Cholera Vaccines

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Cholera causes significant morbidity and mortality worldwide. For travelers, the risk of developing cholera per month of stay in a developing country is ~0.001%–0.01%, and cholera may present as traveler’s diarrhea. In the United States, only a poorly tolerated, marginally effective, parenterally administered, phenol-inactivated vaccine is available. Outside the United States, 2 additional vaccines are commercially available: an oral killed whole cell–cholera toxin recombinant B subunit vaccine (WC-rBS) and an oral live attenuated Vibrio cholerae vaccine (CVD 103-HgR). These oral vaccines are well tolerated. In field trials, WC-rBS provides 80%–85% protection from cholera caused by V. cholerae serogroup O1 for at least 6 months. In volunteer studies, CVD 103-HgR provides 62%–100% protection against cholera caused by V. cholerae for at least 6 months. No commercially available cholera vaccine protects against disease caused by V. cholerae serogroup O139. New cholera vaccines are being developed.

Risk of Cholera

Cholera is watery diarrhea caused by the gram-negative bacillus Vibrio cholerae serogroup O1 or O139 (variants of the lipopolysaccharide O antigen). On the basis of phenotypic characteristics, V. cholerae O1 organisms can be classified as classical or El Tor biotypes; on the basis of differences in antigenic determinants of the lipopolysaccharide O antigen, the organisms can be further subclassified into serotypes Inaba and Ogawa. Worldwide, V. cholerae O1 El Tor biotype is the predominant cause of cholera (and Ogawa is the predominant serotype); in 11 Asian countries, a minority of cholera cases are caused by V. cholerae O139. Since many countries do not accurately report the number of cholera cases, exact figures are unknown; however, it has been estimated that ~5–7 million cases of cholera occur worldwide each year, resulting in >100,000 deaths.

Cholera is transmitted by contaminated food or water and usually results from ingestion of a large inoculum of organisms (107–1011 organisms in individuals with normal gastric acidity; 104–106 in individuals with hypochlorhydria). Infected individuals excrete as many as 1013 V. cholerae organisms per day in stool, and contamination of food or water supplies can lead to rapid dissemination of the infection in a population. If an individual does ingest V. cholerae organisms, a spectrum of disease can result. Asymptomatic stool passage or mild disease is most common in individuals who reside in areas of endemicity and have complete or partial preexisting immunity. Nonimmune individuals can develop disease ranging from moderate diarrhea to voluminous diarrhea that kills within hours of onset (cholera gravis). The severity of cholera is related to many factors, including inoculum size, infecting biotype, presence or absence of preexisting immunity, and blood group, among others. Death rates associated with untreated or poorly treated cholera are often 20%–50% during epidemic disease (with death rates of 70%–100% among individuals with cholera gravis). Proper rehydration therapy decreases the mortality rate associated with cholera to <1% [1].

Although the risk is low, travelers do develop cholera (estimated incidence of 0.2 case per 100,000 European and North American travelers) [2, 3]. Despite the fact that ~20,000,000 Americans travel to developing nations each year, <20–30 cases
of cholera are described in American travelers yearly [4]. In Japan, regular microbiological screening for *V. cholerae* in returning travelers with diarrhea discloses an incidence of cholera for all destinations of 5 cases per 100,000 travelers and 13 cases per 100,000 Japanese travelers to Indonesia, usually to Bali [2, 5]. During the height of a recent cholera outbreak in Lima, Peru, a study of US embassy personnel with diarrhea disclosed that 5 of 317 US citizens were infected with *V. cholerae*. Therefore, the estimated incidence of cholera was 5.3 cases per 1000 population per year or 44 cases per 100,000 population per month of exposure during this outbreak [6]. Overall, the risk of developing cholera per month of stay in a developing country is estimated to be ~0.001%–0.01%, and cholera may present as traveler’s diarrhea [5, 7]. Although often not adhered to, simple food and water precautions can markedly decrease a traveler’s risk of developing cholera. Cholera vaccines have been used for >100 years with varying degrees of success [8–10].

**Parenteral Vaccines**

A number of parenteral cholera vaccines have been developed, including a killed whole cell vaccine, a purified lipopolysaccharide vaccine, killed whole cell vaccines with various adjuvants, and a polysaccharide-cholera toxin conjugate vaccine [8]. Evaluations have disclosed that these parenteral vaccines induce modest, short-lived protection. The parenteral cholera vaccine currently available in the United States has 10³ phenol-killed *V. cholerae* O1 organisms (classical and El Tor Inaba and Ogawa serotypes; table 1); the vaccine is ~50% effective for 3–6 months against cholera caused by *V. cholerae* O1 (the vaccine does not protect against cholera caused by *V. cholerae* O139) [8]. Vaccine efficacy in areas of endemicity is age related (the vaccine has the lowest efficacy among young children), which suggests that parenteral vaccines may boost immunologic responses that are already present (possibly limiting the utility of the vaccine for travelers).

The parenteral cholera vaccine has a high adverse event profile, especially after im or sc administration, and vaccination results in local pain, erythema, induration, fever, malaise, and headache in most individuals. Although intradermal administration of the vaccine is approved for use in individuals aged ≥5 years, few data exist on vaccine efficacy following intradermal administration among immunologically naive individuals. The vaccine should not be administered to infants aged <6 months. The adverse event profile often precludes its use in pregnant women. If the vaccine is employed and if ongoing protection is desired, a booster dose is recommended every 6 months. Simultaneous administration with yellow fever vaccine can decrease subsequent antibody levels induced by both vaccines, although no evidence confirms that protection from either disease is decreased. When feasible, spacing of yellow fever and cholera vaccines at an interval of 3 weeks is recommended. The vaccines can be administered simultaneously, if time constraints exist.

The parenteral vaccine has not been shown to have great effectiveness during cholera outbreaks and has not been shown to interrupt transmission of *V. cholerae* organisms in a community, and its use may impede other more useful sanitary and therapeutic interventions. For these and other reasons, the World Health Assembly removed the requirement for cholera vaccination for international travel in 1973. Because of its poor efficacy and high adverse event profile, the parenteral killed whole cell vaccine currently licensed in the United States has an extremely limited role. Some countries may require documentation of cholera vaccination for individuals traveling during a cholera outbreak.

**Oral Vaccines**

Because of the poor immunogenicity and high reactogenicity of parenteral cholera vaccines and the mucosal nature of *V. cholerae* infection, attempts began in the 1980s to develop oral

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**Table 1.** Summary of data on commercially available cholera vaccines.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Availability</th>
<th>Age</th>
<th>Dose schedule</th>
<th>Route</th>
<th>Time to protection</th>
<th>Time(s) of booster dose(s)</th>
<th>Protective efficacy, %</th>
<th>Adverse event profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral phenol-inactivated vaccine[^a]</td>
<td>US, other countries</td>
<td>≥6 mo</td>
<td>2 doses ≥1-4 w apart</td>
<td>Im, sc, or id[^b]</td>
<td>6 d after 2d dose</td>
<td>6 mo</td>
<td>30–50</td>
<td>High</td>
</tr>
<tr>
<td>Oral killed whole cell–recombinant B subunit vaccine[^c]</td>
<td>Europe</td>
<td>2–6 y</td>
<td>3 doses 7-42 d apart[^d]</td>
<td>Oral</td>
<td>7 d after final dose</td>
<td>6 mo[^d]</td>
<td>50–85</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;6 y</td>
<td>2 doses 7-42 d apart</td>
<td></td>
<td></td>
<td>2 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral live attenuated <em>Vibrio cholerae</em> strain CVD 103-HgR[^e]</td>
<td>Canada, Latin America, Europe</td>
<td>≥2 y</td>
<td>Single dose</td>
<td>Oral</td>
<td>Within 8 d of dose</td>
<td>6 mo</td>
<td>62–100</td>
<td>Low</td>
</tr>
</tbody>
</table>

NOTE: Id, intradermal

[^a]: Cholera vaccine, United States Pharmacopoeia, Wyeth Laboratories, Marietta, PA.

[^b]: Intradermal administration is approved only for individuals aged ≥5 years.

[^c]: WC863: Dukoral/oral cholera vaccine, SBL Vaccin AB, Stockholm, Sweden.

[^d]: According to the manufacturer’s recommendations.

[^e]: Orachol (Europe); Mutacol Berna (North America), Berna, Swiss Serum Vaccine Institute Bern, Bern, Switzerland.
cholera vaccines that might result in mucosal immune responses protective against cholera.

Whole Cell–B Subunit Vaccine (WC-BS)

This vaccine has 1 mg of the nontoxic B subunit of cholera toxin (CtxB) and 10¹⁰ killed V. cholerae O1 organisms (including classical and El Tor Inaba and Ogawa organisms from 3 strains that are either heat or formalin killed; table 1). The vaccine is administrated in 2 doses separated by 7–42 days; it is taken in a glass of water together with an alkaline buffer on an empty stomach (total volume, 150 mL; 75 mL for children aged 2–6 years). Food and drink should be avoided 2 h before and 1 h after ingesting the vaccine. If ongoing protection is required, the manufacturer recommends a booster dose after 2 years for adults and after 6 months for children aged 2–6 years. Mild abdominal discomfort can occur (probably related to the buffer), but the vaccine is well tolerated.

The vaccine has been evaluated in a number of well-designed field trials; the original and largest field trial was carried out in Bangladesh [11, 12]. In this trial, individuals received a total of 3 doses of the vaccine at 6-week intervals. WC-BS induced a high level of protection (85%) during the initial 6 months of the study [11]. At 12 months of follow-up, the vaccine was 62% protective. At 36 months of follow-up (the end of the study), WC-BS was 50% protective. During the first 6 months of evaluation, the vaccine provided protection in both young and older children, as well as in adults. However, the protective effect in young children rapidly decreased, and at 36 months of surveillance, the vaccine had its lowest efficacy (26%) among children aged 2–5 years, compared with 63% among individuals aged >5 years [12]. The vaccine protected equally against mild and severe cholera.

Immunologic responses after exposure to V. cholerae O1 vary by biotype and serotype, and although protection against disease caused by classical or El Tor biotypes was equivalent during the first 6 months of surveillance after vaccination, the longer term efficacy of WC-BS at 3 years was found to be lower against infections due to the El Tor biotype (39%) than against those due to the classical biotype (58%) [12]; the current global pandemic is caused predominantly by V. cholerae O1 El Tor organisms. The protective effect was also lower in individuals with blood group O (a risk factor for cholera gravis). The vaccine induced short-lived protection (67% at 3 months of surveillance and 21% at 12 months of surveillance) against heat-labile enterotoxin–producing enterotoxigenic Escherichia coli (ETEC) [13, 14]. Over the 3-year follow-up period, WC-BS resulted in a 25% reduction in hospital admissions of individuals with all types of diarrhea in Bangladesh, a 50% reduction in hospital admissions for life-threatening diarrhea, and a 45% reduction in mortality in women aged >15 years during a cholera epidemic [10, 15].

A recombinant version of the CtxB component of WC-BS is now being manufactured (WC-rBS). Evaluation of WC-rBS in Peru (an area where cholera has only recently been reintroduced after a 100-year absence) showed that the vaccine induced a 2-fold increase in vibriocidal antibody levels in ~50% of individuals after a primary oral series of 2 (as opposed to 3) doses [16]. Vibriocidal antibody levels decreased to baseline within 1 year, resulting in the recommendation that booster doses of WC-rBS may need to be employed on a yearly basis for immunologically naive individuals. The protective efficacy of WC-rBS against cholera caused by V. cholerae O1 El Tor biotype among adult military personnel in Peru (~86%) matched that induced by WC-BS in Bangladesh (although the Peruvian study was carried out over a mean follow-up period of only 18 weeks; therefore, the study may represent optimal vaccine efficacy) [17]. Many of the individuals in this Latin American trial had blood group O.

Live Attenuated Cholera Vaccines

Many live attenuated V. cholerae strains have been produced, most recently by recombinant techniques. One such strain is CVD 103-HgR, a derivative of V. cholerae O1 classical strain 569B (table 1). CVD 103-HgR does not express the enzymatically active subunit of cholera toxin, CtxA, and contains a mercury resistance gene (hgR) that permits identification of the vaccine strain. CVD 103-HgR has been well studied and found to be both safe and immunogenic in volunteers [18–23]. The vaccine has not been isolated from the environment in field studies after oral administration. The vaccine consists of 2 aluminum foil sachets, one containing buffer and the other containing lyophilized vaccine and aspartame as a sweetener. The vaccine should not be used by phenylketonurics. The 2 sachets are mixed in 100 mL of clean cold or lukewarm water and ingested. The temperature of the liquid should not exceed body temperature (37°C). The vaccine should be ingested 1 h before a meal. The vaccine is very well tolerated; mild nausea, abdominal cramping, and diarrhea are the most common complaints after ingesting the vaccine, although the incidence of such symptoms is not significantly different than that reported by individuals who ingest placebo. Booster regimens have not been evaluated; however, if exposure to cholera is ongoing, a booster dose is recommended every 6 months (although booster doses given up to 2 years after primary vaccination may evoke only modest immune responses, suggesting that ongoing immunity may result in decreased intestinal colonization and decreased immunologic processing of the live vaccine) [19].

A single oral dose of CVD 103-HgR (5 × 10⁶ cfu) in North American volunteers resulted in a significant increase in vibriocidal antibody levels in 92% of individuals, levels that are 3- to 5-fold higher than those seen in individuals given 3 doses of oral killed vaccine [18]. In these volunteer studies, CVD 103-
A large, randomized, placebo-controlled, double-blind field trial of $5 \times 10^9$ cfu of CVD 103-HgR that involved >65,000 individuals in Indonesia was recently completed [25]. The vaccine was very well tolerated and resulted in vibriocidal sero-responses in 64%–70% of vaccinees. The incidence of cholera was lower than expected during the study period, and only 93 evaluable cases of $V. \text{cholerae}$ O1 diarrhea were detected (43 cases in the vaccine group and 50 cases in the placebo group due to $V. \text{cholerae}$ O1 El Tor biotype); only 7 cases occurred within 6 months of vaccination, markedly limiting the ability to assess the short-term efficacy of the vaccine. Unfortunately, in this area of the world where $V. \text{cholerae}$ infection is endemic, the vaccine was not shown to protect against cholera, although a suggestion of protection was observed for individuals with blood group O ($P = .12$). Short-term protection from single-dose administration and longer-term protection from multiple-dose administration of CVD 103-HgR have yet to be evaluated in such an area of the world endemic for cholera.

CVD 103-HgR is a live attenuated vaccine, and its use in immunosuppressed individuals has not been evaluated in detail (although CVD 103-HgR may be safe, albeit less immunogenic, in some noneverly immunocompromised individuals with HIV infection who do not have AIDS) [26]. The vaccine should not be administered concurrently with antibiotics. Concomitant chloroquine can also decrease vaccine efficacy, and chloroquine should be administered no sooner than 1 week after administration of the vaccine. It is interesting that concomitant melfloquine does not effect immune responses to CVD 103-HgR. The administration of oral live attenuated typhoid vaccine (Vivotif [Salmonella typhi Ty21a]; Berna, Swiss Serum Vaccine Institute Bern, Bern, Switzerland) and CVD 103-HgR should be separated by at least 8 h because of the effects of ingestion of the current buffers, although the 2 vaccines may eventually be combined [27].

**Future Cholera Vaccines**

Additional live attenuated $V. \text{cholerae}$ O1 El Tor and $V. \text{cholerae}$ O139 vaccines are in various stages of analysis [21, 28–32]. Many of these vaccines have undergone removal of the entire cholera toxin genetic element (the filamentous phage Ctxφ), including the attRS1 site (the site of reintegration), by molecular genetic techniques. This last modification decreases the likelihood that the vaccine strains will reacquire Ctxφ in the environment and become toxigenic again. In an attempt to decrease reactogenicity, a number of these strains are also deficient in motility. Live combination vaccines ($V. \text{cholerae}$ O1 and O139; $V. \text{cholerae}$ O1 El Tor and classical biotypes) are also being evaluated. Recent identification of transposons and an integrase in $V. \text{cholerae}$ will need to be considered in the development of these live $V. \text{cholerae}$ vaccines, since mobile genetic elements could result in the reacquisition of undesired DNA in vaccine strains. Improved preparations of oral killed vaccines are also being developed, including combination $V. \text{cholerae}$ O1 and/or O139 vaccines [33, 34], and new parenteral cholera vaccines consisting of O antigens conjugated to a variety of proteins, including cholera toxin, are being evaluated [35]. The use of attenuated strains of $V. \text{cholerae}$ as expression vectors to deliver antigens directly to mucosal surfaces is also being explored [36, 37].

**Conclusion**

For now, the risk of cholera for the routine traveler is low (estimated at 0.001%–0.01% per month of stay in a developing nation), and, if contracted, death can be prevented with rehydration therapy. The only US Food and Drug Administration (FDA)–approved vaccine currently available in the United States is a 2-dose parenterally administered vaccine that has a high adverse event profile and is of limited efficacy. WC-rBS (not FDA approved) is better tolerated and provides 80%–85% protection for 6 months against cholera caused by $V. \text{cholerae}$ O1 classical and El Tor biotypes (in young children and adults) and 50% protection for at least 36 months (63% protection for individuals aged ≥6 years). The vaccine is administered in 2 oral doses, and protection is present ~7 days after vaccination. WC-rBS also provides limited protection against traveler’s diarrhea caused by ETEC (the most common cause of traveler’s diarrhea in many studies: 52%–67% protection against ETEC infection for ~3 months, although only 23% protection against “traveler’s diarrhea” as an entity) [14]. CVD 103-HgR (also not FDA approved) is also very well tolerated, is slightly more immunogenic than WC-rBS, and also provides 62%–100% (depending on the challenge strain of $V. \text{cholerae}$ O1) short-term (1–6 months) protection for immunologically naive North American volunteers; it does not appear to protect against traveler’s diarrhea caused by ETEC. The vaccine is administered as a single oral dose, and protection is evident within 8 days of vaccination. Although protective efficacy was not demonstrated in a field trial, the vaccine is effective in cholera challenge studies in North American volunteers [38]. None of the commercially available vaccines protect against cholera caused by $V. \text{cholerae}$ O139 (now reported from 11 Asian countries). Additional cholera vaccines are being developed.

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References


