Obtaining and Evaluating Evidence with Grading of Recommendations, Assessment, Development and Evaluation (GRADE) for Lyophilized CVD 103-HgR Vaccine

Introduction

In 2016, lyophilized CVD 103-HgR (Vaxchora™), a single-dose, live attenuated oral cholera vaccine, was approved for the prevention of cholera caused by *V. cholerae* O1 in adults traveling to cholera-affected areas. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) was adopted by CDC in 2011 as the framework for evaluating the scientific evidence that informs recommendations for vaccine use. The GRADE approach considers benefits and harms, evidence type, values and preferences, and health economic analysis. The main policy question for the GRADE evaluation of CVD 103-HgR use was, "Should live attenuated oral cholera vaccine CVD 103-HgR be recommended for use in adults 18–64 years old at risk of travel-related exposure to toxigenic *Vibrio cholerae* O1?" Factors influencing the strength of the recommendation included the balance between benefits and harms, the importance of key outcomes based on the knowledge and perspective of workgroup members, and the evidence type for each of the outcomes. Economic analyses were not formally considered in the body of evidence, as travel vaccines are usually paid for by the travelers and are often not covered by publically funded health care plans.

Methods

The work group performed a systematic review of Medline, Embase, Cochrane Library, and ClinicalTrials.gov, for papers in any language. Search terms are described in Table 1. Articles were included if they presented data on CVD 103-HgR and 1) involved human subjects; 2) reported primary data; 3) included data relevant to the outcome measures being assessed; and 4) included data for the dose being approved. Studies without adult participants 18 years of age or older were excluded. These studies were further limited to those published between 1988, when CVD 103-HgR was first developed, and January 2016. The work group also pursued available unpublished data from the vaccine manufacturer. After review of the titles and abstracts, 78 studies were identified for further review. Of these, 41 studies, including 1 cost-benefit analysis, did not include CVD 103-HgR data or any primary data, and 8 studies did not include adult participants. This left 29 studies for

inclusion in the GRADE evaluation. The work group reviewed articles of the currently available formulation of lyophilized CVD 103-HgR vaccine as well as literature pertaining to an older formulation of the vaccine (previously marketed as Orochol® or Mutacol®). Bibliographies were reviewed for additional relevant references.

Beneficial and harmful outcomes of vaccination to consider, as well as the importance of these outcomes, were proposed by the work group and presented to ACIP. The work group evaluated disease epidemiology and burden, severity of the disease, vaccine efficacy and effectiveness, vaccine safety, and economic and implementation considerations to propose the recommendation category. The accompanying policy note that summarizes the ACIP findings and conclusions was drafted based on the recommendation and revised based on feedback from ACIP voting members. The CDC Director approved these recommendations prior to publication. Opinions of individual members of ACIP may differ to some extent from the recommendation in this document, as this recommendation is the position of CDC based on the ACIP recommendation to the CDC Director.

Postmarketing surveillance studies and additional data pertaining to use of the vaccine will be reviewed by ACIP as they become available, and recommendations will be updated as needed.

Results

Critically important beneficial outcomes included prevention of cholera death, prevention of life-threatening cholera diarrhea (>5L volume over the illness course), and prevention of severe cholera diarrhea (>3L volume over the illness course). Critically important harmful outcomes included serious adverse events, systemic adverse events, and a decrease in the effectiveness of co-administered vaccines or medications. Prevention of cholera diarrhea of any severity and induction of a vibriocidal antibody response were considered important beneficial outcomes (Table 2).

Efficacy of CVD 103-HgR in prevention of cholera diarrhea: challenge and field studies

The efficacy of CVD 103-HgR vaccine has been evaluated with cholera challenge studies, in which vaccinated individuals ingest toxigenic *V. cholerae* O1, and by immunogenicity studies. Vibriocidal antibodies are a marker

for protection against *V. cholerae* infection. Efficacy was evaluated using evidence from the older and newer formulations of CVD 103-HgR vaccine, where available. The body of evidence indicates that the vaccine is effective. Evidence for specific outcomes is described below.

***Prevention of death from cholera*:** The available evidence was insufficient to determine whether CVD 103-HgR prevented death from cholera (Table 3). Challenge studies were not designed to examine this outcome. A large Indonesian field randomized controlled trial (RCT) with the older vaccine formulation did not assess deaths from cholera, but it found no difference between vaccinated and unvaccinated populations in deaths from diarrhea of any etiology over four years, using verbal autopsy method *(1)*. Of note, this study was not cluster-randomized, and incidence of cholera in the study setting was much lower than anticipated in both vaccinated and unvaccinated groups.

***Prevention of life-threatening cholera diarrhea (>5L)*:** One RCT found that CVD 103-HgR significantly reduced the proportion of volunteers who developed cholera diarrhea of >5L after challenge with toxigenic *V. cholerae* O1 in the vaccinated group compared with the placebo group *(2)* (Table 3). The vaccine efficacy (VE) was 93% for those challenged 10 days post-vaccination and 86% for those challenged 3 months post-vaccination.

Prevention of severe cholera diarrhea (>3L): Two challenge studies (RCTs) found that CVD 103-HgR significantly reduced the proportion of volunteers who developed cholera diarrhea of >3L after challenge with toxigenic *V. cholerae* O1 in the vaccinated group compared with the placebo group. In one study, challenge occurred 3 months after vaccination (VE 91%), and in the other, challenge occurred 10 days (VE 90%) or 3 months (VE 79%) after vaccination *(2)* (Table 3). The large field RCT in Indonesia, was not cluster-randomized and had lower-than-expected incidence of cholera overall, raising the possibility that herd immunity may have led to a decrease in incidence in unvaccinated as well as vaccinated participants *(3)*. This study found no difference in severe cholera diarrhea, as assessed by sentinel surveillance over four years, in vaccinated versus unvaccinated individuals *(1)*.

***Prevention of cholera diarrhea of any severity*:** Evidence for prevention of cholera diarrhea was evaluated with four RCTs and three observational studies (Table 3). There were five challenge studies in adults *(2, 4-7)*, which

include one RCT conducted with the new formulation of the vaccine *(2)*. The challenge studies showed consistent results indicating effectiveness of CVD 103-HgR in reducing the proportion who developed cholera diarrhea of any severity in the vaccinated group compared with the placebo group. The lowest VE in these studies was 51% at 3 months post-vaccination *(2)*; in two observational challenge studies, no vaccinated individuals developed cholera diarrhea, and the VE approached 100% *(5, 6)*. The Indonesia field RCT, which was not cluster-randomized and had lower-than-expected incidence of cholera overall, showed no difference between the vaccinated and unvaccinated population in cholera diarrhea detected by sentinel hospital surveillance over four years *(1)*. When CVD 103-HgR was used for a mass vaccination campaign during a cholera outbreak in Micronesia, the incidence of cholera diarrhea was lower in the vaccinated population than the unvaccinated population (0.3% versus 1.6%) *(8)*.

***Immunogenicity*:** Twenty RCTs and three observational studies were used to assess the evidence for immunogenicity of CVD 103-HgR, including four studies using the newer formulation of the vaccine (Table 4). The 19 studies using the older formulation of the vaccine show a consistent effect of induction of vibriocidal antibodies; VE in most studies was >90%, and the time frame for most serologic studies was within 1 week to 1 month of vaccination. The four RCTs with the newer formulation of the vaccine show that seroconversion (defined as a ≥4-fold rise in vibriocidal antibodies from baseline) occurred in 89–93% of vaccinated adults, with a VE of ≥96% *(2, 9-11)*.

Safety

***Serious adverse events*:** There were 21 RCTs and 4 observational studies that examined the occurrence of serious adverse events (Table 5). In a large Indonesian field study that was not cluster-randomized, there was no difference in overall mortality between the vaccinated and unvaccinated populations over four years *(1)*. The remaining 23 studies reported no serious adverse events linked to the vaccine among 6,589 individuals who received CVD 103-HgR.

***Systemic adverse events*:** There were 21 RCTs and 4 observational studies that examined the occurrence of systemic adverse events. None of these individual studies detected differences between the vaccinated and

unvaccinated groups in the occurrence of any systemic adverse events (Table 5). When studies of the new formulation were pooled *(2, 10, 11)*, there was a slight increase in diarrhea (≥4 loose stools per 24 hours), which was mostly mild, in vaccine versus placebo recipients (3.8 versus 1.6%; p=0.008).

***Post-marketing data*:** CVD 103-HgR was previously marketed as Orochol or Mutachol in several countries before manufacture ceased for business reasons. Of more than 500,000 Orochol doses sold, the following adverse events after vaccination were spontaneously reported: hospitalization with fever, gastroenteritis, vomiting, and hemorrhagic cerebrospinal fluid in one 11-month-old infant; Guillain Barré syndrome in a person who received CVD 103-HgR, yellow fever vaccine, Ty21a vaccine, and diphtheria and polio vaccines; angioedema (one report); and loss of hair (one report) *(12, 13)*. Of more than 250,000 Orochol E (a higher dose formulation) doses sold, there were no spontaneously reported adverse reactions.

Co-administration

Three randomized controlled trials and one observational cohort study reported co-administration of an older formulation of CVD 103-HgR with Ty21a vaccine and measured anti-*Salmonella* serotype Typhi LPS antibodies among study participants receiving both vaccines *(14-17)*. Anti-Typhi LPS antibodies were detected in 62–83% of participants (470 adults) after primary immunization; in comparison, one RCT reported that 66% of participants who received Ty21a alone developed anti-Typhi LPS antibodies. One study examined the immunogenicity of yellow fever (YF) 17D vaccine in combination with an older formulation of CVD 103-HgR or CVD 103-HgR and Ty21a; all 58 individuals who received both YF 17D and CVD 103-HgR developed anti-YF antibodies *(18)*.

One study evaluated an older formulation of CVD 103-HgR in combination with different medications and vaccines including Ty21a, YF 17D, oral polio vaccine, mefloquine, chloroquine, and proguanil *(16)*. Significantly lower rates of vibriocidal seroconversion were noted when CVD 103-HgR was co-administered with chloroquine (67%) versus alone (91%). No decrease in immunogenicity was noted for CVD 103-HgR when co-administered with mefloquine, proguanil, YF 17D, or oral polio vaccine.

Summary of quality of evidence across outcomes

The evidence type was downgraded for indirectness for studies using the older formulation of CVD 103-HgR vaccine, which is slightly different from the currently available formulation of CVD 103-HgR. Studies that evaluated the immunogenicity of CVD 103-HgR rather than effectiveness against oral cholera challenge were downgraded for indirectness. The overall body of evidence, which included studies with the newer lyophilized CVD 103-HgR formulation, studies with oral cholera challenge, as well as other studies, consistently indicated strong efficacy. The overall evidence type for efficacy of CVD 103-HgR was graded as 1 (RCTs or overwhelming evidence from observational studies), indicating the strongest level of evidence (Table 6).

While many studies evaluated the safety of the older formulation of CVD 103-HgR vaccine, there were relatively few recipients of the newer lyophilized vaccine formulation. Few studies evaluated the effectiveness of CVD 103-HgR when co-administered with other vaccines or medications, and all of these were with the older formulation of the vaccine. The evidence type for safety outcomes was downgraded for indirectness and imprecision for an overall evidence type of 3 (observational studies, or RCTs with notable limitations).

Summary

After reviewing available evidence and the GRADE evaluation for use of CVD 103-HgR, ACIP voted in June 2016 to recommend use of lyophilized CVD 103-HgR vaccine in adults 18–64 years old traveling to areas of active toxigenic *V. cholerae* O1 transmission (recommendation Category A). See *Recommendations of the Advisory Committee on Immunization Practices (ACIP) for use of cholera vaccine*.

Table 1: Evidence retrieval strategy

Database	Search terms
Medline (OVID) 1946-	Cholera Vaccines/ OR PXVX0200 OR PaxVax OR CVD 103-HgR OR Mutacol OR Vaxchora OR ((Vaccines, Attenuated/ OR ((live OR attenuated OR oral) ADJ2 vaccin*).ti,ab.) AND (exp Vibrio cholerae/ OR Cholera Toxin/ OR Cholera/ OR cholera*.ti,ab.)) NOT (Exp animals/ not exp humans/)
Embase (OVID) 1947-	Cholera Vaccine/ OR PXVX0200 OR PaxVax OR CVD 103-HgR OR Mutacol OR Vaxchora OR ((live vaccine/ OR ((live OR attenuated OR oral) ADJ2 vaccin*).ti,ab.) AND (exp Vibrio cholerae/ OR Cholera Toxin/ OR Cholera/ OR cholera*.ti,ab.)) NOT (Exp animals/ not exp humans/)
Cochrane Library	[mh "Cholera Vaccines"] OR PXVX0200 OR PaxVax OR "CVD 103-HgR" OR Mutacol OR Vaxchora OR (([mh "Vaccines, Attenuated"] OR ((live OR attenuated OR oral) NEAR/2 vaccin*):ti,ab) AND ([mh "Vibrio cholera"] OR [mh "Cholera Toxin"] OR [mh Cholera] OR cholera*:ti,ab))
Clinical Trials.gov	PXVX0200 OR PaxVax OR CVD 103-HgR OR Mutacol OR Vaxchora OR cholera vaccine

Table 2: CVD 103-HgR vaccination outcomes, importance, and data availability

Outcome	Importance	Data available
Benefits		
Prevent cholera death	Critical	Yes, limited
Prevent life-threatening (>5L*) cholera diarrhea	Critical	Yes, limited
Prevent severe (>3L*) cholera diarrhea	Critical	Yes
Prevent cholera diarrhea of any severity	Important	Yes
Induce vibriocidal antibody response	Important	Yes
Harms		
Serious adverse events	Critical	Yes
Systemic adverse events	Critical	Yes
Decrease effectiveness of co-administered vaccines or medications	Critical	Yes, limited

* Diarrhea volume over course of illness

Table 3: CVD 103-HgR prevention of cholera diarrhea: challenge and field studies

Study	Setting	Type	Population	Time between vaccination and challenge/outcome	Vaccinated persons, n/N (%)	Comparison persons, n/N (%)	RR (95% CI)[†]	VE[†]
Cholera death (0 studies)								
No studies assessed this outcome								
Life-threatening cholera diarrhea (>5L) (1 RCT, VE 86–93%)								
Chen, Cohen 2014 *(2)*	U.S.	RCT	Adults (18-45y)	10 days	1/35 (2.9)	28/66 (42.4)	0.1 (0.01–0.5)	93%
				3 months	2/33 (6.1)		0.1 (0.04–0.6)	86%
Severe cholera diarrhea (>3L) (3 RCTs, VE 79–91%)								
Tacket 1999 *(7)*	U.S.	RCT	Adults (18-40y)	3 months	1/28 (3.6)	9/23 (39.1)	0.1 (0.01–0.7)	91%
			Adults (18-40y) Blood Group O	3 months	1/15 (6.7)	4/8 (50)	0.1 (0.02–1)	87%
Richie 2000 *(1)*	Indonesia	RCT	Adults and children, 2-41y	Up to 54 months	11/33696 (<1)	7/33812 (<1)	1.6 (0.6–4.1)	N/A

Chen, Cohen 2014 *(2)*	U.S.	RCT	Adults (18-45y)	10 days	2/35 (5.7)	39/66 (59.1)	0.1 (0.02–0.4)	90%
				3 months	4/33 (12.1)		0.2 (0.1–0.5)	79%
Any severity cholera diarrhea (4 RCTs, 3 Observational, VE range 14% to approaching 100%)								
Levine 1988 *(4)*	U.S.	RCT	Adult college students	1 month	2/6 (33.3)	7/8 (87.5)	0.4 (0.1–1.2)	62%
Tacket 1992 *(5)*	U.S.	Obs	Adults (18-39y)	8 days	0/11 (0)	8/11 (72.7)	Small	Large
				4 to 6 months	0/14 (0)	10/15 (66.7)	Small	Large
Losonsky 1993 *(6)*	U.S.	Obs	Adults	8 days	0/36 (0)	8/11 (72.7)	Small	Large
				30 days	0/36 (0)	7/13 (53.8)	Small	Large
				6 months	0/36 (0)	10/15 (66.7)	Small	Large
Tacket 1999 *(7)*	U.S.	RCT	Adults (18-40y)	3 months	5/28 (17.9)	21/23 (91.3)	0.2 (0.1–0.4)	80%
			Adults (18-40y) Blood group O	3 months	4/15 (26.7)	7/8 (87.5)	0.3 (0.1–0.7)	70%

Richie 2000 *(1)*	Indonesia	RCT	Adults and children, 2–41y	Up to 54 months	43/33696 (0.1)	50/33812 (0.1)	0.9 (0.6–1.3)	14%
Calain 2004 *(8)*	Micronesia	Obs	Adults and children, ≥2y	Up to 4 months	50/14587 (0.3)	258/15664 (1.6)	0.2 (0.2–0.3)	79%
Chen, Cohen 2014 *(2)*	U.S.	RCT	Adults (18-45y)	10 days	5/35 (14.3)	61/66 (92.4)	0.2 (0.1–0.3)	85%
				3 months	15/33 (45.5)	61/66 (92.4)	0.5 (0.3–0.7)	51%

* VE calculated from studies as 100*(1-relative risk).

† Relative risk reported as “Small” and VE as “Large” for studies in which zero individuals in the intervention group developed the outcome of interest.

Abbreviations: RCT, randomized controlled trial; Obs, observational study; VE, vaccine efficacy; RR, relative risk; CI, confidence interval.

Table 4: CVD 103-HgR vibriocidal antibody seroconversion (20 RCTs, 3 observational; VE range 68% to approaching 100%)

Study	Setting	Type	Population	Serotype or Subgroup	Time between vaccination and measurement	Vaccinated persons, n/N (%)	Comparison persons, n/N (%)	RR (95% CI)*	VE*, †
Levine 1988 *(4)*	U.S.	RCT	Adult college students	Inaba	1 month	24/25 (96)	Not assessed		
Migasena 1989 *(19)*	Thailand	RCT	Adults (20-30y)	Inaba	10, 21, & 28 days (peak given)	11/12 (91.7)	0/12 (0)	Large	Large
				Ogawa	10, 21 & 28 days (peak given)	9/12 (75)	0/12 (0)	Large	Large
Cryz 1990 *(20)*	Switzerland	RCT	Adults (21-45y)	Inaba	10 days	19/25 (76)	0/25 (0)	Large	Large
					21 days	22/25 (88)		Large	Large
				Ogawa	10 days	14/25 (56)		Large	Large
					21 days	17/25 (68)		Large	Large
Cryz 1992 *(21)*	Switzerland	Obs	Adults	Inaba - booster	21 days post-booster	9/31 (29)	Not assessed		
				Ogawa - booster		7/31 (22.6)	Not assessed		

Kotloff 1992 *(22)*	U.S.	RCT	Adult college students (18-40y)	Inaba	8, 15, 21, or 28 days (at least one)	91/94 (96.8)	Not assessed		
Su-Arehawaratana 1992 *(23)*	Thailand	RCT	Adult soldiers, 10^8 dose	Inaba	9 or 28 days	13/33 (39.4)	Not assessed		
			Adult civilians, 10^8 dose	Inaba	9 or 28 days	19/30 (63.3)	Not assessed		
			Adult soldiers, 10^8 dose	Inaba	7, 14, 21, or 28 days	13/39 (33.3)	1/39 (2.6)	13 (1.8–94.6)	92%
			Adult soldiers, 10^9 dose	Inaba	7, 14, 21, or 28 days	17/40 (42.5)	1/39 (2.6)	16.6 (2.3–118.6)	94%
Tacket 1992 *(5)*	U.S.	Obs	Adults (18-39y)	Inaba, dose 3–5 x 10^8	10 days, 28 days, 4 to 6 months	20/21 (95.2)	Not assessed		
				Inaba, dose 3–5 x 10^9	10 days, 28 days, 4 to 6 months	7/7 (100)	Not assessed		

Gotuzzo 1993 *(24)*	Peru	RCT	Adults (18-38y), low SES	Inaba, 5 x 10^8 dose	7 days or 28 days	19/39 (48.7)	6/38 (15.8)	3.1 (1.4–6.9)	68%
				Inaba, 5 x 10^9 dose		28/39 (71.8)	6/38 (15.8)	4.5 (2.1–9.7)	78%
			Adults (18-38y), high SES	Inaba, 5 x 10^8 dose		31/40 (77.5)	8/41 (19.5)	4 (2.1–7.6)	75%
				Inaba, 5 x 10^9 dose		31/40 (77.5)	8/41 (19.5)	4 (2.1–7.6)	75%
Lagos 1993 *(25)*	Chile	RCT	Healthy adults (18-35y)	Inaba	8 or 28 days	34/40 (85)	2/41 (4.9)	17.4 (4.5–67.8)	94%
Wasserman 1993 *(26)*	U.S.	RCT	Adult college students (18-40y)	Inaba	20 days or 28 days	§			
Cryz 1995 *(14)*	Austria	RCT	Adults (16-56y)	Inaba	---	24/29 (82.8)	2/29 (6.9)	12 (3.1–46.2)	92%
Kollaritsch 1996 *(15)*	Austria	RCT	Adults	Inaba	14 days	244/260 (93.8)	6/65 (9.2)	10.2 (4.7–21.8)	90%

				Ogawa		208/260 (80)	0/65 (0)	Large	Large
Kollaritsch 1997 *(16)*	Austria	RCT	Adults (>18)	Inaba	14 days	41/45 (91.1)	Not assessed		
Taylor 1997 *(27)*	U.S.	RCT	Adults (18-40y)	Inaba	7 or 10 days	14/14 (100)	0/4 (0)	Large	Large
				Ogawa		13/14 (92.9)			
	Peru			Inaba	7 or 10 days	122/165 (73.9)	0/55 (0)	Large	Large
				Ogawa		95/165 (57.6)			
Perry 1998 *(28)*	Mali	RCT	Adults, HIV+ (18-46y)	Inaba	12 or 24 days	21/36 (58.3)	Not assessed		
			Adults, HIV- (18-47y)			22/31 (71)	Not assessed		
Tacket 1999 *(7)*	U.S.	RCT	Adults (18-40y)	Inaba	10 days	39/43 (90.7)	1/42 (2.4)	38.1 (5.5–264.8)	97%
Taylor 1999 *(29)*	Panama	RCT	Adults (18-40y)	Inaba	10-14 days	21/32 (65.6)	0/35 (0)	Large	Large
				Ogawa	10-14 days	17/32 (53.1)	0/35 (0)	Large	Large

Kollaritsch 2000 *(17)*	Austria	Obs	Adults, mean age 23.6-28.6y	Primary immunization		42/52 (80.8)	Not assessed		
				Reimmunization at 2.5y		29/51 (56.9)	Not assessed		
				Reimmunization at 3.5y		17/26 (65.4)	Not assessed		
Richie 2000 *(1)*	Indonesia	RCT	Children and adults (≥10y)	Inaba	10 days	85/142 (59.9)	4/107 (3.7)	16 (6.1–42.3)	94%
Chen, Cohen 2014 *(2)*	U.S.	RCT	Adults (18-45y)	Inaba	7 days	75/94 (79.8)	2/102 (2)	40.7 (10.3–161.1)	98%
					10 days	84/94 (89.4)		45.6 (11.5–180.1)	98%
					28 days	85/94 (90.4)		46.1 (11.7–182.2)	98%

					90 days	85/94 (90.4)		46.1 (11.7–182.2)	98%
					180 days	85/94 (90.4)		46.1 (11.7–182.2)	98%
Chen, Greenberg 2014 *(9)*	U.S.	RCT	Adults (21-48y)	Inaba	10 days	45/54 (83.3)	0/11 (0)	Large	Large
					14 days	48/54 (88.9)			
					28 days	44/54 (81.5)			
PaxVax study PXVX-VC-200-004 *(11)*	U.S.	RCT	Adults (18–46y)	Inaba	11 days	2513/2687 (93.5)	14/334 (4)	22.3 (13.4–37.3)	96%
PaxVax study PXVX-VC-200-005 *(10)*	U.S.	RCT	Adults (46–64y)	Inaba	11 days	263/291 (90.4)	0/99 (0)	Large	Large

* Relative risk and VE reported as “Large” for studies in which zero individuals in the comparison (non-vaccinated) group developed the outcome of interest.

[†] VE calculated as 100*(1-inverse of relative risk).

[§] Mean GMTs reported for vaccinated and comparison groups. Proportions of participants developing vibriocidal antibodies were not reported.

Abbreviations: RCT, randomized controlled trial; Obs, observational study; VE, vaccine efficacy; RR, relative risk; CI, confidence interval.

Table 5: Serious and systemic adverse events reported for studies of CVD 103-HgR (21 RCTs, 4 Observational)

Study	Setting	Type	Population	Outcome	Vaccine, n/N (%)	Comparison, n/N (%)	RR (95% CI)
Levine 1988 *(4)*	U.S.	RCT	Adult college students	diarrhea	1/25 (4)	Not assessed	
Migasena 1989 *(19)*	Thailand	RCT	Adults (20-30y)	adults	0/12 (0)	0/12 (0)	—
Cryz 1990 *(20)*	Switzerland	RCT	Adults (21-45y)	abdominal pain	0/25 (0)	1/25 (4)	—
				diarrhea	2/25 (8)	2/25 (8)	1 (0.2–6.6)
Cryz 1992 *(21)*	Switzerland	Obs	Adults	diarrhea	1/31 (3.2)	Not assessed	—
Kotloff 1992 *(22)*	U.S.	RCT	Adult college students (18-40y)	abdominal pain	9/94 (9.6)	11/94 (11.7)	0.8 (0.4–1.9)
				anorexia	3/94 (3.2)	1/94 (1.1)	3 (0.3–28.3)
				borborygmi	49/94 (52.1)	51/94 (54.3)	1 (0.7–1.3)
				diarrhea	8/94 (8.5)	3/94 (3.2)	2.7 (0.7–9.7)
				fever	2/94 (2.1)	2/94 (2.1)	1 (0.1–7)

				headache	8/94 (8.5)	10/94 (10.6)	0.8 (0.3–1.9)
				malaise	1/94 (1.1)	3/94 (3.2)	0.3 (0–3.1)
				vomiting	2/94 (2.1)	0/94 (0)	—
Su-Arehawaratana 1992 *(23)*	Thailand	RCT	Adults, soldiers, and civilians (18-26y)	study 1 diarrhea	11/102 (10.8)	13/104 (12.5)	0.9 (0.4–1.8)
				study 4 diarrhea	3/119 (2.5)	2/79 (2.5)	1 (0.2–5.8)
Tacket 1992 *(5)*	U.S.	RCT	Adult college students (18-40y)	study group 1	0/14 (0)	0/15 (0)	—
				study group 2	0/11 (0)	0/11 (0)	—
Gotuzzo 1993 *(24)*	Peru	RCT	Adults (18-38y), high SES, 5 x 10^8 dose	diarrhea	0/41 (0)	2/44 (4.5)	—
				vomiting	0/41 (0)	0/44 (0)	—
				abdominal pain	3/41 (7.3)	3/44 (6.8)	1.1 (0.2–5)
				fever	1/41 (2.4)	2/44 (4.5)	0.5 (0.1–5.7)
			Adults (18-38y), low SES, 5 x 10^8 dose	diarrhea	2/41 (4.9)	3/40 (7.5)	0.7 (0.1–3.7)
				vomiting	3/41 (7.3)	1/40 (2.5)	2.9 (0.3–27)

				abdominal pain	17/41 (41.5)	16/40 (40)	1 (0.6–1.8)
				fever	3/41 (7.3)	4/40 (10)	0.7 (0.2–3.1)
			Adults (18-38y), high SES, 5 x 10^9 dose	diarrhea	1/40 (2.5)	2/44 (4.5)	0.6 (0.1–5.8)
				vomiting	0/40 (0)	0/44 (0)	—
				abdominal pain	1/40 (2.5)	3/44 (6.8)	0.4 (0–3.4)
				fever	0/40 (0)	2/44 (4.5)	—
			Adults (18-38y), low SES, 5 x 10^9 dose	diarrhea	4/41 (9.8)	3/40 (7.5)	1.3 (0.3–5.4)
				vomiting	0/41 (0)	1/40 (2.5)	—
				abdominal pain	15/41 (36.6)	16/40 (40)	0.9 (0.5–1.6)
				fever	1/41 (2.4)	4/40 (10)	0.2 (0–2.1)
Lagos 1993 *(25)*	Chile	RCT	Adults (18-35y)	*			
Losonsky 1993 *(6)*	U.S.	Obs	Adults	diarrhea	0/36 (0)	Not assessed	
Cryz 1995 *(14)*	Austria	RCT	Adults (16-56y)	abdominal pain	11/102 (10.8)	4/90 (4.4)	2.4 (0.8–7.4)

				diarrhea	11/102 (10.8)	18/90 (20)	0.5 (0.3–1.1)
				fever	0/102 (0)	2/90 (2.2)	—
				nausea	3/102 (2.9)	5/90 (5.6)	0.5 (0.1–2.2)
				other	1/102 (1)	1/90 (1.1)	0.9 (0.1–13.9)
				rash	1/102 (1)	0/90 (0)	—
				vomiting	0/102 (0)	0/90 (0)	—
Kollaritsch 1996 *(15)*	Austria	RCT	Adults	nausea	38/256 (14.8)	6/65 (9.2)	1.6 (0.7–3.6)
				vomiting	6/256 (2.3)	1/65 (1.5)	1.5 (0.2–12.4)
				diarrhea	77/256 (30.1)	19/65 (29.2)	1 (0.7–1.6)
				abdominal pain	40/256 (15.6)	6/65 (9.2)	1.7 (0.8–3.8)
				fever	7/256 (2.7)	1/65 (1.5)	1.8 (0.2–14.2)
				headache	96/256 (37.5)	28/65 (43.1)	0.9 (0.6–1.2)
				fatigue	127/256 (49.6)	37/65 (56.9)	0.9 (0.7–1.1)

				rash	8/256 (3.1)	3/65 (4.6)	0.7 (0.2–2.5)
Kollaritsch 1997 *(16)*	Austria	RCT	Adults (>18)	diarrhea	10/45 (22.2)	Not assessed	
				nausea	9/45 (20)		
				vomiting	0/45 (0)		
				abdominal pain	10/45 (22.2)		
				headache	23/45 (51.1)		
				malaise	20/45 (44.4)		
				cutaneous	3/45 (6.7)		
Taylor 1997 *(27)*	Peru, U.S.	RCT	Adults (18-40y), Peru	abdominal pain	23/165 (13.9)	9/55 (16.4)	0.9 (0.4–1.7)
				diarrhea	4/165 (2.4)	1/55 (1.8)	1.3 (0.2–11.7)
				fever	1/165 (0.6)	0/55 (0)	—
				vomiting	2/165 (1.2)	0/55 (0)	—
			Adults (18-40y), U.S.	diarrhea	2/14 (14.3)	¼ (25)	0.6 (0.1–4.8)
Perry 1998 *(28)*	Mali	RCT	Adults (18-50y), HIV+	Diarrhea	2/27 (7.4)	1/27 (3.7)	2 (0.2–20.8)

				Vomiting	1/34 (2.9)	1/34 (2.9)	1 (0.1–15.3)
				fever	6/36 (16.7)	6/36 (16.7)	1 (0.4–2.8)
			Adults (18-50y), HIV-	Diarrhea	1/27 (3.7)	2/27 (7.4)	0.5 (0–5.2)
				Vomiting	1/34 (2.9)	1/34 (2.9)	1 (0.1–15.3)
				fever	5/34 (14.7)	6/34 (17.6)	0.8 (0.3–2.5)
Wiedermann 1998 *(30)*	Austria	Obs	Adults and children <1-81y	abdominal pain	137/1963 (7)	Not assessed	
				diarrhea	308/1963 (15.7)		
				vomiting	23/1963 (1.2)		
				nausea	167/1963 (8.5)		
				rash	56/1963 (2.9)		
				fever	38/1963 (1.9)		
Tacket 1999 *(7)*	U.S.	RCT	Adults (18-40y)	diarrhea	2/43 (4.7)	1/42 (2.4)	2 (0.2–20.7)

				fever	0/42 (0)	0/42 (0)	—
				headache	15/43 (34.9)	13/42 (31)	1.1 (0.6–2.1)
				malaise	10/43 (23.3)	14/42 (33.3)	0.7 (0.3–1.4)
				nausea	10/43 (23.3)	9/42 (21.4)	1.1 (0.5–2.4)
				vomiting	5/43 (11.6)	1/42 (2.4)	4.9 (0.6–40.1)
Taylor 1999 *(29)*	Panama	RCT	U.S. military in Panama	abdominal pain	4/32 (12.5)	0/35 (0)	—
				diarrhea	0/32 (0)	0/35 (0)	—
				fever	0/32 (0)	1/35 (2.9)	—
				nausea	0/32 (0)	2/35 (5.7)	—
				vomiting	0/32 (0)	3/35 (8.6)	—
Kollaritsch 2000 *(17)*	Austria	Obs	Adults, mean age 23.6y, primary immunization	Diarrhea	15/52 (28.8)	Not assessed	
				Nausea	8/52 (15.4)		
				Vomiting	1/52 (1.9)		
				Abd pain	4/52 (7.7)		

				Headache	20/52 (38.5)		
				Fatigue	21/52 (40.4)		
				Rash	5/52 (9.6)		
				Other	11/52 (21.2)		
				Any	38/52 (73.1)		
			Adults, mean age 28.6y, reimmunization @ 2.5y	Diarrhea	13/51 (25.5)		
				Nausea	5/51 (9.8)		
				Vomiting	0/51 (0)		
				Abd pain	7/51 (13.7)		
				Headache	16/51 (31.4)		
				Fatigue	11/51 (21.6)		
				Rash	0/51 (0)		
				Other	8/51 (15.7)		
				Any	31/51 (60.8)		

			Adults, mean age 23.7y, reimmunization @ 3.5y	Diarrhea	6/26 (23.1)		
				Nausea	7/26 (26.9)		
				Vomiting	0/26 (0)		
				Abd pain	2/26 (7.7)		
				Headache	12/26 (46.2)		
				Fatigue	12/26 (46.2)		
				Rash	1/26 (3.8)		
				Other	3/26 (11.5)		
				Any	19/26 (73.1)		
Richie 2000 *(1)*	Indonesia	RCT	Adults and children 2–41y	abdominal pain	19/538 (3.5)	19/539 (3.5)	1 (0.5–1.9)
				diarrhea	30/538 (5.6)	27/539 (5)	1.1 (0.7–1.8)
				fever	26/538 (4.8)	37/539 (6.9)	0.7 (0.4–1.1)
				headache	46/538 (8.6)	39/539 (7.2)	1.2 (0.8–1.8)
				itching	8/538 (1.5)	4/539 (0.7)	2 (0.6–6.6)

				nausea	18/538 (3.3)	16/539 (3)	1.1 (0.6–2.2)
				rash	2/538 (0.4)	2/539 (0.4)	1 (0.1–7.1)
				seizure	0/538 (0)	0/539 (0)	—
				vomiting	11/538 (2)	8/539 (1.5)	1.4 (0.6–3.4)
Leyten 2005 *(31)*	Netherlands	RCT	Adult traveling internationally	abdominal pain	7/65 (10.8)	12/69 (17.4)	0.6 (0.3–1.5)
Chen, Cohen 2014 *(2)*	U.S.	RCT	Adults (18-45y)	abdominal pain	20/95 (21.1)	20/102 (19.6)	1.1 (0.6–1.9)
				anorexia	17/95 (17.9)	23/102 (22.5)	0.8 (0.5–1.4)
				asthenia	32/95 (33.7)	33/102 (32.4)	1 (0.7–1.6)
				diarrhea	1/95 (1.1)	3/102 (2.9)	0.4 (0–3.4)
				fever	2/95 (2.1)	1/102 (1)	2.1 (0.2–23.3)
				headache	23/95 (24.2)	31/102 (30.4)	0.8 (0.5–1.3)
				nausea/vomiting	14/95 (14.7)	21/102 (20.6)	0.7 (0.4–1.3)
Chen, Greenberg 2014 *(9)*	U.S.	RCT	Adults (21-48y)	abdominal pain	10/55 (18.2)	3/11 (27.3)	0.7 (0.2–2)
				anorexia	3/55 (5.5)	1/11 (9.1)	0.6 (0.1–5.2)

				asthenia	6/55 (10.9)	0/11 (0)	—
				diarrhea	1/55 (1.8)	0/11 (0)	—
				fever	1/55 (1.8)	1/11 (9.1)	0.2 (0–3)
				headache	8/55 (14.5)	2/11 (18.2)	0.8 (0.2–3.3)
				nausea/vomiting	4/55 (7.3)	1/11 (9.1)	0.8 (0.1–6.5)
PaxVax study PXVX-VC-200-004 *(11)*	U.S.	RCT	Adults (18–46y)	tiredness	856/2734 (31.3)	94/343 (27.4)	1.1 (1-1.4)
				headache	791/2734 (28.9)	81/343 (23.6)	1.2 (1-1.5)
				abdominal pain	510/2734 (18.7)	58/343 (16.9)	1.1 (0.9-1.4)
				nausea/vomiting	501/2734 (18.3)	52/343 (15.2)	1.2 (0.9-1.6)
				lack of appetite	451/2734 (16.5)	57/343 (16.6)	1 (0.8-1.3)

				diarrhea	106/2734 (3.9)	4/343 (1.2)	3.3 (1.2-9)
				fever	17/2734 (0.6)	4/343 (1.2)	0.5 (0.2-1.6)
				headache	60/295 (20.3)	30/99 (30.3)	0.7 (0.5-1)
PaxVax study PXVX-VC-200-005 *(10)*	U.S.	RCT	Adults (46–64y)	tiredness	59/295 (20)	36/99 (36.4)	0.6 (0.4-0.8)
				abdominal pain	42/295 (14.2)	13/99 (13.1)	1.1 (0.6-1.9)
				nausea/vomiting	35/295 (11.9)	12/99 (12.1)	1 (0.5-1.8)
				lack of appetite	24/295 (8.1)	12/99 (12.1)	0.7 (0.3-1.3)
				diarrhea	7/295 (2.4)	2/99 (2)	1.2 (0.2-5.6)
				fever	2/295 (0.7)	0/99 (0)	Large

* No significant differences in systemic adverse events, including fever, vomiting, anorexia, abdominal pain, headache, borborygmi, liquid stools, diarrhea.

Abbreviations: RCT, randomized controlled trial; Obs, observational study; RR, relative risk; CI, confidence interval.

Table 6: Evidence type for outcomes for CVD 103-HgR vaccine in adult travelers

Outcome	Studies	Initial evidence	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Other	Final evidence type	Overall evidence type
Prevent cholera death	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Insufficient evidence to evaluate outcome
Prevent life-threatening cholera diarrhea	1 RCT	1	No serious	No serious	No serious	No serious	No serious	Strength of assoc. (+2)	1	1
Prevent severe cholera diarrhea	3 RCTs	1	No serious	Serious (-1)	No serious	No serious	No serious	Strength of assoc. (+2)	1	1
Prevent cholera diarrhea of any severity	4 RCTs	1	No serious	Serious (-1)	No serious	No serious	No serious	Strength of assoc. (+2)	1	1

	3 Obs	3	Serious (-1)	No serious	Serious (-1)	No serious	No serious	Strength of assoc. (+2)	3	
Induce vibriocidal antibody response	20 RCTs	1	No serious	No serious	No serious	No serious	No serious	Strength of assoc. (+2)	1	1
	3 Obs	3	No serious	No serious	Serious (-1)	No serious	No serious	Strength of assoc. (+2)	2	
Serious/systemic adverse events	21 RCTs	1	No serious	No serious	Serious (-1)	Serious (-1)	No serious	None	3	3
	4 Obs	3	No serious	No serious	Serious (-1)	No serious	No serious	None	4	
Decrease effectiveness of	3 RCTs	1	No serious	No serious	Serious (-1)	No serious	No serious	None	2	2

co-administered vaccines and medications	1 Obs	3	No serious	No serious	Serious (-1)	No serious	No serious	None	4	

Abbreviations: RCT, randomized controlled trial; Obs, observational study

References

1. Richie E, Punjabi NH, Sidharta Y, Peetosutan K, Sukander M, Wasserman SS. Efficacy trial of single dose live oral vaccine CVD 103-HgR in North Jakarta, Indonesia, a cholera endemic area. Vaccine [serial on the Internet]. 2000; 18: Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/803/CN-00835803/frame.html.

2. Chen WH, Cohen MB, Kirkpatrick BD, Brady R, Galloway D, Gurwith M, et al. Single-dose live attenuated oral cholera vaccine (CVD 103-HGR) protects against cholera at 10 days following vaccination: Results of a Vibrio Cholerae O1 EL Tor Inaba challenge study. American journal of tropical medicine and hygiene [serial on the Internet]. 2014; 91(5 suppl. 1): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/363/CN-01056363/frame.html.

3. Levine MM, Chen WH, Kaper JB, Lock M, Danzig L, Gurwith M. PaxVax CVD 103-HgR single-dose live oral cholera vaccine. Expert review of vaccines. 2017 Mar;16(3):197-213.

4. Levine MM, Kaper JB, Herrington D, Ketley J, Losonsky G, Tacket CO, et al. Safety, immunogenicity, and efficacy of recombinant live oral cholera vaccines, CVD 103 and CVD 103-HgR. Lancet. 1988 Aug 27;2(8609):467-70.

5. Tacket CO, Losonsky G, Nataro JP, Cryz SJ, Edelman R, Kaper JB, et al. Onset and duration of protective immunity in challenged volunteers after vaccination with live oral cholera vaccine CVD 103-HgR. Journal of infectious diseases [serial on the Internet]. 1992; 166(4): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/122/CN-00087122/frame.html.

6. Losonsky GA, Tacket CO, Wasserman SS, Kaper JB, Levine MM. Secondary Vibrio cholerae-specific cellular antibody responses following wild-type homologous challenge in people vaccinated with CVD 103-HgR live oral cholera vaccine: Changes with time and lack of correlation with protection. Infection and immunity [serial on the Internet]. 1993; 61(2): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/648/CN-00381648/frame.html.

7. Tacket CO, Cohen MB, Wasserman SS, Losonsky G, Livio S, Kotloff K, et al. Randomized, double-blind, placebo-controlled, multicentered trial of the efficacy of a single dose of live oral cholera vaccine CVD 103-HgR in preventing cholera following challenge with Vibrio cholerae O1 El tor inaba three months after vaccination. Infection and immunity [serial on the Internet]. 1999; 67(12): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/359/CN-00264359/frame.html.

8. Calain P, Chaine JP, Johnson E, Hawley ML, O'Leary MJ, Oshitani H, et al. Can oral cholera vaccination play a role in controlling a cholera outbreak? Vaccine. 2004 Jun 23;22(19):2444-51.

9. Chen WH, Greenberg RN, Pasetti MF, Livio S, Lock M, Gurwith M, et al. Safety and immunogenicity of single-dose live oral cholera vaccine strain CVD 103-HgR, prepared from new master and working cell banks. Clinical and vaccine immunology : CVI [serial on the Internet]. 2014; 21(1): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/134/CN-00979134/frame.html.

10. PaxVax, Inc. Clinical Study Report: A Phase III Randomized, Double-blind, Placebo-controlled Study in Older Adults to Assess Immunogenicity and Clinical Acceptability of a Single-dose of the Live Oral Cholera Vaccine Candidate PXVX0200 *Vibrio cholerae* O1 Serotype Inaba Vaccine Strain CVD 103-HgR. California2015 September 16, 2015 Contract No.: CSR: Phase 3 PXVX-VC-200-005.

11. PaxVax, Inc. Clinical Study Report: A Phase III Randomized, Double-blind, Placebo-Controlled Three-Lot Consistency Study in Healthy Adult Volunteers to Assess Immunogenicity, and Clinical Acceptability of a Single-dose of the Live Oral Cholera Vaccine Candidate PXVX0200, Vibrio cholerae O1 Serotype Inaba Vaccine Strain CVD 103-HgR. California2015 September 1, 2015 Contract No.: CSR: Phase 3 PXVX-VC-200-004.

12. Berna Biotech AG. Orochol® / Orochol® E: Spontaneously reported adverse reactions January 12,1994 - March 31, 20042004.

13. Berna Biotech AG. Periodic Safety Update Report for: Orochol(R) 2008 February 26, 2008. Report No.: 06.

14. Cryz SJ, Que JU, Levine MM, Wiedermann G, Kollaritsch H. Safety and immunogenicity of a live oral bivalent typhoid fever (Salmonella typhi Ty21a)-cholera (Vibrio cholerae CVD 103-HgR) vaccine in healthy adults.

Infection and immunity [serial on the Internet]. 1995; 63(4): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/946/CN-00111946/frame.html.

15. Kollaritsch H, Furer E, Herzog C, Wiedermann G, Que JU, Cryz SJ. Randomized, double-blind placebo-controlled trial to evaluate the safety and immunogenicity of combined Salmonella typhi Ty21a and Vibrio cholerae CVD 103-HgR live oral vaccines. Infection and immunity [serial on the Internet]. 1996; 64(4): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/537/CN-00123537/frame.html.

16. Kollaritsch H, Que JU, Kunz C, Wiedermann G, Herzog C, Cryz SJ, Jr. Safety and immunogenicity of live oral cholera and typhoid vaccines administered alone or in combination with antimalarial drugs, oral polio vaccine, or yellow fever vaccine. The Journal of infectious diseases. 1997 Apr;175(4):871-5.

17. Kollaritsch H, Cryz SJ, Jr., Lang AB, Herzog C, Que JU, Wiedermann G. Local and systemic immune responses to combined vibrio cholerae CVD103-HgR and salmonella typhi ty21a live oral vaccines after primary immunization and reimmunization. Vaccine. 2000 Jul 01;18(26):3031-9.

18. Tsai TF, Kollaritsch H, Que JU, Cropp CB, Kunz C, Wiedermann G, et al. Compatible concurrent administration of yellow fever 17D vaccine with oral, live, attenuated p6olera CVD103-HgR and typhoid ty21a vaccines. The Journal of infectious diseases. 1999 Feb;179(2):522-4.

19. Migasena S, Pitisuttitham P, Prayurahong B, Suntharasamai P, Supanaranond W, Desakorn V, et al. Preliminary assessment of the safety and immunogenicity of live oral cholera vaccine strain CVD 103-HgR in healthy Thai adults. Infection and immunity [serial on the Internet]. 1989; 57(11): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/343/CN-00063343/frame.html.

20. Cryz SJ, Levine MM, Kaper JB, Fürer E, Althaus B. Randomized double-blind placebo controlled trial to evaluate the safety and immunogenicity of the live oral cholera vaccine strain CVD 103-HgR in Swiss adults. Vaccine [serial on the Internet]. 1990; 8(6): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/732/CN-00074732/frame.html.

21. Cryz SJ, Jr., Levine MM, Losonsky G, Kaper JB, Althaus B. Safety and immunogenicity of a booster dose of Vibrio cholerae CVD 103-HgR live oral cholera vaccine in Swiss adults. Infect Immun. 1992 Sep;60(9):3916-7.

22. Kotloff KL, Wasserman SS, O'Donnell S, Losonsky GA, Cryz SJ, Levine MM. Safety and immunogenicity in North Americans of a single dose of live oral cholera vaccine CVD 103-HgR: results of a randomized, placebo-controlled, double-blind crossover trial. Infection and immunity [serial on the Internet]. 1992; 60(10): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/511/CN-00087511/frame.html.

23. Su-Arehawaratana P, Singharaj P, Taylor DN, Hoge C, Trofa A, Kuvanont K, et al. Safety and immunogenicity of different immunization regimens of CVD 103-HgR live oral cholera vaccine in soldiers and civilians in Thailand. Journal of infectious diseases [serial on the Internet]. 1992; 165(6): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/025/CN-00084025/frame.html.

24. Gotuzzo E, Butron B, Seas C, Penny M, Ruiz R, Losonsky G, et al. Safety, immunogenicity, and excretion pattern of single-dose live oral cholera vaccine CVD 103-HgR in Peruvian adults of high and low socioeconomic levels. Infection and immunity [serial on the Internet]. 1993; 61(9): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/344/CN-00095344/frame.html.

25. Lagos R, Avendaño A, Horwitz I, Prado V, Ferreccio C, Sotomayor V, et al. [Tolerance and immunogenicity of an oral dose of CVD 103-HgR, a live attenuated Vibrio cholerae 01 strain: a double-blind study of Chilean adults]. Revista médica de Chile [serial on the Internet]. 1993; 121(8): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/616/CN-00098616/frame.html.

26. Wasserman SS, Kotloff KL, Losonsky GA, Levine MM. Immunologic response to oral cholera vaccination in a crossover study: a novel placebo effect. American journal of epidemiology [serial on the Internet]. 1993; 138(11): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/606/CN-00097606/frame.html.

27. Taylor DN, Tacket CO, Losonsky G, Castro O, Gutierrez J, Meza R, et al. Evaluation of a bivalent (CVD 103-HgR/CVD 111) live oral cholera vaccine in adult volunteers from the United States and Peru. Infection and immunity [serial on the Internet]. 1997; 65(9): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/165/CN-00199165/frame.html.

28. Perry RT, Plowe CV, Koumare B, Bougoudogo F, Kotloff KL, Losonsky GA, et al. A single dose of live oral cholera vaccine CVD 103-HgR is safe and immunogenic in HIV-infected and HIV-noninfected adults in Mali. Bull World Health Organ. 1998;76(1):63-71.

29. Taylor DN, Sanchez JL, Castro JM, Lebron C, Parrado CM, Johnson DE, et al. Expanded safety and immunogenicity of a bivalent, oral, attenuated cholera vaccine, CVD 103-HgR plus CVD 111, in United States military personnel stationed in Panama. Infection and immunity [serial on the Internet]. 1999; 67(4): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/585/CN-00309585/frame.html.

30. Wiedermann G, Kollaritsch H, Jeschko E, Kundi M, Herzog C, Wegmuller B. Adverse events after oral vaccination against cholera with CVD103-HgR. Wien Klin Wochenschr. 1998 May 22;110(10):376-8.

31. Leyten EM, Soonawala D, Schultsz C, Herzog C, Ligthelm RJ, Wijnands S, et al. Analysis of efficacy of CVD 103-HgR live oral cholera vaccine against all-cause travellers' diarrhoea in a randomised, double-blind, placebo-controlled study. Vaccine [serial on the Internet]. 2005; 23(43): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/683/CN-00528683/frame.html.