in cholera stools. In 1884, Robert Koch first isolated *V cholerae* in pure culture in work that began in Egypt and continued in Calcutta (Kolkata), India.

The continuing seventh cholera pandemic began in Indonesia in 1961 and spread through Asia to Africa, Europe, and Latin America. This pandemic is caused by a new biotype of *V cholerae* first isolated in 1905 in El Tor, Egypt.[3] Although cholera is vastly under-reported, WHO estimates that 3–5 million cases occur per year,[5] predominantly in Asia and Africa, with periodic major epidemics including that in Haiti in 2010.[6] Diarrhoeal diseases including cholera are the second leading cause of mortality worldwide among children younger than 5 years, and are one of the main causes of morbidity.[7] Cholera is also a major cause of severe dehydrating diarrhoea in adults.

Causative agent

V cholerae is a member of the Vibrionaceae family of curved, Gram-negative rods that are found in coastal waters and estuaries.[1,3] These organisms grow best in the presence of salt, although *V cholerae* can grow in water of low salinity when it is warm and contains sufficient organic nutrients.[8] *V cholerae* is often associated with zooplankton and shellfish in water,[8] and it can use chitin as a carbon and nitrogen source.[9] Chitin induces natural competence in *V cholerae*, suggesting that lateral gene transfer occurs in water, especially during zooplankton blooms.[10] In water, *V cholerae* enter a viable but non-culturable form,[11] also called active but non-culturable or conditionally viable environmental cells.[4,12]

V cholerae is classified into more than 200 serogroups based on the O antigen of the lipopolysaccharide;[1] of these, only O1 and O139 serogroups cause epidemic cholera. *V cholerae* O1 is further classified into two biotypes, classical and El Tor.[3] Two major serotypes exist, Ogawa and Inaba, which vary in prevalence with time.[13] In 1992, *V cholerae* O139 was first recognised in south Asia as a cause of epidemic cholera.[14,15] This organism is derived from *V cholerae* O1 El Tor by lateral transfer of a genomic island substituting the O139 for the O1 antigen, but is otherwise almost identical to *V cholerae* O1 El Tor.[16,17] Although classical *V cholerae* O1 caused the fifth and sixth pandemics (and presumably the earlier pandemics), the seventh pandemic is attributed to the El Tor biotype, which has now replaced the classical biotype.

Although early isolates of *V cholerae* O1 were susceptible to most antibiotics, *V cholerae* O139, and some isolates of *V cholerae* O1 El Tor, have acquired an SXT element that mediates resistance to co-trimoxazole and streptomycin;[18] this element is found in almost all strains isolated during the past decade.[19] In the past few years, strains of *V cholerae* O1 resistant to tetracycline, erythromycin, or ciprofloxacin, or combinations thereof, have been recovered in Asia;[19,20] some of these strains have acquired additional resistance genes in the SXT element. These multiresistant strains have not yet been recognised in other locations.

Search strategy and selection criteria

We searched Medline and Cochrane Library databases with the terms "cholera" or "*Vibrio cholerae*", and "randomised controlled trials" from Jan 1, 1966 to Sept 30, 2011, in all languages.

Pathogenesis and pathophysiology

After ingestion of *V cholerae*, most of the bacteria are killed by gastric acid. Surviving organisms colonise the small intestine and elaborate cholera toxin, the major virulence factor for pathogenic strains.[3] Cholera toxin is a protein exotoxin that consists of one A subunit associated with five B subunits.[21] The B subunit pentamer binds to the ganglioside GM_1 on eukaryotic cells, and the A subunit is translocated intracellularly, where it acts enzymatically to activate adenylate cyclase and raise intracellular cyclic AMP; this leads to chloride secretion through the apical chloride channel and secretory diarrhoea.[22–24] The second major virulence factor of pathogenic strains of *V cholerae* is the toxin-coregulated pilus, a colonisation factor whose expression is regulated in parallel to cholera toxin.[25,26]

The genes for cholera toxin are encoded within the genome of a filamentous bacteriophage, CTXϕ.[27] Classical and El Tor strains have different versions of this bacteriophage, which can insert at one or two attachment sites in the genome depending on the biotype. The bacterial cell surface receptor for CTXϕ is the toxin-coregulated pilus,[27] which is itself encoded within a genomic island—vibrio pathogenicity island (VPI-1).[28,29] Evolution of virulence in *V cholerae* involves sequential acquisition of VPI-1 followed by CTXϕ.

All seventh pandemic strains of *V cholerae* O1 El Tor contain VPI-1, and a second vibrio pathogenicity island VPI-2. Two genomic islands are specific to the seventh pandemic strains, vibrio seventh pandemic islands 1 and 2.[30] Recent seventh pandemic strains have been described that have the classical CTXϕ instead of the El Tor CTXϕ, or a variant of the El Tor CTXϕ encoding the B subunit of cholera toxin that occurs in classical *V cholerae* O1 strains.[31] These variant El Tor strains have largely replaced the earlier El Tor strains and might be associated with more severe diarrhoea.

Epidemiology

Cholera occurs in both endemic and epidemic patterns. It is endemic in many areas of Asia and Africa. In Asia, cholera occurs seasonally before and after the monsoon rains,[3] the incidence is highest in children, and the disease can occur in neonates.[32,33] Cholera epidemics arise in a long cycle superimposed on existing endemic disease. This pattern relates to declining levels of population-level immunity from a previous outbreak, overlaid on cycles of climate variability.[34] In the past decade, devastating epidemics of cholera have occurred in Angola, Ethiopia, Zimbabwe, Pakistan, Somalia, Sudan, Vietnam, and Haiti.[35] Among immunologically naive populations, cholera affects all age groups, and epidemics can be associated with high case-fatality rates.[35] This pattern was recorded in Haiti, where cholera had been notably absent before 2010. Population density, poor sanitation and health infrastructure, and logistical obstacles to appropriate case management also contribute to a high case-fatality rate in epidemic settings.

Environmental factors are important in the epidemiology of cholera. Changes in surface water temperature and terrestrial nutrient discharge lead to a proliferation of phytoplankton and zooplankton and a consequent increase in *V cholerae*.[8,36,37] Cholera rates also increase substantially during floods compared with non-flood periods.[38] Natural disasters that disrupt public health facilities, such as cyclones and earthquakes, also contribute to cholera epidemics.

The infectious dose of *V cholerae* O1 has been estimated to be 10^5–10^8 in experimental human infection, but could be as low as 10^3 in the presence of achlorhydria.[39] The incubation period ranges between 12 h and 5 days.[1,40]

Molecular epidemiology

The genome of a *V cholerae* O1 El Tor strain was sequenced in 2000;[41] as with all vibrios, this organism has a large circular chromosome and a small circular chromosome.[42] All Vibrionaceae have a super-integron in the small chromosome that acts as a gene capture system.[43,44] A comparison of genomic sequences of patient and environmental strains isolated for nearly 100 years showed 12 distinct lineages of *V cholerae* O1; the classical and El Tor O1 biotypes were one lineage in this phylogeny.[31] All strains of *V cholerae* O1 El Tor shared a highly conserved core genome, with variations attributable mainly to laterally transferred genetic elements and single nucleotide variation.

An analysis suggested that the seventh pandemic strains originated from a single source in the Bay of Bengal that has spread to distant locations in three independent but overlapping waves.[45] The first wave, which spread from Asia into Africa and South America, lacked the SXT element. The second wave acquired the SXT element and replaced the isolate in the first wave; the third wave also contains the SXT element. Isolates in the Haiti outbreak are closely related to south Asian strains in the third pandemic wave.[46]

Transmission

Patients infected with *V cholerae* O1 or O139 who have no symptoms generally shed the organism for only a few days; however, patients who are symptomatic shed the organism for between 2 days and 2 weeks, and rarely longer.[4,40] Transmission of cholera within households has been documented.[40] *V cholerae* are present in human stool both as individual planktonic cells and in biofilm-like aggregates.[47,48] In environmental water, organisms convert to conditionally viable environmental cells[12] within 24 h.[49] These organisms are infectious on reintroduction into people, although the infectious dose in this form is not known. Filtration of water through sari cloth reduces cholera transmission by nearly 50%, consistent with removal of organisms attached to zooplankton.[50]

The peak of a cholera epidemic is often preceded by increasing prevalence of the pathogenic strain in the environment.[12] Bacteriophages that are lytic for *V cholerae* O1 or O139 are also found in the stools of patients and in environmental water.[12,51] Bacteriophage density increases as an outbreak proceeds, and these bacteriophages could modulate the severity and duration of an outbreak.[12,51,52]

As *V cholerae* O1 leave a person, the organisms have a phenotype referred to as hyperinfectivity—that is, the infectious dose is 10–100 times lower than for non-human-shed organisms.[53] Hyperinfectivity of recently shed organisms persists in water for 5–24 h, suggesting that organisms transmitted from person to person might be more infectious than those that have acclimatised to the environment. When hyperinfectivity is incorporated into a mathematical model of a cholera outbreak, the characteristically explosive nature of such an outbreak is better reproduced than if hyperinfectivity is not included.[54] Other key components of cholera transmission models[4,52,55,56] include the concentration of *V cholerae* O1 or O139 in stool, the difference of infectivity between planktonic cells and stool aggregates, the rapidity of spread of the organism from person to person, the

Figure: **Presentation and management of cholera**
(A) Rice water stool in a patient with cholera. (B) Cholera cot used in management of patients with cholera to monitor continuing volume losses in stool. (C) Patient with cholera before rehydration. (D) Patient with cholera 8 h after starting rehydration therapy. (A, C, and D) reproduced from Chowdhury and colleagues,[78] by permission of *PLoS*.

presence of lytic bacteriophage in stool and water, and the concentration in water of the conditionally viable environmental cells for environment-to-person transmission.

Host susceptibility

Concomitant infection with enteropathogenic bacteria or parasites exerts an immunomodulatory effect on *V cholerae*-specific immunity,[57,58] and several host factors contribute to susceptibility to cholera. In particular, retinol deficiency is associated with an increased risk of *V cholerae* infection and with a raised risk of symptomatic disease.[59,60] Blood group O has been associated with severe cholera in different populations.[61–63] The prevalence of blood group O is lower in south Asia than in other regions, perhaps related to evolutionary pressure from cholera.[64] Results of a family-based study from Bangladesh[59] showed that first-degree relatives of a patient with cholera had greater odds of being infected than did less closely related contacts in the same household independent of blood group, suggesting that additional genetic factors have a role in susceptibility. A variant in the promoter region of *BPIFB1* (also known as *LPLUNC1*), a component of the innate immune system, was associated with cholera in a candidate gene study.[65,66] Additional studies of host genetic factors related to cholera could provide further insights into the interaction between *V cholerae* and the host.

Diagnosis

According to WHO,[67] a case of cholera should be suspected when a patient aged 5 years or older develops severe dehydration or dies from acute watery diarrhoea, even in an area where cholera is not known to be present, or when a patient aged 2 years or more develops acute watery diarrhoea in an area known to have cholera. Where microbiology facilities are available, *V cholerae* infection can be confirmed by isolation of the organism from stool on selective media, followed by biochemical tests, and serogrouping and serotyping with specific antibodies.[68] Enrichment of stool in alkaline peptone water can increase the sensitivity of culture.[69] Cholera can be rapidly diagnosed by examining fresh human stool under ×400 darkfield microscopy for vibrio-shaped cells with darting motility that is abrogated with specific antibody;[70] about half of culture-positive stools are positive on darkfield microscopy.[47]

Immunoassays that detect cholera toxin[71,72] or *V cholerae* O1 and O139 lipopolysaccharide[73–75] directly in stool have also been developed. Such assays can be used in settings with limited laboratory capacity and enable early detection of cases during an outbreak. One such commercially available dipstick for both O1 and O139-associated cholera has a 97% sensitivity and 71–76% specificity compared with PCR under field conditions.[76] Dipstick assays seem to be more sensitive for detection of *V cholerae* in patients previously treated with antibiotics than is culture.

Clinical signs and symptoms

Few diseases have a clinical presentation as striking as that of cholera. Massive watery diarrhoea, up to 1 L per hour, can lead to hypotensive shock and death within hours of the first symptom (so-called cholera gravis). Death rates in untreated patients with severe cholera can exceed 70%.[77] Although the stools of patients with cholera can contain faecal matter or bile in the early phases, the characteristic rice-water stool of cholera develops with continued purging (figure[78]); this term refers to the similarity of the stool to water in which rice has been washed. Vomiting is a common feature, particularly early in illness. The diarrhoea of cholera is typically painless and not accompanied by tenesmus; some patients have abdominal discomfort or cramping due to fluid distension of the bowel. Fever is rare and should raise suspicion for secondary infection.

Dehydration and electrolyte abnormalities are the most important complications of cholera. Patients can be lethargic, and might have sunken eyes (figure), dry mouth, cold clammy skin, decreased skin turgor, or wrinkled hands and feet. Kussmaul breathing can occur because of acidosis from stool bicarbonate losses and lactic acidosis associated with poor perfusion.[79] The

	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Bicarbonate (mmol/L)	Carbohydrate*
Electrolyte losses in stools*					
Cholera stool, adult	130	20	100	45	None
Cholera stool, child	100	30	90	30	None
Non-cholera stool, child	50	35	25	20	None
Intravenous therapy†					
Lactated Ringer's solution	130	4	109	28	None (278 mmol/L if D5LR available)
Normal saline	154	0	154	0	None
Cholera saline (Dhaka solution)	133	13	98	48	140 mmol/L
Oral rehydration therapy‡					
ORS (WHO 2002)§	75	20	65	10 (citrate)	75 g (glucose)
Rice based ORS	75	20	65	10 (citrate)	27 g rice syrup solids
Homemade ORS[95] (half teaspoon of salt plus six teaspoons of sugar in 1 L of safe water)	About 75	0	About 75	0	About 75 g

A useful resource is the Cholera Outbreak Training and Shigellosis Program that provides free online information about the management of patients with cholera, based on WHO standards. D5LR=dextrose 5% lactated Ringer's solution. ORS=oral rehydration solution. *Compositions are estimates of the mean electrolyte composition of stools and are provided to show the substantial difference in the pathophysiology of paediatric and adult cholera and non-cholera childhood gastroenteritis. The mean maximal rate of purging in severe cholera exceeds 10 mL/kg per h. Sodium losses in cholera stools exceed those recorded for other causes of diarrhoeal illness. †Lactated Ringer's solution is usually readily available and preferred to normal saline because it contains potassium and bicarbonate. The optimum infusion for cholera, such as Dhaka solution, contains more potassium and bicarbonate than lactated Ringer's solution, and also contains dextrose to address complications of severe cholera including hypokalaemia, hypoglycaemia, and metabolic acidosis. ‡WHO ORS has glucose as a carbohydrate source. In randomised trials, rice-based ORS formulations reduced the duration of diarrhoea and stool losses in severe cholera.[93] §In 2002, WHO replaced its previous formulation of ORS with the present lower osmolarity formulation. Subclinical hyponatraemia is common among patients with cholera with the present WHO formulation of ORS,[96,97] but the rates of symptomatic hyponatraemia in patients with cholera do not seem to be significantly increased.[98]

Table 1: **Comparison of the composition of cholera stools and acceptable therapeutic fluids for cholera**[67,94]

peripheral pulse is rapid and thready, and can become difficult to palpate as blood pressure drops; urine output decreases with time.[80,81] Muscle cramping and weakness due to electrolyte losses and ion shifts (particularly potassium and calcium) are common. In children, depletion of glycogen stores and inadequate gluconeogenesis can lead to severe hypoglycaemia, shown by altered consciousness, seizures, or even coma.[82,83] Cholera sicca is an unusual form of the disease in which fluid accumulates in the intestinal lumen, and circulatory collapse and even death can occur before the passage of the first loose stool.[84]

The presentation of cholera differs between endemic and epidemic settings. In endemic settings, rates of asymptomatic *V cholerae* infection range from 40% to 80%,[4] and cholera can present as mild diarrhoea indistinguishable from infection with other enteropathogens. The most severe cases of cholera in endemic settings are concentrated among young children and previously unexposed individuals. In the epidemic setting, severe disease occurs in adults as frequently as in children and is associated with high case-fatality rates.[85] Laboratory tests are not required to care for most patients with cholera although they can be useful in patients with ileus, confusion, coma, or seizures, or in those with no urine output in response to fluid replacement. Laboratory abnormalities include changes in serum electrolytes (hypokalaemia, hyponatraemia, hypocalcaemia), renal dysfunction, the effects of haemoconcentration, and in a few children, hypoglycaemia. The clinical features of cholera due to *V cholerae* O1 and O139 are much the same.[86,87] Complications from severe hypotension can include stroke (especially in elderly patients) and renal compromise, and vomiting can lead to aspiration pneumonia,[88] but cholera itself is an acute infection with no chronic symptoms.

	No dehydration (<5%)	Some dehydraton (5–10%)	Severe dehydration (>10%)
Clinical assessment for degree of dehydration			
General appearance	Well, alert	Restless, irritable	Lethargic or unconscious
Eyes	Normal	Sunken	Sunken
Thirst	Drinks normally	Thirsty, drinks eagerly	Drinks poorly or unable to drink
Skin turgor	Instantaneous recoil	Non-instantaneous recoil	Very slow recoil (>2 s)
Pulse	Normal	Rapid, low volume	Weak or absent
Approach to rehydration*			
Requirement for fluid replacement	Ongoing losses only	75 mL/kg in addition to ongoing losses	>100 mL/kg in addition to ongoing losses
Preferred route of administration	Oral†	Oral or intravenous	Intravenous
Timing	Usually guided by thirst	Replace fluids over 3–4 h	As rapidly as possible until circulation is restored, complete the remainder of fluids within 3 h
Monitoring	Observe until ongoing losses can definitely be adequately replaced by ORS	Observe every 1–2 h until all signs of dehydration resolve and patient urinates	Once circulation is established monitor every 1–2 h

A useful resource is the Cholera Outbreak Training and Shigellosis Program that provides free online information about the management of patients with cholera, based on WHO standards. ORS=oral rehydration solution. *Patients with comorbid disorders including severe malnutrition, significant complications, infants and elderly patients might require adjustments from this standard which are detailed in the references. †If losses are in excess of 10 mL/kg per h, use of oral therapy might not be possible initially.

Table 2: **Approach to rehydration in a patient with suspected cholera[67]**

Management

Rehydration is the cornerstone of management of patients with cholera. Early attempts at oral rehydration met with little success because the physiological requirements for sodium-glucose cotransport were not recognised. The introduction of oral rehydration solution in the late 1960s, with equimolar concentrations of sodium and glucose to maximise sodium uptake in the small intestine, and careful replacement of preceding and continuing fluid losses, ushered in present cholera treatment.[84,89]

With the present standard of care, the mortality of severe cholera can be reduced to less than 0·2%, even in resource-limited settings.[3] However, obstacles exist to administration of best possible rehydration, and mortality rates can still exceed 10% early in cholera epidemics before appropriate resources are available.[90,91] In the epidemic in Haiti, the median time between onset of symptoms and death within the community was 12 h.[92] Decentralised treatment centres (such as oral rehydration points) improve access to therapy, reduce time to initial rehydration, and are crucial in management of outbreaks.

The approach to rehydration during severe cholera differs substantially from the approach to patients with gastroenteritis in developed countries because: patients with severe cholera present with a greater degree of initial dehydration, these patients have more rapid continuing losses once they come to medical attention, and they have proportionally greater electrolyte losses than in non-cholera gastroenteritis (table 1[93–98]).

For these reasons, the most common error in caring for patients with cholera is to underestimate the speed and volume of fluids required. Patients with severe cholera typically require an average of 200 mL/kg of isotonic oral or intravenous fluids in the first 24 h of therapy, and might require more than 350 mL/kg.[67,99] Estimation and replacement of ongoing losses, even during correction for the initial fluid deficit, is crucial. The rate of continuing fluid loss might exceed 20 mL/kg per h; cholera cots are inexpensive and useful for estimation of continuing volume losses (figure). In the absence of cholera cots, continuing losses can be estimated as 10–20 mL/kg of bodyweight for each diarrhoeal stool or episode of vomiting.

In severe cholera, the initial fluid deficit should be replaced within 3–4 h of presentation. The route of administration of fluids depends on the severity of dehydration (table 2[67]). Patients with severe (≥10%)

dehydration are in hypovolaemic shock and require immediate intravenous rehydration administered as rapidly as possible until circulation is restored. Oral rehydration should begin as soon as patients are capable of drinking (typically 3–4 h), because more potassium, bicarbonate, and glucose are available in oral rehydration solution than in standard intravenous fluids. In patients with some dehydration, the initial deficit should be replaced rapidly, with oral rehydration solution whenever possible, and patients should be monitored until signs of dehydration have resolved. Patients with some dehydration but with profound vomiting or continuing stool losses can rapidly progress to severe dehydration if only oral rehydration solution is provided, and should receive concomitant intravenous and oral rehydration. In patients without dehydration, management consists of oral fluids to replace continuing losses. WHO oral rehydration solution has glucose as the carbohydrate source. Rice-based oral rehydration solution formulations, if available, have been recorded in randomised trials to reduce the duration of diarrhoea and stool losses in severe cholera.[93] Homemade oral rehydration solution can be used in an emergency situation (table 1). In patients with symptomatic hypoglycaemia, 0·25–0·50 g/kg of intravenous glucose can be administered and correction of the hypoglycaemia monitored until fluid repletion and the ability to take oral rehydration solution has occurred.[83]

Antibiotics are adjunctive therapy in patients with moderate to severe dehydration from cholera.[39] As in other infections, use of antibiotics in cholera might contribute to increasing antimicrobial resistance. However, effective antibiotics shorten the duration of diarrhoea and reduce the volume of stool losses by up to 50%; they also reduce the duration of shedding of viable organisms in stool from several days to 1–2 days.[77,100] Antibiotics can be administered once the initial fluid deficit is corrected and vomiting has resolved, ideally within 4 h of initiation of therapy. Antibiotic therapy should be based on prevailing local resistance patterns (table 3[101–106]).

Nutritional interventions include the resumption of a high energy diet immediately after the initial fluid deficit is corrected to prevent malnutrition and immediate complications including hypokalaemia and hypoglycaemia. For infants, breastfeeding should be encouraged in concert with oral rehydration solution. In a randomised trial, zinc supplementation reduced the duration of diarrhoea and volume of stool in children with cholera.[107] Zinc supplementation after childhood diarrhoea also reduced the incidence of subsequent episodes of diarrhoea for several months;[108,109] WHO recommends zinc for children younger than 5 years of age with diarrhoea (10 mg/day for children younger than 6 months and 20 mg/day for 10 days for children aged 6 months to 5 years[67]). Children with diarrhoea in developing countries also benefit from supplementation with vitamin A.[110] Antimotility agents and antiemetics have no established benefit for treatment of cholera, and might prolong infection or have sedating effects that interfere with effective oral rehydration.[67,111]

	Paediatric dose*	Adult dose	Comments
Tetracyclines			
Tetracycline	12·5 mg/kg per dose, four times daily, for 3 days	500 mg, four times daily, for 3 days	Antibiotic resistance to all tetracyclines is common.[101] Empirical use is most appropriate in outbreaks caused by documented susceptible isolates. Tetracyclines are not recommended for pregnant women or children younger than 8 years because of risk of irreversible discoloration of permanent teeth
Doxycycline	4–6 mg/kg, single dose	300 mg, single dose	As for tetracycline
Fluoroquinolones			
Ciprofloxacin	15 mg/kg per dose, twice a day, for 3 days	500 mg, twice a day, for 3 days	In highly susceptible strains, single dose ciprofloxacin compares favourably against erythromycin[102] and doxycycline[103] in randomised trials. However, reduced susceptibility to fluoroquinolones has become common in endemic areas, and is associated with treatment failure[104,105]
Macrolides			
Erythromycin	12·5 mg/kg per dose, four times a day, for 3 days	250 mg, four times a day, for 3 days	There are rare reports of macrolide resistance
Azithromycin	20 mg/kg, single dose	1 g, single dose	Single dose azithromycin is the preferred therapy in children and has been shown to be more effective than ciprofloxacin in randomised trials in regions where reduced susceptibility to fluoroquinolones is common[106,107]

*Paediatric doses, based on weight, should not exceed maximum adult dose.

Table 3: **Antibiotics for cholera**

In an outbreak, clinicians and public health officials often need to manage many patients at the same time. Crucial response features include creation of cholera treatment centres; training of staff in case recognition and management; and provision of safe water and sanitation. Dependent on the local situation, radio advertisements, mobile phone messaging, messages on billboards, community volunteers, and other methods can be important ways to educate the public about seeking medical care, oral rehydration use, sanitation, and other ways to prevent or minimise transmission. Other important components of the public health response include disinfectants, proper disposal of waste and the bodies of those who die, and coordination of the response with community, regional, national, and international health authorities. The Cholera Outbreak Training and Shigellosis Program is an online resource that can assist with management of such features. Some countries are reluctant to declare a cholera epidemic because of concern about creating panic and the implications for tourism and exports; however, rapid reporting and a coordinated public health response should be encouraged to minimise the extent of the outbreak and prevent further spread.

For the **Cholera Outbreak Training and Shigellosis Program** see http://www.cotsprogram.com

Prevention

The response to the cholera pandemics of the 19th century led to the development of systems to provide safe water and adequate sanitation, but 1 billion people still do not have access to safe water and remain at risk of cholera.[112] Continued progress in provision of safe water and adequate sanitation is a Millennium Development Goal but could take decades to achieve.[113] During a cholera outbreak, the major response should focus on case detection, rehydration-based treatment, and provision of safe water, in conjunction with adequate sanitation, hand-washing, and safe food preparation.[114] These goals have been used for decades in areas that remain at risk for cholera, without reducing the continuing effect of this disease, suggesting that consideration of additional control strategies, such as vaccination, is warranted.[113,115,116]

Although safe and effective cholera vaccines exist, cholera vaccination is not yet part of cholera control programmes outside of Vietnam; discussions are in progress regarding potential use in Haiti and elsewhere. The reasons for this are logistical, financial, and historical. Cholera vaccines are given orally, have an excellent safety profile, and target induction of mucosal immunity. Two oral killed vaccines, prequalified for use by WHO, are licensed and commercially available. Dukoral (WC-rBS, Crucell, Sweden) contains several biotypes and serotypes of *V cholerae* O1 supplemented with 1 mg per dose of recombinant cholera toxin B subunit. Shanchol (Shantha Biotechnics-Sanofi Pasteur, India) contains several biotypes and serotypes of *V cholerae* O1 and *V cholerae* O139 without supplemental cholera toxin B subunit. Shanchol is the bivalent vaccine that is internationally available; mORCVAX (VaBiotech, Vietnam) is the locally produced Vietnamese version of this vaccine.[5]

Oral killed cholera vaccines have been administered to millions of recipients and are safe and immunogenic. The vaccines are administered as two or three doses depending on age and vaccine (table 4[117–131]). Overall, the vaccines provide 60–85% protective efficacy for 2–3 years, although protection among young children is of shorter duration.[117–127] Dukoral has been safely administered to individuals with HIV infection.[123]

Reanalysis of original studies of oral cholera vaccine in Bangladesh in the 1980s disclosed a measurable herd effect,[132] and modelling suggests that vaccination of 50% of a population could result in a greater than 90% reduction in cholera incidence in that population overall.[133] A cost-effectiveness model suggested that oral cholera vaccine could be cost effective in areas endemic for cholera.[134]

Several live attenuated oral cholera vaccines have also been developed, including CVD 103-HgR (PaxVax, USA), Peru-15 (Haikou VTI Biological Insitute, China) and others.[135] These genetically modified vaccine strains have in common the inability to express cholera toxin. These vaccines have been shown to be safe and immunogenic in volunteer studies;[136–140] however, CVD 103-HgR failed to show protective efficacy when assessed in an initial field study.[141] Peru-15 has been shown to be safe and immunogenic in different age groups in Bangladesh,[142] but has not yet been investigated in field studies. Several other cholera vaccines are in various stages of development, including subunit vaccines, other live attenuated vaccines, and conjugate vaccines.[143,144]

WHO has endorsed the inclusion of oral vaccine in cholera control programmes in endemic areas in conjunction with other preventive and control strategies.[5] WHO also recommends that oral vaccine be considered as part of an integrated control programme in areas at risk for outbreaks.[5] The use of vaccine in reactive situations (ie, after an outbreak has occurred) is less certain. A case-control study in Vietnam suggested that

	Doses*	Dosing interval*	Dosing volume*	Boosters*	Protective efficacy	Comments
Dukoral†[118-123,128,129]						
Children aged 2–5 years	3	14 days (7–42 permissible)	3 mL vaccine and 75 mL buffer	Every 6 months	60–85% protective efficacy within 6 months of vaccination, decreasing to baseline during 24–36 months	Pre-qualified for use by WHO Licensed in many countries Has been safely administered to individuals with HIV infection Provides short-term protection against diarrhoea caused by heat labile toxin expressing strains of enterotoxigenic *E coli*
≥6 years	2	14 days (7–42 permissible)	3 mL vaccine and 150 mL buffer	Every 2 years	As for children 2–5 years of age	As for children 2–5 years of age
Shanchol[117,124-127,130,131]						
≥1 year of age	2	14 days (window probably same as Dukoral)	1·5 mL	Every 2 years	60–70% protective efficacy over 24–36 months	Pre-qualified for use by WHO More affordable than Dukoral Does not require buffer to administer vaccine Undergoing field studies in Kolkata and Orissa, India and Dhaka, Bangladesh, and pilot roll-out in Haiti

*Per manufacturer. †Listed field studies have involved both the present preparation of WC-rBS vaccine, supplemented with recombinant cholera toxin B subunit, and a previously available preparation of WC-BS containing non-recombinant B subunit.

Table 4: **Internationally available killed-cell cholera vaccines for oral administration**

such use could be of benefit,[145] and modelling further supports such potential use.[55,56,146–148] At present, WHO suggests that oral cholera vaccine be considered as part of an integrated programme in reactive situations in both epidemic and endemic settings in conjunction with provision of safe water, adequate sanitation, case detection, and rehydration strategies, but that collection of additional data to support vaccination in such settings is warranted.[5] Creation of an international cholera vaccine stockpile is being discussed.

Unanswered questions

Cholera has had an immense effect on human history. Unfortunately, present control strategies have not proven highly effective in areas of the world bearing the global burden of cholera.[113] Many questions remain. Will a new serogroup of *V cholerae* arise, as O139 did? Why are altered variants of *V cholerae* O1 El Tor developing? Will severe weather events such as regional flooding associated with global warming result in increased cholera? What role would surveillance, screening, vaccination, or empirical treatment have in limiting the spread of cholera into immunologically naive populations? Would short course targeted chemotherapy with highly active antimicrobials for close community contacts of patients with cholera limit transmission, or only lead to drug resistance? How can safe water and improved sanitation be attained in the many parts of the world without them? What are the obstacles to incorporation of cholera vaccines into immunisation programmes in countries where cholera is endemic, and how can these be overcome? Who will support and pay for the manufacture, distribution, and use of cholera vaccines? Will a vaccine stockpile be developed? And, if so, who will maintain, monitor, and activate its use? Will the development of more effective or longer acting cholera vaccines than are currently available simplify some these decisions?

We do not yet know the answers to these important questions, but the way forward will require scientific, medical, public health, environmental, financial, and political cooperation and action. As it has in the past, cholera remains largely a disease of impoverishment, social unrest and displacement, and continues to be a disease of major public health concern.

Contributors

All authors contributed equally to this Seminar.

Conflicts of interest

SBC, ETR, RCL, FQ, and JBH receive support from grants from the National Institutes of Health for research into immunity to cholera. FQ receives grants from the Bill & Melinda Gates Foundation and the Swedish International Development Agency (Sida) for research into vaccines and immunology in cholera. JBH receives a grant from the Charles H Hood Foundation for research into cholera immunology, and RCL receives a grant from the Howard Hughes Medical Institute for research into human genetic susceptibility to cholera. SBC, ETR, and FQ are co-inventors on institutional patents related to cholera vaccine development. SBC and ETR are editors for the infectious diseases sections of UpToDate, a medical education programme that includes topics related to cholera, and receive editorial payments from the publisher.

Acknowledgments

This work was supported by the International Centre for Diarrhoeal Research, Dhaka, and grants from the National Institutes of Health, AI058935 (SBC, ETR, FQ), U01 AI077883 (ETR, FQ) and an International Research Scientist Development Award, K01 TW07409 (JBH), a Physician-Scientist Early Career Award from the Howard Hughes Medical Institute (RCL), and a Charles H Hood Foundation Child Health Research Award (JBH).

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