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Oral killed cholera vaccines for preventing cholera (Review)

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[Intervention Review]

Oral killed cholera vaccines for preventing cholera

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ABSTRACT

Background

Cholera causes acute watery diarrhoea and death if not properly treated. Outbreaks occur in areas with poor sanitation, including refugee camps. Several vaccines have been developed and tested over the last 50 years. This is an update of a Cochrane review, originally published in 1998, which explored the effects of all vaccines for preventing cholera. This review examines oral vaccines made from killed bacteria.

Objectives

To assess the effectiveness and safety of the available World Health Organization (WHO)-prequalified oral killed cholera vaccines among children and adults.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register; CENTRAL, MEDLINE; Embase; LILACS; and two trials registers (February 2023).

Selection criteria

We included randomized controlled trials (RCTs), including cluster-RCTs. There were no restrictions on the age and sex of the participants or the setting of the study. We considered any available WHO-prequalified oral killed cholera vaccine as an intervention. The control group was given a placebo, another vaccine, or no vaccine. The outcomes were related to vaccine effectiveness and safety. We included articles published in English only.

Data collection and analysis

Two review authors independently applied the inclusion criteria and extracted data from included studies. We assessed the risk of bias using the Cochrane ROB 1 assessment tool. We used the generic inverse variance and a random-effects model meta-analysis to estimate

the pooled effect of the interventions. We assessed the certainty of the evidence using the GRADE approach. For vaccine effectiveness (VE), we converted the overall risk ratio (RR) to vaccine effectiveness using the formula: VE = (1 - RR) x 100%.

Main results

Five RCTs, reported in 12 records, with 462,754 participants, met the inclusion criteria.

We identified trials on whole-cell plus recombinant vaccine (WC-rBS vaccine (Dukoral)) from Peru and trials on bivalent whole-cell vaccine (BivWC (Shanchol)) vaccine from India and Bangladesh. We did not identify any trials on other BivWC vaccines (Euvichol/Euvichol-Plus), or Hillchol.

Two doses of Dukoral with or without a booster dose reduces cases of cholera at two-year follow-up in a general population of children and adults, and at five-month follow-up in an adult male population (overall VE 76%; RR 0.24, 95% confidence interval (CI) 0.08 to 0.65; 2 trials, 16,423 participants; high-certainty evidence).

Two doses of Shanchol reduces cases of cholera at one-year follow-up (overall VE 37%; RR 0.63, 95% CI 0.47 to 0.85; 2 trials, 241,631 participants; high-certainty evidence), at two-year follow-up (overall VE 64%; RR 0.36, 95% CI 0.16 to 0.81; 2 trials, 168,540 participants; moderate-certainty evidence), and at five-year follow-up (overall VE 80%; RR 0.20, 95% CI 0.15 to 0.26; 1 trial, 54,519 participants; high-certainty evidence).

A single dose of Shanchol reduces cases of cholera at six-month follow-up (overall VE 40%; RR 0.60, 95% CI 0.47 to 0.77; 1 trial, 204,700 participants; high-certainty evidence), and at two-year follow-up (overall VE 39%; RR 0.61, 95% CI 0.53 to 0.70; 1 trial, 204,700 participants; high-certainty evidence).

A single dose of Shanchol also reduces cases of severe dehydrating cholera at six-month follow-up (overall VE 63%; RR 0.37, 95% CI 0.28 to 0.50; 1 trial, 204,700 participants; high-certainty evidence), and at two-year follow-up (overall VE 50%; RR 0.50, 95% CI 0.42 to 0.60; 1 trial, 204,700 participants; high-certainty evidence).

We found no differences in the reporting of adverse events due to vaccination between the vaccine and control/placebo groups.

Authors' conclusions

Two doses of Dukoral reduces cases of cholera at two-year follow-up.

Two doses of Shanchol reduces cases of cholera at five-year follow-up, and a single dose of Shanchol reduces cases of cholera at two-year follow-up.

Overall, the vaccines were safe and well-tolerated.

We found no trials on other BivWC vaccines (Euvichol/Euvichol-Plus). However, BivWC products (Shanchol, Euvichol/Euvichol-Plus) are considered to produce comparable vibriocidal responses. Therefore, it is reasonable to apply the results from Shanchol trials to the other BivWC products (Euvichol/Euvichol-Plus).

PLAIN LANGUAGE SUMMARY

Oral killed cholera vaccines for preventing cholera

Key messages

Two doses of the whole-cell plus recombinant vaccine (WC-rBS vaccine (Dukoral)), with or without a booster dose, reduces cases of cholera for two years.

Two doses of the bivalent whole-cell vaccine (BivWC vaccine (Shanchol)) reduces cases of cholera for five years.

A single dose of Shanchol reduces cases of cholera and cases of severe dehydrating cholera for two years.

The vaccines are considered safe, with similar side effects reported by all groups.

Further studies are required to assess the effectiveness of a single-dose of Shanchol and two doses of Dukoral for five years of follow-up.

We found no trials on other BivWC vaccines, such as Euvichol or Euvichol-Plus. However, all BivWC vaccines are equal in their ability to kill cholera bacteria. Therefore, it is reasonable to apply the results from the Shanchol trials to Euvichol and Euvichol-Plus.

What is cholera?

Cholera is a disease that is caused by the bacteria *Vibrio cholerae*. People become infected by eating food or drinking water that is contaminated with these bacteria. Cholera is found throughout much of the world, in areas with poor sanitation or a lack of clean water,

and is a particular risk during humanitarian crises. People with cholera can develop severe cases of diarrhoea, which can lead to severe dehydration. Without treatment, many people die.

How is cholera prevented?

Cholera vaccines have been in development for many years. Cholera vaccines taken by mouth (orally) can be cost-effective, and easy to administer. They can be stored and delivered to areas during humanitarian crises.

Several trials have investigated how effective oral cholera vaccines are in children and adults in different settings, when given in different doses, and followed up for different lengths of time. The World Health Organization (WHO) has prequalified some oral cholera vaccines made with killed bacteria. This means they have used standard procedures to assess the safety and efficacy of a vaccine (that is, how well it works and how many side effects it causes). They provide this service to United Nations organizations that obtain vaccines, such as UNICEF.

A vaccine that is easy to give to children and adults and is very effective in preventing cholera, or protecting people from severe dehydrating cholera would be very valuable in the control of this potentially fatal disease. If the vaccine is easy to take and has few side effects, it would encourage more people to take it in countries where it is needed.

What did we want to find out?

We wanted to know how effective and safe the available WHO-prequalified oral cholera vaccines made with killed bacteria were for children and adults.

What did we do?

We searched the medical literature for trials that answered our question. We screened, collected, and analysed all relevant studies. We followed standard Cochrane methods to do this.

What did we find?

We included five trials, with 462,754 participants, which were conducted in three different countries; Peru, India, and Bangladesh.

Main results

Two doses of Dukoral, with or without a booster dose, reduced cases of cholera for two years.

Two doses of Shanchol reduced cases of cholera for five years.

One dose of Shanchol reduced cases of cholera and cases of severe dehydrating cholera for two years.

Generally, participants found that oral cholera vaccines made with killed bacteria were easy to use and safe. Side effects were similar in both the vaccine and comparison groups.

What are the limitations of the evidence?

We did not find any studies that examined the effects of any BivWC vaccines besides Shanchol. However, their effects on cholera bacteria are equal, so the results for Shanchol should be applicable to Euvichol and Euvichol-Plus.

How up to date is this evidence?

We searched for trials on 7 February 2023.

SUMMARY OF FINDINGS

Summary of findings 1. WC-rBS vaccine (Dukoral): two doses ± booster dose versus placebo

Patient or population: healthy children and adults; high risk population

Setting: community; regions with endemic cholera and seasonal epidemic peaks in Peru; 1993 to 1994

Intervention: WC-rBS (Dukoral) vaccine: two doses ± booster dose
Comparison: placebo: two doses ± booster dose

Outcomes	Relative effectiveness, RR (95% CI)	No of participants	Certainty of the evidence (GRADE)	Impact
Cases of cholera *(follow-up: 2 years *)*	0.24 (0.08 to 0.65)	16,423 (2 RCTs)	⊕⊕⊕⊕ High	Two doses ± booster of WC-rBS vaccine (Dukoral) reduces cases of cholera better than a placebo at 2 years; VE 76%

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect
The meta-analyses were based on per-protocol data.
For vaccine effectiveness, review authors converted the overall RR to vaccine effectiveness using the formula: % vaccine effectiveness = (1 - RR) x 100%.
* Follow-up in one study in a general population of children and adults was 2 years; in the other study with adult males, it was 5 months.
CI: confidence interval; **RR:** risk ratio; **VE**: vaccine effectiveness

Summary of findings 2. BivWC vaccine (Shanchol): two doses versus placebo

Patient or population: healthy children and adults; high risk population

Setting: hospital-based and community-based trials, in regions with endemic cholera and seasonal epidemic peaks in Bangladesh and India; 2006 to 2014

Intervention: BivWC (Shanchol) vaccine: two doses
Comparison: placebo: two doses

Outcomes	Relative effectiveness, RR (95% CI)	No of participants	Certainty of the evidence (GRADE)	Impact
Cases of cholera *(follow-up: 5 years)*	0.20 (0.15 to 0.26)	54,519 (1 RCT)	⊕⊕⊕⊕ High	Two doses of BivWC vaccine (Shanchol) reduces cases of cholera better than a placebo at 5 years; VE 80%.
Cases of cholera *(follow-up: 2 years)*	0.36 (0.16 to 0.81)	168,540 (2 RCTs)	⊕⊕⊕⊖ Moderate[a]	Two doses of BivWC vaccine (Shanchol) reduces cases of cholera better than a placebo at 2 years; VE 64%.
Cases of cholera *(follow-up: 1 year)*	0.63 (0.47 to 0.85)	241,631 (2 RCTs)	⊕⊕⊕⊕ High	Two doses of BivWC vaccine (Shanchol) reduces cases of cholera better than a placebo at 1 year; VE 37%.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect
[a]Downgraded by one level for the inconsistency of results (unexplained heterogeneity of results). However, the uncertainty was because of the differences in the magnitude of the effect estimate.
The meta-analyses were based on per-protocol data.
For vaccine effectiveness, we converted the overall RR to vaccine effectiveness using the formula: % vaccine effectiveness = (1 - RR) x 100%.
Cluster-adjusted analysis used ICC 0.005.
CI: confidence interval; **RR:** risk ratio; **VE**: vaccine effectiveness

Summary of findings 3. BivWC vaccine (Shanchol): single dose versus placebo

Patient or population: healthy children and adults, male and female; high risk population

Setting: hospital and community; in regions with endemic cholera and seasonal epidemic peaks; Bangladesh; 2014 to 2016

Intervention: BivWC vaccine (Shanchol): single dose
Comparison: placebo: single dose

Outcomes*	Relative effectiveness, RR (95% CI)	No of participants	Certainty of the evidence (GRADE)	Impact
Cases of cholera *(follow-up: 2 years)*	0.61 (0.53 to 0.70)	204,700 (1 RCT)	⊕⊕⊕⊕ High	A single dose of BivWC vaccine (Shanchol) reduces cases of cholera better than a placebo at 2 years; VE 39%.
Cases of severe dehydrating cholera *(follow-up: 2 years)*	0.50 (0.42 to 0.60)	204,700 (1 RCT)	⊕⊕⊕⊕ High	A single dose of BivWC vaccine (Shanchol) reduces cases of severe dehydrating cholera better than a placebo at 2 years; VE 50%.
Cases of cholera *(follow-up: 6 months)*	0.60 (0.47 to 0.77)	204,700 (1 RCT)	⊕⊕⊕⊕ High	A single dose of BivWC vaccine (Shanchol) reduces cases of cholera better than a placebo at 6 months; VE 40%.
Cases of severe dehydrating cholera *(follow-up: 6 months)*	0.37 (0.28 to 0.50)	204,700 (1 RCT)	⊕⊕⊕⊕ High	A single dose of BivWC vaccine (Shanchol) reduces cases of severe dehydrating cholera better than a placebo at 6 months; 63%.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect
The meta-analyses were based on per-protocol data.
For vaccine effectiveness, we converted the overall RR to vaccine effectiveness using the formula: % vaccine effectiveness = (1 - RR) x 100%.
CI: confidence interval; **RR:** risk ratio; **VE**: vaccine effectiveness

BACKGROUND

Description of the condition

The bacteria *Vibrio cholerae* (*V cholerae)* is responsible for the intense diarrhoeal disease, cholera. *V cholerae* is transmitted via the faecal-oral route, with contaminated food and water acting as the vehicle (Finkelstein 1996). Not all people who are infected with *V cholerae* develop the disease, with a proportion demonstrating the typical cholera manifestations of acute onset watery stool, generally joined by vomiting, which may lead to severe dehydration (WHO 2022). An untreated infection has a case-fatality rate between 25% and 50%. However, with adequate rehydration therapy, this can be reduced to less than 1% (WHO 2022). It is estimated there are approximately 2.8 million reported cholera cases each year, with 91,000 deaths (Sousa 2020).

Despite a lack of reporting, cholera is known to be prevalent in countries with poor sanitation and drinking water infrastructure, and is a particular risk during humanitarian crises. Between 2001 and 2005, the World Health Organization (WHO) reported 49 different outbreaks of cholera in 36 different countries (WHO 2006). The effect of an epidemic is catastrophic among vulnerable groups. In 1994, the refugee camps of Goma, in the Democratic Republic of Congo, experienced approximately 70,000 cases and 12,000 deaths (Sánchez 1997). Several epidemics have been reported in Zimbabwe (WHO 2009), and Haiti (WHO 2010). Cholera outbreaks have been reported across different regions of the world (WHO 2022; WHO 2023). In 2021, several cholera outbreaks were reported in Africa and the Eastern Mediterranean region (WHO 2023). In 2020, a total of 323,369 cholera cases, and 857 deaths from cholera were reported from 24 different countries (WHO 2022).

V cholerae colonizes the small intestine by attaching to the receptors of the upper intestinal mucosa (Sack 2004). The cholera toxin, which is composed of A and B subunits, is responsible for the pathogenicity of the organism. Using the B subunit, the bacteria bind with the epithelial surface of the cell. Though the toxin is devoid of any toxicity, it triggers the immune system of the host. Consequently, the A subunit is released into the mucosal cells and is responsible for the hypersecretion of fluid and electrolytes, which results in the onset of diarrhoea (Girard 2006). Host antibodies produced in response to past infection may inhibit the colonization process in the intestine.

Among the over 200 serological groups of *V cholerae*, only two serogroups*;* serogroups O1 and O139, cause epidemics. *V cholerae* O1 has two further biotypes; classical and El Tor. Each biotype has three distinct serotypes; Ogawa, Inaba, and Hikojima (Heymann 2008). The El Tor biotype of *V cholerae* O1 is currently responsible for most of the epidemics. This was identified first in Indonesia in 1961, and spread to Asia, Africa, Europe, and Latin America. *V cholerae* O139, also known as the Bengal strain, has been responsible for the epidemic in India and Bangladesh since 1992, and has remained confined to Asia (WHO 2022). Previous epidemics were caused by the classical biotype *V cholerae* O1, but this is now less common. However, other strains, such as non-O1/non-O139 are responsible for occasional sporadic events of gastroenteritis (Heymann 2008).

Evidence suggests that individuals with blood group O are at lower risk of developing cholera, but their susceptibility to developing severe cholera is higher if they are infected (Harris 2005). This provides the hypothesis that there may be a genetic imprint left by cholera infection in endemic areas (Harris 2016). It may also indicate that as cholera spreads to areas with a higher prevalence of blood group O, the prevalence of severe cholera will be higher in those places. Though the mechanism of this phenomenon is still unknown, it should be considered while assessing the effectiveness of the cholera vaccine.

Description of the intervention

The development of the cholera vaccine has a long history. Large-scale vaccination programmes against cholera started in the 1960s. Whole *V cholerae* O1 cells were injected into humans after being killed by either heat, formalin, or phenol. In the 1970s, it was reported that these whole-cell vaccines had low efficacy with short-term immunity, and a significant side effect profile (Bhadra 1994). The first Cochrane review on cholera vaccines was published in 1998, and reported that the effectiveness of the killed whole-cell vaccine was 54% at seven months, and 46% at the end of one year. The level of protection diminished by the end of the second year among children under five years of age, but remained among children over five years of age for as long as three years post-vaccination (Graves 2010).

Over time, injectable vaccines have been replaced by oral cholera vaccines. However, a highly effective vaccine (protective efficacy > 85%) has not yet been introduced to endemic countries, due to the inability to generate similar protection (vaccine efficacy down to 61% even after three doses), and the challenge of delivery within the field (recommended storage is -20 °C (Lopez 2014)).

Both inactivated oral cholera vaccines (killed whole cells of *V cholerae*), and live attenuated oral cholera vaccines (genetically modified, non-pathogenic strains of *V cholerae*) have been tested in clinical trials. Subunit vaccines consisting of cell components only (antigens) have also been tested. Among those, several safe and reasonably effective, licenced or WHO-prequalified vaccines are available to use (WHO 2022). WHO prequalification is an assessment of the safety and efficacy of a vaccine, using standard procedures, to determine the requirements of the vaccination programme. It is a service provided for United Nations organizations, such as UNICEF, that procure vaccines. Currently, these WHO-prequalified vaccines are available.

- Whole-cell plus recombinant vaccine (WC-rBS) - Dukoral®: an inactivated monovalent vaccine containing killed whole cells of *V cholerae* O1 and additional recombinant cholera toxin B subunit. It is produced by SBL Vaccine/Crucell, Sweden. It must be administered with a buffer solution.
- Bivalent whole-cell vaccine (BivWC) - Shanchol® and Euvichol/ Euvichol-Plus®:
  - Shanchol® is an inactivated bivalent vaccine containing killed whole cells of *V cholerae* O1 and *V cholerae* O139. It is produced by Shantha Biotechnics, India. Shanchol is a killed bivalent oral cholera vaccine containing whole cells of both *V cholerae* O1 and O139 serogroups. It received WHO prequalification in 2011. It is usually administered in a two-dose regimen. However, in resource poor settings, and under certain conditions, such as natural calamities and humanitarian crises, administration of a second dose might be challenging. Therefore, a large trial was conducted in Bangladesh using a single dose of Shanchol (Qadri 2016). It is important to note that the manufacturer of Shanchol decided to stop the production of the vaccine by the end of 2023.

- Euvichol/Euvichol-Plus®: an inactivated vaccine containing *V cholerae* O1 and *V cholerae* O139. It is produced by EuBiologics Co, Ltd, Republic of Korea with the help of the International Vaccine Institute. Euvichol-Plus and Shanchol have the same vaccine formula. Both Euvichol and Shanchol resulted from the tech transfer of the vaccine formulation from the International Vaccine Institute, using the same strains and the same procedures. Euvichol-Plus is the same as Euvichol. It is manufactured by the same company in the same facility, but Euvichol-Plus is presented as a plastic tube with the thimerosol removed, while Euvichol is in a glass vial. The antigenic perspective of Euvichol and Euvichol-Plus is identical.

Another killed whole-cell vaccine is under development and waiting for WHO prequalification.

- Hillchol®: a single stable recombinant *V cholerae* O1 El Tor Hikojima strain (MS1568) that expresses roughly the equivalent amounts of Ogawa and Inaba O1 lipopolysaccharide antigens. It is produced by MSD Wellcome Trust Hilleman Laboratories Pvt. Ltd., in collaboration with the University of Gothenburg, Sweden (Chowdhury 2021).

Dukoral, Shanchol, and Euvichol/Euvichol-Plus are the only three vaccines currently available for mass vaccination campaigns, through the Global Oral Cholera Vaccine Stockpile, which is supported by Gavi, the Vaccine Alliance (WHO 2017; WHO 2022). However, the production of Shanchol will be halted by the end of 2023.

How the intervention might work

Cholera vaccines stimulate the immune system of the host, resulting in either the prevention of, or reduction in the severity of the natural infection. The immunogenicity and effectiveness of the vaccine are often influenced by the route of administration. Oral cholera vaccines stimulate the local mucosal immunity of the gut, and thus prevent the multiplication and colonization of the infective agent. As cholera is transmitted through the faecal-oral route, oral vaccines might be more effective than injectable vaccines that need to generate systemic immunity. Oral vaccines are convenient to administer, with higher compliance; at the same time, they reduce the risk of blood-borne transmission of infection (Holmgren 2005).

Oral killed cholera vaccines (e.g. Dukoral, Shanchol, Euvichol/Euvichol-Plus) induce local immunity. They stimulate the IgA antibody response by their action in the gastrointestinal tract. These antibacterial antibodies intercept the bacterial attachment in the intestinal wall. Thus, the colonization of *V cholerae* O1 and O139 is hindered, providing protection against the disease.

Why it is important to do this review

The globally recommended and WHO-prequalified oral cholera vaccines are Dukoral, Shanchol, and Euvichol/Euvichol-Plus (WHO 2022). A trial for another killed whole-cell vaccine has recently been conducted (Chowdhury 2021). Many countries have provided a licence for oral vaccines that are mostly used by travellers (Hill 2006). A recent systematic review explored the effectiveness of oral cholera vaccines, including both Shanchol and ORC-Vax (Vabiotech; Vietnam), as a reactive measure in cholera outbreaks (Schwerdtle 2018). Another systematic review estimated the efficacy and effectiveness of the oral killed cholera vaccine for protection against cholera (Bi 2017).

Oral cholera vaccines are important in the prevention of cholera in endemic regions, during outbreaks of cholera where the incidence of the disease is very high. This is an update of the previous Cochrane review, Vaccines for preventing cholera, first published in 1998 and updated in 2001 (Graves 2001). The topic of cholera vaccines was updated and split into injected (Graves 2010), and oral vaccines (Sinclair 2011). In 2011, the review of oral vaccines considered seven large efficacy trials, four small artificial challenge studies, and 29 safety trials; it included both killed vaccines and live attenuated vaccines. In this update of Sinclair 2011, we considered only the killed cholera vaccines, because the live vaccines do not have WHO prequalification. We also considered only currently available WHO-prequalified killed cholera vaccines (Dukoral, Shanchol, and Euvichol/Euvichol-Plus).

OBJECTIVES

To assess the effectiveness and safety of the available World Health Organization (WHO)-prequalified oral killed cholera vaccines among children and adults.

METHODS

Criteria for considering studies for this review

Types of studies

Individually randomized controlled trials (RCTs) and cluster-RCTs.

Types of participants

All adults and children without any manifestation of active cholera infection.

Types of interventions

Intervention

Oral killed cholera vaccines (whole-cell plus recombinant vaccine (WC-rBS) - Dukoral, bivalent whole-cell vaccine (BivWC) - Shanchol, Euvichol/Euvichol-Plus).

Control

Placebo or another vaccine.

Types of outcome measures

Primary outcomes

1. Cases of cholera: cases were defined by stool culture-confirmed cases of *Vibrio cholerae* (*V cholerae*). The number of cases in a specific intervention/control group was considered the numerator; the number of study participants in that intervention/control group was the denominator.

Secondary outcomes

1. Cases of severe dehydrating cholera: the number of participants with severe dehydrating cholera. According to the WHO, lethargy or unconsciousness, inability to drink or poor drinking, reduced urine output, cool and moist extremities, low blood pressure, and a rapid and feeble pulse are the signs of severe dehydration.

2. Serious adverse events (SAE) leading to hospital admission or death: the number of SAEs. An SAE is defined as an adverse event (AE) meeting one of the following five conditions:
   a. Death during the period of protocol-defined surveillance
   b. Life-threatening event (defined as a study participant at immediate risk of death at the time of the event)
   c. An event requiring hospitalization, or which prolongs the existing hospitalization during the period of protocol-defined surveillance. In the case of diarrhoea, an SAE is one that requires admission to an inpatient ward for more than 24 hours.
   d. Congenital anomaly or birth defect, or malignancy
   e. A persistent or significant disability/incapacity
3. Other AEs: the number of AEs. An AE is defined as any untoward medical event (e.g. diarrhoea, vomiting, abdominal pain/cramps, or any other local or systemic symptoms, or both) within a pre-defined period (usually 28 days) after receipt of any dose of intervention/control, which may or may not be associated with the intervention/control.

Search methods for identification of studies

We attempted to identify all relevant trials, regardless of publication status (published, unpublished, in press, or in progress). However, we excluded reports that were solely available in abstract form.

Electronic searches

Search strategy for identification of studies

We described the search terms and strategies for different databases in Appendix 1.

Databases

We searched the following databases:

1. Cochrane Infectious Diseases Group Specialized Register (searched 7 February 2023);
2. Cochrane Central Register of Controlled Trials (CENTRAL; 2023, Issue 2), published in the Cochrane Library (searched 7 February 2023);
3. MEDLINE Ovid (1946 to 7 February 2023);
4. Embase Ovid (1947 to 7 February 2023); and
5. LILACS (Latin American and Caribbean Health Science Information database; BIREME; 1982 to 7 February 2023).

We also searched ClinicalTrials.gov (clinicaltrials.gov), and the WHO International Clinical Trial Registry Platform (ICTRP; www.who.int/ictrp/search/en) from 1980 to 7 February 2023, to identify ongoing or recently completed trials. We searched from 1980 onwards because trials of the currently available oral killed cholera vaccines were initiated in the 1990s (Sanchez 1994).

Searching other resources

Reference lists

We checked the references of all included reports and previously published reviews, and included those that fulfilled the inclusion criteria.

Data collection and analysis

Selection of studies

After removing duplicates, two review authors (KMSUR and RM) independently screened the titles and abstract of the search results. A third review author (AK) resolved any disagreements between the two review authors. We selected the articles that potentially met the inclusion criteria for full-text assessment. We listed all articles excluded after a full-text assessment, along with the reasons for exclusion, in the Characteristics of excluded studies table.

We excluded articles published with data other than the effectiveness and safety issues of oral killed cholera vaccines. Two review authors (KMSUR and RM) independently screened the full text of included articles for final data extraction.

We collated the same study with several publications under the same reference.

Data extraction and management

For each included trial, two review authors (MH and RM) independently extracted data, using the prespecified data extraction tool. We extracted information on: characteristics of the trials, such as study design, study period, population, the setting of the trial, study area, sample size, age and sex of participants, the dose of vaccine, type of placebo, follow-up period, cases of cholera, cases of severely dehydrating cholera, adverse events, and severe adverse events. We also extracted information on the number of participants randomized to each group, and the number of participants with specific outcomes.

We extracted data on the adverse events for each study. We extracted data based on doses of the vaccine, the duration of the follow-up period, and the number of events reported by participants. In cases of disagreement, one review author (KMSUR) cross-checked and resolved the disagreement through discussion.

In addition, we extracted information related to cluster-RCTs, such as number of clusters, average cluster size, intracluster correlation coefficient, and method of adjustment for clustering.

Assessment of risk of bias in included studies

Two review authors (KMSUR, RM) independently assessed the risk of bias in the included trials, using the Cochrane RoB 1 tool (Higgins 2022). This guideline includes six domains: random sequence generation; allocation concealment; blinding (of participants, personnel, and outcome assessors); incomplete outcome data; selective outcome reporting; and other sources of bias. As per the description of the guidelines, we classified the risk of bias as low risk of bias, unclear risk of bias, or high risk of bias.

We judged the process of sequence generation and allocation concealment by the method described in the articles. For blinding, we checked whether blinding was applied, if applicable. We checked incomplete outcome data and lost-to-follow-up data in the report. For selective outcome reporting, we checked the discrepancy between the technique outlined in the method and their corresponding results, i.e. outcome measured or reported. For other biases, we checked whether the results of the trials had been affected by any features, such as early stoppage of the trial or

contamination in a cluster-RCT. A third review author resolved any conflicts between the two independent review authors.

For the cluster-RCTs, we also considered the (i) recruitment bias; (ii) baseline imbalance; (iii) loss of clusters; (iv) incorrect analysis; and (v) comparability with individually-randomized trials (Higgins 2022).

We presented the risk of bias in risk of bias tables. We considered the overall risk of bias as low if all the domains were assessed at low risk of bias. We considered the overall risk of bias as unclear if at least one domain was unclear risk of bias. We considered the overall risk of bias as high if there was at least one domain at high risk of bias.

Measures of treatment effect

We reported the effectiveness of the intervention as reported in the article. In the meta-analysis, we used data from the per-protocol analysis for the meta-analysis (where mentioned). Therefore, we converted the vaccine effectiveness (VE) reported in the primary studies to a risk ratio (RR). We used this RR as the measure of the effect, and used the generic inverse variance method to pool the data in a meta-analysis. We expressed all the results for dichotomous outcomes as RR with 95% confidence intervals (CIs). This ratio measures the relative probability of an outcome, such as cases of cholera and cases of severe dehydrating cholera, occurring in the vaccinated group compared to the control group. As these ratios can be difficult to interpret directly, we transformed them into a vaccine effectiveness measure. This was expressed as a percentage, using the formula: vaccine effectiveness (VE) = 1 – risk ratio (RR) x 100. The transformed effect estimates were reported with their corresponding 95% confidence intervals (CIs), providing a measure of the precision of the vaccine effect estimate.

Unit of analysis issues

If a trial had multiple relevant treatment arms, we split the control group and the placebo group, and analyzed them separately. In cluster-RCTs, we converted the cluster-adjusted VE to a RR. We did not further adjust for the clustering effect in the meta-analysis.

Dealing with missing data

In future updates, if there are missing or insufficient data, we will try to contact the corresponding authors for additional information. If the missing data distort the results or make them unclear, we will exclude that portion from the analysis. For this update, we did not notice any missing or insufficient data.

Assessment of heterogeneity

We assessed the heterogeneity between studies, and tested it by using the Chi^2 test. We considered an I^2 statistic with a value of 30% to 60% as a moderate level of heterogeneity (Higgins 2022).

Assessment of reporting biases

We planned to assess reporting bias using funnel plot asymmetry. Had we included 10 or more studies in an outcome, we planned to examine a funnel plot for the primary outcome, estimating the precision of trials (plotting the RR against the standard error (SE) of the log of RR) to estimate potential asymmetry.

Data synthesis

We compared the interventions directly, using pairwise comparisons. We estimated the pooled effect of the intervention with a meta-analysis. We pooled the data that were available for the same outcome. In this analysis, we used the generic inverse variance statistical method with a random-effects model. For safety issues, we reported the number of adverse events per age group (where applicable). We used a narrative synthesis for data that we were unable to pool. We conducted all analyses in RevMan Web (RevMan Web 2023).

Subgroup analysis and investigation of heterogeneity

We planned to conduct the following subgroup analyses, when data were available:

- Age groups: (adult and child, or age under five years and over five years)
- Vaccine protection period: duration of protection is another important aspect of oral killed vaccines. It varies from study to study (Kanungo 2015; Qadri 2015; Qadri 2016). The vaccine effectiveness is commonly reported in oral killed cholera vaccine studies at different time points, such as 6 months, 12 months, 24 months, 36 months, and 60 months (Bhattacharya 2013; Kanungo 2015; Qadri 2015; Qadri 2016).
- Blood group (group O versus other blood groups): vaccine response is associated with the ABO blood group (Clemens 1989; Ramamurthy 2010)

We planned to investigate the difference between subgroups with the I^2 statistic. Alternatively, we planned to test the differences between subgroups with a meta-regression. However, we did not have sufficient data to conduct subgroup analyses.

Sensitivity analysis

We planned to conduct a sensitivity analysis using an intention-to-vaccinate analysis. However, we had insufficient data to undertake a sensitivity analysis.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to assess the certainty of the evidence, using these criteria (Schünemann 2013).

- Study design, risk of bias
- Inconsistency
- Indirectness
- Imprecision
- Publication bias

Two review authors independently made judgements on the certainty of the evidence. We resolved any disagreements through discussion with the lead review author. We documented the justifications for the judgements and incorporated them into the reporting. We downgraded the certainty of the evidence if there was a high risk of bias in the included studies, unexplained heterogeneity (inconsistency), indirectness of evidence, if the included studies had very small sample sizes and the CI was wide across the estimate of the effect, and if there was any publication bias.

We used GRADEpro GDT to generate the summary of findings tables for each comparison of interest. We developed separate summary of findings tables to report the effectiveness of the different vaccines:

- two doses of an oral killed cholera vaccine (WC-rBS; Dukoral) with or without a booster dose
  - Outcome: cases of cholera
- two doses of an oral killed cholera vaccine (BivWC; Shanchol)
  - Outcome: cases of cholera
- single dose of an oral killed cholera vaccine (BivWC; Shanchol)
  - Outcomes: cases of cholera, cases of severe dehydrating cholera

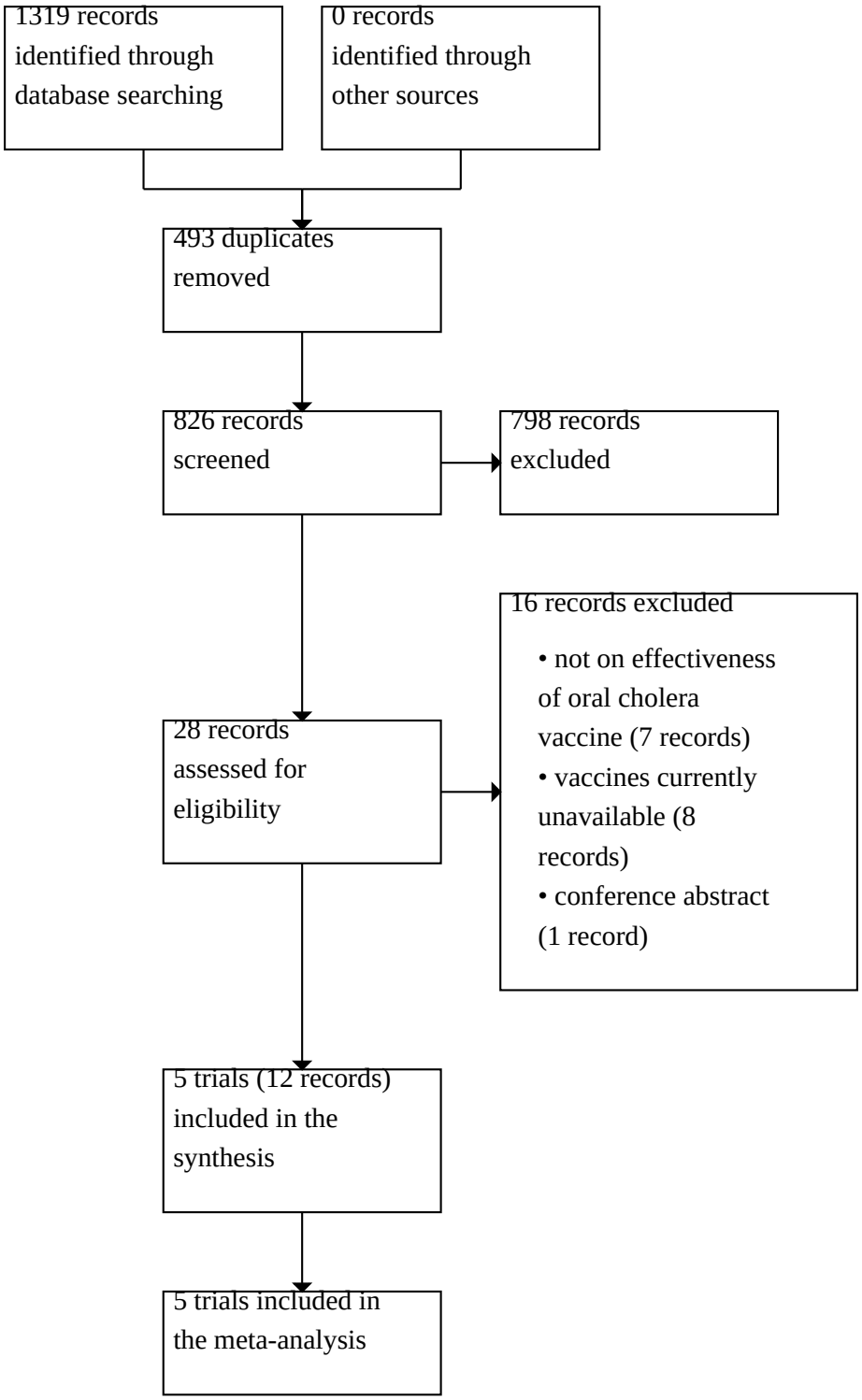
RESULTS

Description of studies

Results of the search

We searched for trials up to 7 February 2023. We identified 1319 reports from the database search and removed 493 duplicates. After screening 826 reports by titles and abstracts, we excluded 798, and screened the full text of 28 records. We included five trials (12 records), and illustrated the study selection process in Figure 1.

Figure 1. PRISMA flow diagram



Included studies

All five included studies were randomized controlled trials (RCTs), including two cluster-RCTs.

We identified trials on the whole-cell plus recombinant (WC-rBS) vaccine (Dukoral) from Peru, and trials on the bivalent whole-cell (BivWC) vaccine (Shanchol) from India and Bangladesh. We did not identify any trials on other BivWC vaccines (Euvichol/Euvichol-Plus) or Hillchol. However, there was a non-inferiority immunogenicity study of Euvichol carried out in the Philippines, comparing it with Shanchol (Baik 2014). The only trial on Hillchol is a phase I/phase II trial that evaluated the safety and immunogenicity of the vaccine (Chowdhury 2021). However, we excluded trials reporting only on safety and immunogenicity.

All included trials took place in low- and middle-income countries (LMICs): India (one trial), Bangladesh (two trials), and Peru (two trials). All trials included both adults and children except one trial that was conducted on military volunteers (Sanchez 1994). All trials assessed the effectiveness of the oral killed cholera vaccine.

One trial on Dukoral used two doses of vaccine, and followed up for five months (Sanchez 1994). The study recruited participants in January and March 1994, and the study ended in June 1994. The other trial used two doses of vaccine with a booster dose, and followed up for two years (Taylor 2000).

Two trials on Shanchol used two doses of vaccine (Bhattacharya 2013; Qadri 2015); one trial evaluated the effectiveness of a single dose of Shanchol (Qadri 2016). The two-dose trial of Shanchol in Bangladesh had three arms: vaccination only, vaccination and behavioural change, or no intervention (Qadri 2015).

Excluded studies

We excluded 16 records after a full-text assessment, for the following reasons, listed in the Characteristics of excluded studies table:

- not on the effectiveness of oral cholera vaccine (seven articles)
- vaccines not currently available (eight articles)
- conference abstract (one article)

Risk of bias in included studies

We presented the overall risk of bias in Figure 2 and Figure 3.

Figure 2. Summary of risk of bias assessments for each domain.

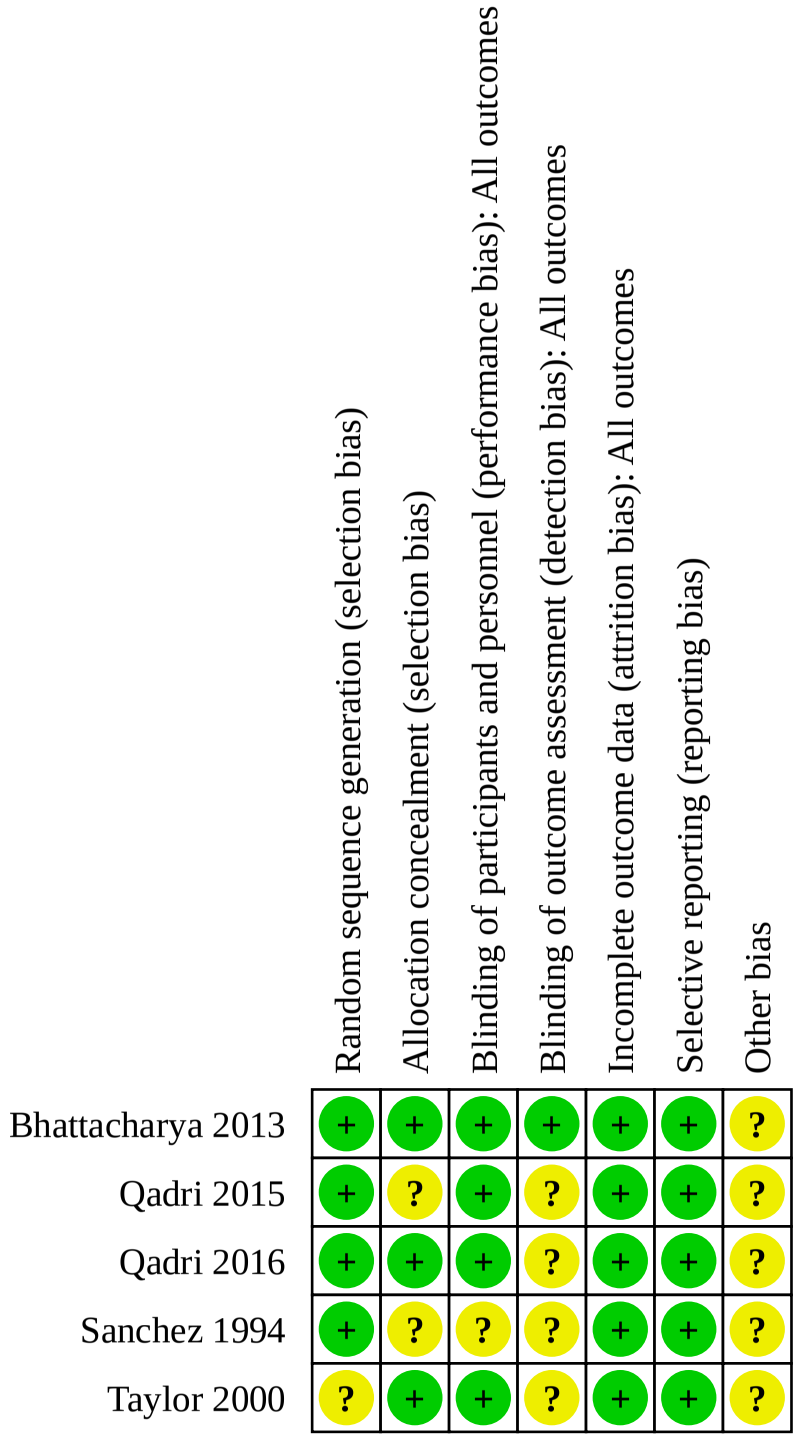
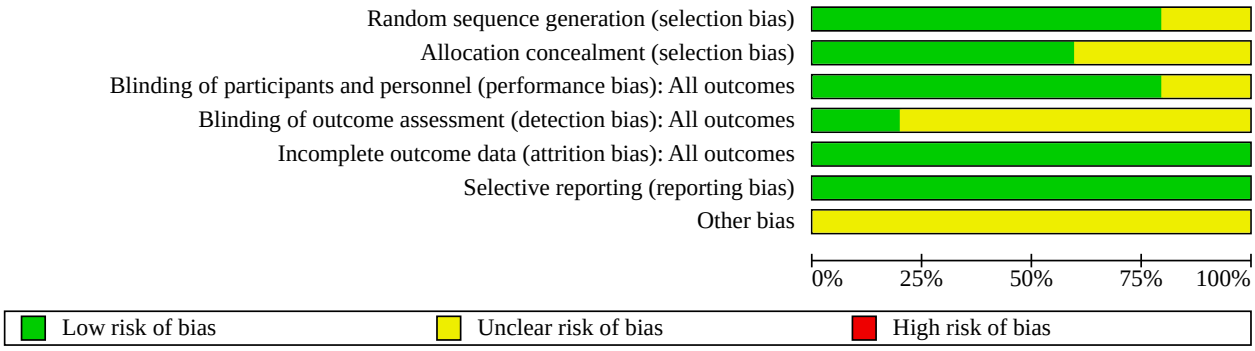


Figure 3. Summary of risk of bias as percentages across all studies.



We categorized two trials at low risk of bias (Bhattacharya 2013; Qadri 2016). Both trials had at least five of the seven domains categorized as low risk of bias. We judged two domains as unclear risk of bias, due to a lack of detailed information.

We considered additional points for assessing the risk of bias in the included cluster-RCTs (Bhattacharya 2013; Qadri 2015). We had no concerns regarding baseline imbalance, loss of clusters, or incorrect analysis in either trial. We had no concern about recruitment bias or comparability with individually randomized trials in Bhattacharya 2013. However, we identified some concerns in Qadri 2015 regarding recruitment bias because of the open-label design. We also identified some concerns in Qadri 2015 regarding comparability with individually randomized trials. We noticed that the authors mentioned diluted vaccine coverage and contamination of the control group due to the migration of participants from the intervention to the non-intervention cluster.

Allocation

For random sequence generation, we judged four trials at low risk of bias (Bhattacharya 2013; Qadri 2015; Qadri 2016; Sanchez 1994). Taylor 2000 reported insufficient information regarding random sequence generation.

We judged three trials at low risk of bias for concealment of the allocation sequence (Bhattacharya 2013; Qadri 2016; Taylor 2000). The other two trials reported insufficient information to allow us to make a judgement.

Blinding

We judged four trials at low risk for performance bias. Sanchez 1994 reported insufficient information to enable us to make a judgement.

We judged one trial at low risk of detection bias (Bhattacharya 2013), however, the remaining trials were unclear.

Incomplete outcome data

We judged all included trials at low risk of bias, as they reported sufficient information.

Selective reporting

All trials reported on pre-planned outcomes, and therefore, we considered them at low risk of bias.

Other potential sources of bias

We judged all the trials as unclear risk of bias, as we did not have information regarding any other potential bias.

Effects of interventions

See: **Summary of findings 1** WC-rBS vaccine (Dukoral): two doses ± booster dose versus placebo; **Summary of findings 2** BivWC vaccine (Shanchol): two doses versus placebo; **Summary of findings 3** BivWC vaccine (Shanchol): single dose versus placebo

Effectiveness and safety of WC-rBS vaccine (Dukoral)

We identified two trials on the effectiveness and safety of the WC-rBS vaccine, Dukoral. Taylor 2000 evaluated the effectiveness of two doses of Dukoral and a booster dose compared to placebo. Sanchez 1994 evaluated the effectiveness of two doses of Dukoral compared to placebo. There were differences between the age groups, population (one trial was on military volunteers), follow-up duration (Sanchez 1994 followed up for five months; Taylor 2000 followed up for two years), and the number of vaccine doses (one trial used two doses of vaccine, and the other used two doses plus a booster dose).

Primary outcome

Cases of cholera

Dukoral reduced cases of cholera better than a placebo at two years, with a vaccine effectiveness (VE) of 61% (RR 0.39, 95% CI 0.31 to 0.51; 1 trial, 14,997 participants; Analysis 1.1). The pooled analysis showed that two doses ± booster of Dukoral reduced cases of cholera better than a placebo at five months and two years, with a VE of 76% (RR 0.24, 95% CI 0.08 to 0.65; 2 trials, 16,423 participants; Analysis 1.2). However, Analysis 1.2 demonstrated high heterogeneity (96%).

Secondary outcomes

Cases of severe dehydrating cholera

These two trials did not specifically report the cases of severe dehydrating cholera.

Serious adverse events (SAE)

Taylor 2000 reported that there were no serious adverse events. Sanchez 1994 did not specifically report serious adverse events.

Other adverse events

Taylor 2000 reported there were 0.2% of participants in both the vaccine and placebo groups with adverse events. The most common symptom was diarrhoea. Sanchez 1994 reported that the rate of non-cholera diarrhoea was similar in the vaccine group and the placebo group.

Effectiveness and safety of two doses of BivWC vaccine (Shanchol)

We identified two trials that evaluated the effectiveness of two doses of BivWC (Shanchol) vaccine compared to placebo (Bhattacharya 2013; Qadri 2015).

Primary outcome

Cases of cholera

Two doses of Shanchol reduced cases of cholera better than a placebo at one year, with a VE of 37% (RR 0.63, 95% CI 0.47 to 0.85; 2 trials, 241,631 participants; Analysis 2.1). Two doses of Shanchol reduced cases of cholera better than a placebo at two years, with a VE of 64% (RR 0.36, 95% CI 0.16 to 0.81; 2 trials, 168,540 participants; Analysis 2.2). Two doses of Shanchol reduced cases of cholera better than a placebo at five years, with a VE of 80% (RR 0.20, 95% CI 0.15 to 0.26; 1 trial, 54,519 participants; Analysis 2.3).

Secondary outcomes

Cases of severe dehydrating cholera

These two trials did not specifically report the cases of severe dehydrating cholera.

Serious adverse events (SAE)

One trial reported that the number of participants with one or more SAEs after the first dose was 13 in the vaccine group and 11 in the placebo group. It also reported that the number of participants with one or more SAEs after the second dose was 11 in the vaccine group and 16 in the placebo group (Bhattacharya 2013).

Other adverse events

One trial reported that the number of adverse plus severe adverse events were similar in the Shanchol group (n = 51) and the control group (n = 48) after the first dose. After the second dose, the number of adverse and severe adverse events was 27 in the Shanchol group, and 33 in the control group (Bhattacharya 2013; Table 1).

Effectiveness and safety of a single dose of BivWC vaccine (Shanchol)

We identified one trial that explored the effectiveness of a single dose of BivWC (Shanchol) compared to placebo (Qadri 2016).

Primary outcome

Cases of cholera

A single dose of Shanchol reduced cases of cholera better than a placebo at six months, with a VE of 40% (RR 0.60, 95% CI 0.47 to 0.77; 1 trial, 204,700 participants; Analysis 2.4) and at 2 years with a VE of 39% (RR 0.61, 95% CI 0.53 to 0.70; 1 trial, 204,700 participants; Analysis 2.6).

Secondary outcomes

Cases of severe dehydrating cholera

A single dose of BivWC vaccine (Shanchol) reduces cases of severe dehydrating cholera better than a placebo at six months with a VE of 63% (RR 0.37, 95% CI 0.28 to 0.50; 1 trial, 204,700 participants; Analysis 2.5), and at two years, with a VE of 50% (RR 0.50, 95% CI 0.42 to 0.60; 1 trial, 204,700 participants; Analysis 2.7).

Serious adverse events (SAE)

This trial did not specifically report serious adverse events.

Other adverse events

Qadri 2016 reported adverse events after a single dose of Shanchol (Table 2). Within 14 days of vaccination, active surveillance noted 45 adverse events in the Shanchol group and 47 in the control group. Within 28 days of vaccination, active surveillance noted 33 adverse events in the Shanchol group and 30 in the control group.

DISCUSSION

Summary of main results

We included five randomized controlled trials (RCTs; reported in 12 records) in our synthesis that explored the effects of oral killed cholera vaccines compared with a control group (placebo) among children and adults.

Two doses of whole-cell plus recombinant vaccine (WC-rBS; Dukoral), with or without a booster dose, reduced cases of cholera at five months and at two years, in both a general population (2 to 65 years), and an adult male population (17 to 65 years; vaccine effectiveness (VE) 76%; high-certainty evidence; 2 trials; Summary of findings 1).

Two doses of bivalent whole-cell vaccine (BivWC; Shanchol) reduced cases of cholera at one year (2 trials; VE 37%, high-certainty evidence), at two years (2 trials; VE 64%, moderate-certainty evidence), and at five years (1 trial; VE 80%, high-certainty evidence; Summary of findings 2).

A single-dose of Shanchol reduced cases of cholera at six months (VE 40%, high-certainty evidence), and at two years (VE 39%, high-certainty evidence; 1 trial; Summary of findings 3).

Generally, oral killed cholera vaccines were found to be safe. The adverse events were similar in both the Dukoral vaccine group and the placebo group. There was no difference in adverse events between the Shanchol vaccine and the control groups within 14 days of a dose, in either the two-dose or single-dose regimen.

Overall completeness and applicability of evidence

The included articles explored the outcomes aligned with the objectives of this Cochrane review, which was to assess the effectiveness and safety measures of oral killed cholera vaccines.

Two trials measured the effectiveness of the WC-rBS vaccine (Dukoral), based on two trials conducted in Peru, one of which was conducted in military training centres in Peru. They followed-up for five months and two years.

The effectiveness of two doses of BivWC vaccine (Shanchol) was measured at one year, at two years, and at five years; the

effectiveness of the single dose of Shanchol was measured at six months and at two years. Adverse events within 14 days of each of the two doses were also reported. The trials were conducted in low- and middle-income settings, including India and Bangladesh.

There were no trials on other BivWC vaccines (Euvichol/Euvichol-Plus). However, all BivWC (Shanchol, Euvichol/Euvichol-Plus) products are considered to produce comparable vibriocidal responses. Therefore, it is reasonable to apply the results from the Shanchol trials to the other BivWC products (Euvichol/Euvichol-Plus).

Our review suggests that oral killed cholera vaccines are effective in reducing cases of cholera in high-risk, cholera-prone populations, living in endemic regions. While the absolute risk reduction demonstrates a small population-level effect, it is important to recognize that the trials included in the review were conducted in high-risk populations living in cholera endemic regions, such as Dhaka, Bangladesh, Kolkata, India, and Lima, Peru. These regions experienced occasional outbreaks during or before the trials started, suggesting that a small effect could contribute a larger impact in settings that experienced fewer endemic outbreaks, or in non-endemic settings. In cholera-endemic countries or during outbreaks, WC-rBS (Dukoral) and BivWC vaccines can provide protection against cholera and save thousands of lives by controlling the extent of these epidemics.

Certainty of the evidence

We assessed the certainty of the evidence as high for the effectiveness of Dukoral at two years (Summary of findings 1). There were some limitations in study design or execution. However, we did not downgrade the evidence, as those limitations did not impact the outcome.

We assessed the certainty of the evidence as high for the effectiveness of two doses of Shanchol at one year and at five years, and moderate at two years (Summary of findings 2). We downgraded the certainty of the evidence to moderate due to the inconsistency of results (unexplained heterogeneity of results). However, the uncertainty was because of the differences in the magnitude of the effect estimate.

We assessed the certainty of the evidence as high for the effectiveness of a single dose of Shanchol at six-month and two-year follow-up (Summary of findings 3).

Potential biases in the review process

We minimized any methodological limitations by using the rigorous methods for Cochrane systematic reviews and the GRADE Working Group. Two review authors independently curated data, which were checked and finalized through a discussion with the lead review author. Assessment of the risk of bias and grading of the evidence was independently conducted by two review authors. The lead review author resolved the conflict between the independent reviewer's judgement if necessary.

Agreements and disagreements with other studies or reviews

To our knowledge, this is a comprehensive review of oral killed cholera vaccines for preventing cholera. We pooled data, in a meta-analysis, to determine the effectiveness of the WC-rBS vaccine (Dukoral) and the BivWC vaccine (Shanchol), in reducing cases of cholera.

The previous Cochrane review considered both oral killed vaccines and live attenuated vaccines (Sinclair 2011). Other systematic reviews and meta-analyses have considered the effectiveness of common oral cholera vaccines in controlling cholera in specific situations, such as outbreaks.

The evidence generated from the current review is comparable to the other available systematic reviews conducted within the last 10 years (Lopez 2018; Panda 2020; Schwerdtle 2018; Sinclair 2011; Teoh 2018).

AUTHORS' CONCLUSIONS

Implications for practice

There is high-certainty evidence that two doses of whole-cell plus recombinant (WC-rBS) vaccine (Dukoral), with or without a booster, reduces cases of cholera better than a placebo, up to two-year follow-up, in an at-risk population.

There is high-certainty evidence that two doses of bivalent whole-cell (BivWC) vaccine (Shanchol) reduces cases of cholera better than a placebo at one-year and five-year follow-up, and moderate-certainty evidence that it is better at two-year follow-up, in an at-risk population.

There is high-certainty evidence that a single dose of Shanchol reduces cases of cholera better than a placebo at six-month and two-year follow-up, in an at-risk population. However, the effectiveness of a single-dose of Shanchol should be further explored, as the conclusion is based on a single study.

We found that the adverse events were similar in both the Dukoral group and the placebo group. We found no difference in the number of participants experiencing adverse events from either dose of the two doses of Shanchol. In the case of a single dose of Shanchol, the risk of adverse events was also similar.

Implications for research

This review graded the effectiveness of a single dose of BivWC (Shanchol) based on the results of a single trial. This implies the potential scope of further large-scale randomised controlled trials with a single dose of BivWC vaccine with six-month, one-year, two-year, and five-year follow-up.

We did not identify any RCTs on the effectiveness of newer vaccines, such as other BivWC vaccines (Euvichol/Euvichol-Plus) and Hillchol. Also, the manufacturer of Shanchol decided to stop the production of the vaccine by the end of 2023. However, all BivWC products (Shanchol, Euvichol/Euvichol-Plus) are considered to produce comparable vibriocidal responses. Therefore, it is reasonable to apply the results from Shanchol trials to the other BivWC products (Euvichol/Euvichol-Plus). There is also scope for large-scale randomized controlled trials with Hillchol.

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Lawrence Mbuagbaw, CIDG Editor; Paul Garner, CIDG Editor
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Deirdre Walshe, CIDG Managing Editor
- Copy Editor (copy editing and production): Victoria Pennick, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision):
  - One peer reviewer provided clinical peer review, but chose not to be publicly acknowledged.
  - Marty Chaplin, Cochrane Infectious Diseases Group (statistical peer review)
  - Ina Monsef Cochrane Haematology, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany (search review)
  - Brian Duncan (consumer review)

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bhattacharya 2013

Study characteristics	
Methods	Cluster-RCT (double-blind, placebo-controlled) Duration: 5 years, from 2006 to 2011
Participants	Number: 66,900 Inclusion criteria: residents of the study area aged 1 year or older Exclusion criteria: pregnancy
Interventions	Shanchol: 2 doses (14 days apart) Placebo: same as intervention
Outcomes	1. Effectiveness 2. Adverse event
Notes	Location: Kolkata, India Setting: community-based trials Funding source: Bill & Melinda Gates Foundation and the governments of South Korea and Sweden

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	We used stratified randomization to pre-assign all eligible participants in each dwelling to one of the codes, which were printed in vaccination books for use during dosing. (In reference paper, Sur 2009). An external statistician, who was masked to the identities of the codes, randomly assigned dwellings to the four codes in a 1:1:1:1 ratio within each of the strata.
Allocation concealment (selection bias)	Low risk	The vaccine and placebo were identical in appearance and packaged in single-use vials containing a 1·5 mL liquid dose. The vials were labelled with one of four letters, two each for vaccine and placebo (reference paper, Sur 2009).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Project staff and study participants are unaware of the identities of the codes. (reference paper, Sur 2009)

Bhattacharya 2013 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Before analysis, data were frozen, and the analytic plan was approved by the data and safety monitoring board.
Incomplete outcome data (attrition bias) All outcomes	Low risk	per-protocol and intent to vaccinate analyses was the date of second dose and first dose, respectively.
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were pre-specified.
Other bias	Unclear risk	Nothing mentioned

Qadri 2015

Study characteristics	
Methods	Cluster-RCT (open-label) Duration: 2 years
Participants	Number: 267,270 Inclusion criteria: male and female at age 1 year and above Exclusion criteria: pregnancy
Interventions	1. Shanchol (2 doses 14 days apart) 2. Shanchol with behavioural change (2 doses 14 days apart and a bottle of soapy water and an initial sachet of soap) 3. No intervention
Outcomes	1. Effectiveness 2. Adverse event
Notes	Location: Dhaka, Bangladesh Setting: community-based trial Funding source: Bill & Melinda Gates Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	We randomly assigned (with a computer-generated randomization sequence) 90 geographical clusters to one of three groups (1:1:1):
Allocation concealment (selection bias)	Unclear risk	Nothing mentioned about these issues.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	We did not use a placebo for the control group, so our study could not be masked. However, our analyses of protection against enterotoxigenic E coli diarrhoea suggest that bias was not the explanation for our findings of protection against cholera in the vaccination only group.

Qadri 2015 *(Continued)*

		No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Didn't give enough information about the outcome measurement, but is not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, for similar reasons
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were pre-specified.
Other bias	Unclear risk	Not mentioned clearly

Qadri 2016

Study characteristics	
Methods	RCT (double-blind, placebo-controlled) Duration: 2 years
Participants	Number: 204,700 Inclusion criteria: participants age at least 12 months, could have no severe illness (defined as being too ill to leave bed), and could not have a history of previous intake of an oral cholera vaccine. Exclusion criteria: pregnancy
Interventions	1. Shanchol (1 dose) 2. Placebo (Same as intervention)
Outcomes	1. Effectiveness 2. Adverse event
Notes	Location: Dhaka, Bangladesh Setting: community-based trial Funding source: Bill and Melinda Gates Foundation and others

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization of participants to vaccine or placebo was done on the basis of the census. Vaccine and placebo single-dose vials were randomly ordered within blocks of six, given consecutive unique numbers, and placed in boxes. The identities of the numbered vials were kept by designees at the manufacturer and IVI who were not otherwise involved in the trial.
Allocation concealment (selection bias)	Low risk	Teams were instructed to deliver a dose of vaccine or placebo to each successive eligible participant according to the numerical order of the vial in the box.

Qadri 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding was ensured; nobody knew the identities of the numbered vials.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Nothing mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	We used a passive surveillance system for detecting cholera cases, which might have missed some cases, particularly those that were less severe and thereby provided estimates of overall vaccine protection that were weighted towards them. Missing outcome data were balanced in numbers across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were pre-specified.
Other bias	Unclear risk	Nothing mentioned

Sanchez 1994

Study characteristics	
Methods	RCT (double-blind, placebo-controlled) Duration: 1994
Participants	Number: 1426 Inclusion criteria: 17 to 65 years old military volunteers from 3 military training centres near Lima, Peru
Interventions	WC/rBS: 2 doses of inactivated whole cell/ recombinant B subunit (WC/rBS) cholera vaccine Placebo: 2 doses of placebo
Outcomes	1. Effectiveness 2. Adverse event
Notes	Location: Lima, Peru Setting: military training centres near Lima, Peru Funding source: not mentioned.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization was done in blocks of 10 (5 to vaccine, 5 to placebo) to ensure equal study groups.
Allocation concealment (selection bias)	Unclear risk	Nothing mentioned

Sanchez 1994 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Nothing mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Nothing mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition reported
Selective reporting (reporting bias)	Low risk	Published reports include all expected outcomes, including those that were pre-specified
Other bias	Unclear risk	Nothing mentioned

Taylor 2000

Study characteristics	
Methods	RCT (double-blind, placebo-controlled) Duration: 2 years, from 1993 to 1994
Participants	Number: 17,799 Inclusion criteria: children and adults (2 to 65 years old)
Interventions	WC/rBS: 2 doses of oral inactivated whole cell Vibrio cholerae plus recombinant B subunit cholera vaccine (WC/rBS) and a 3rd booster dose Placebo: 3 doses of placebo
Outcomes	1. Effectiveness 2. Adverse event
Notes	Location: Lima, Peru Setting: field trials Funding source: US Army Medical Materiel and Development Command, Fort Detrick, Maryland

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Nothing mentioned
Allocation concealment (selection bias)	Low risk	During the study, the vaccine codes were kept locked by the manager of the data center of the US Naval Medical Research Institute Detachment (NAMRID), who was not involved in the study; the codes were not known to any of the persons conducting the trial.

Taylor 2000 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	During the study, the vaccine codes were kept locked by the manager of the data center of the US Naval Medical Research Institute Detachment (NAMRID), who was not involved in the study; the codes were not known to any of the persons conducting the trial.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Nothing mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Low risk	Published reports include all expected outcomes, including those that were pre-specified
Other bias	Unclear risk	Nothing mentioned

RCT: randomized controlled trial.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Baik 2014	Not on the effectiveness of oral cholera vaccine.
Chowdhury 2022	Not on the effectiveness of oral cholera vaccine.
Clemens 1986	Vaccine currently unavailable
Hashim 2012	Not on the effectiveness of oral cholera vaccine.
Khan 2016	Conference abstract
Mahalanabis 2008	Not on the effectiveness of oral cholera vaccine.
Mwaba 2021	Not on the effectiveness of oral cholera vaccine.
Russo 2018	Not on the effectiveness of oral cholera vaccine.
Savarino 2002	Not on the effectiveness of oral cholera vaccine.
Trach 1997	Vaccine currently unavailable

DATA AND ANALYSES

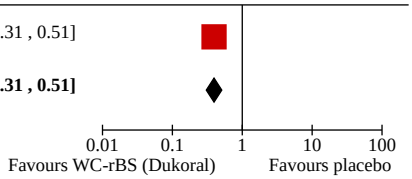
Comparison 1. WC-rBS vaccine (Dukoral) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Cases of cholera (2 doses + booster dose; 2-year follow-up; per-protocol analysis)	1	14997	Risk Ratio (IV, Random, 95% CI)	0.39 [0.31, 0.51]
1.2 Cases of cholera (2 doses ± booster dose; 5-month and 2-year follow-up; per-protocol analysis)	2	16423	Risk Ratio (IV, Random, 95% CI)	0.24 [0.08, 0.65]

Analysis 1.1. Comparison 1: WC-rBS vaccine (Dukoral) versus placebo, Outcome 1: Cases of cholera (2 doses + booster dose; 2-year follow-up; per-protocol analysis)

Study or Subgroup	log[Risk Ratio]	SE	WC-rBS (Dukoral) Total	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Taylor 2000	-0.93	0.13	7594	7403	100.0%	0.39 [0.31 , 0.51]
Total (95% CI)			**7594**	**7403**	**100.0%**	**0.39 [0.31 , 0.51]**

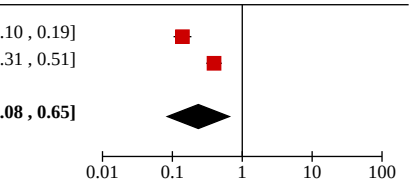
Heterogeneity: Not applicable
Test for overall effect: Z = 7.15 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: WC-rBS vaccine (Dukoral) versus placebo, Outcome 2: Cases of cholera (2 doses ± booster dose; 5-month and 2-year follow-up; per-protocol analysis)

Study or Subgroup	log[Risk Ratio]	SE	WC-rBS (Dukoral) Total	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Sanchez 1994	-1.97	0.15	710	716	49.7%	0.14 [0.10 , 0.19]
Taylor 2000	-0.93	0.13	7594	7403	50.3%	0.39 [0.31 , 0.51]
Total (95% CI)			**8304**	**8119**	**100.0%**	**0.24 [0.08 , 0.65]**

Heterogeneity: Tau² = 0.52; Chi² = 27.45, df = 1 (P < 0.00001); I² = 96%
Test for overall effect: Z = 2.78 (P = 0.005)
Test for subgroup differences: Not applicable



Comparison 2. BivWC vaccine (Shanchol) versus placebo

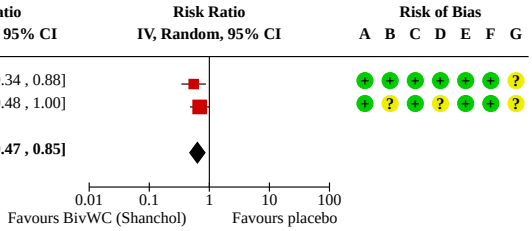
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Cases of cholera (2 doses; 1-year follow-up; per-protocol analysis)	2	241631	Risk Ratio (IV, Random, 95% CI)	0.63 [0.47, 0.85]
2.2 Cases of cholera (2 doses; 2-year follow-up; per-protocol analysis)	2	168540	Risk Ratio (IV, Random, 95% CI)	0.36 [0.16, 0.81]
2.3 Cases of cholera (2 doses; 5-year follow-up; per-protocol analysis)	1	54519	Risk Ratio (IV, Random, 95% CI)	0.20 [0.15, 0.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4 Cases of cholera (1 dose; 6-month follow-up; per-protocol analysis)	1	204700	Risk Ratio (IV, Random, 95% CI)	0.60 [0.47, 0.77]
2.5 Cases of severe dehydrating cholera (1 dose; 6-month follow-up; per-protocol analysis)	1	204700	Risk Ratio (IV, Random, 95% CI)	0.37 [0.28, 0.50]
2.6 Cases of cholera (1 dose; 2-year follow-up; per-protocol analysis)	1	204700	Risk Ratio (IV, Random, 95% CI)	0.61 [0.53, 0.70]
2.7 Cases of severe dehydrating cholera (1 dose; 2-year follow-up; per-protocol analysis)	1	204700	Risk Ratio (IV, Random, 95% CI)	0.50 [0.42, 0.60]

Analysis 2.1. Comparison 2: BivWC vaccine (Shanchol) versus placebo, Outcome 1: Cases of cholera (2 doses; 1-year follow-up; per-protocol analysis)

Study or Subgroup	log[Risk Ratio]	SE	BivWC (Shanchol) Total	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Bhattacharya 2013	-0.6	0.24	31932	34968	38.5%	0.55 [0.34 , 0.88]
Qadri 2015	-0.37	0.19	94675	80056	61.5%	0.69 [0.48 , 1.00]
Total (95% CI)			**126607**	**115024**	**100.0%**	**0.63 [0.47 , 0.85]**

Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 3.08 (P = 0.002)
Test for subgroup differences: Not applicable

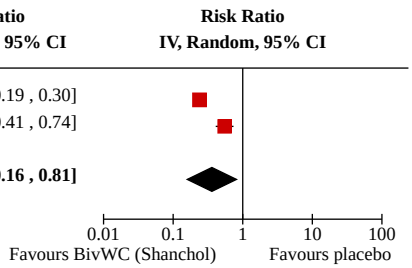


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.2. Comparison 2: BivWC vaccine (Shanchol) versus placebo, Outcome 2: Cases of cholera (2 doses; 2-year follow-up; per-protocol analysis)

Study or Subgroup	log[Risk Ratio]	SE	BivWC (Shanchol) Total	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Bhattacharya 2013	-1.43	0.11	30532	33466	50.8%	0.24 [0.19 , 0.30]
Qadri 2015	-0.6	0.15	53170	51372	49.2%	0.55 [0.41 , 0.74]
Total (95% CI)			**83702**	**84838**	**100.0%**	**0.36 [0.16 , 0.81]**

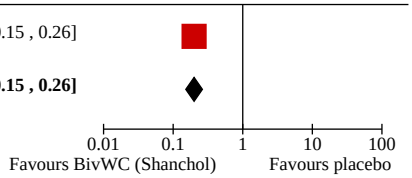
Heterogeneity: Tau² = 0.33; Chi² = 19.91, df = 1 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.46 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: BivWC vaccine (Shanchol) versus placebo, Outcome 3: Cases of cholera (2 doses; 5-year follow-up; per-protocol analysis)

Study or Subgroup	log[Risk Ratio]	SE	BivWC (Shanchol) Total	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Bhattacharya 2013	-1.61	0.14	25964	28555	100.0%	0.20 [0.15 , 0.26]
Total (95% CI)			**25964**	**28555**	**100.0%**	**0.20 [0.15 , 0.26]**

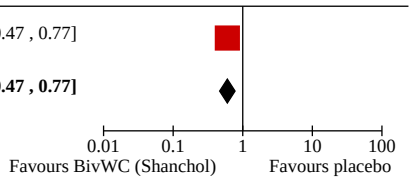
Heterogeneity: Not applicable
Test for overall effect: Z = 11.50 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: BivWC vaccine (Shanchol) versus placebo, Outcome 4: Cases of cholera (1 dose; 6-month follow-up; per-protocol analysis)

Study or Subgroup	log[Risk Ratio]	SE	BivWC (Shanchol) Total	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Qadri 2016	-0.51	0.13	102552	102148	100.0%	0.60 [0.47 , 0.77]
Total (95% CI)			**102552**	**102148**	**100.0%**	**0.60 [0.47 , 0.77]**

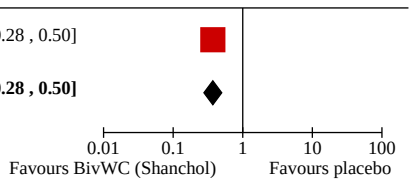
Heterogeneity: Not applicable
Test for overall effect: Z = 3.92 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: BivWC vaccine (Shanchol) versus placebo, Outcome 5: Cases of severe dehydrating cholera (1 dose; 6-month follow-up; per-protocol analysis)

Study or Subgroup	log[Risk Ratio]	SE	BivWC (Shanchol) Total	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Qadri 2016	-0.99	0.15	102552	102148	100.0%	0.37 [0.28 , 0.50]
Total (95% CI)			**102552**	**102148**	**100.0%**	**0.37 [0.28 , 0.50]**

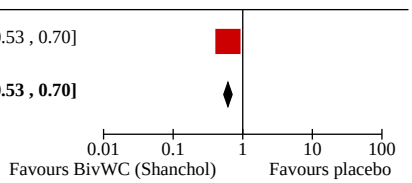
Heterogeneity: Not applicable
Test for overall effect: Z = 6.60 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: BivWC vaccine (Shanchol) versus placebo, Outcome 6: Cases of cholera (1 dose; 2-year follow-up; per-protocol analysis)

Study or Subgroup	log[Risk Ratio]	SE	BivWC (Shanchol) Total	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Qadri 2016	-0.49	0.07	102552	102148	100.0%	0.61 [0.53 , 0.70]
Total (95% CI)			**102552**	**102148**	**100.0%**	**0.61 [0.53 , 0.70]**

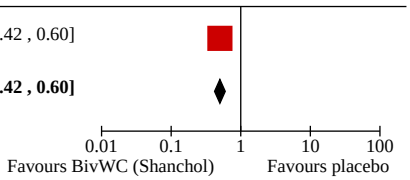
Heterogeneity: Not applicable
Test for overall effect: Z = 7.00 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2: BivWC vaccine (Shanchol) versus placebo, Outcome 7: Cases of severe dehydrating cholera (1 dose; 2-year follow-up; per-protocol analysis)

Study or Subgroup	log[Risk Ratio]	SE	BivWC (Shanchol) Total	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Qadri 2016	-0.69	0.09	102552	102148	100.0%	0.50 [0.42 , 0.60]
Total (95% CI)			**102552**	**102148**	**100.0%**	**0.50 [0.42 , 0.60]**

Heterogeneity: Not applicable
Test for overall effect: Z = 7.67 (P < 0.00001)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Adverse events for all participants within 14 days after first and second dose of BivWC vaccine (Shanchol)

Bhattacharya 2013	BivWC (Shanchol)		Placebo	
	Adverse events	No. recipients	Adverse events	No. recipients
Adverse events (AE)/severe adverse events (SAE) after the 1st dose	51	31,932	48	34,968
AE/SAE after the 2nd dose	27	31,932	33	34,968
Number of participants with one or more AE/SAE after the 1st dose	33	31,932	36	34,968
Number of participants with one or more SAE after the 1st dose	13	31,932	11	34,968
Number of participants with one or more AE/SAE after the 2nd dose	16	31,932	20	34,968
Number of participants with one or more SAE after the 2nd dose	11	31,932	16	34,968

AE: adverse events; No: number; SAE: severe adverse events

Table 2. Adverse events for all participants after a single dose BivWC vaccine (Shanchol)

Qadri 2016	BivWC (Shanchol)		Control	
	Adverse events	No. recipients	Adverse events	No. recipients
Adverse events within 14 days (active surveillance)	45	2987	47	3034
Adverse events within 28 days (active surveillance)	33	2848	30	2892
Adverse events within 28 days (passive surveillance)	121	102,954	125	102,357

APPENDICES

Appendix 1. Detailed search strategies

MEDLINE OVID search strategy

1 Cholera/

2 cholera.tw,kf.

3 Vibrio cholerae/

4 1 or 2 or 3

5 Vaccines/

6 (vaccin* or immuniz* or immunis*).tw,kf.

7 5 or 6

8 4 and 7

9 Cholera Vaccines/

10 shanchol.mp.

11 Cholvax.tw.

12 (Euvichol or Dukoral).mp.

13 hillchol.mp.

14 (rBS-WC or mORC-Vax or Oravacs).mp.

15 (ORC-Vax or Biv-WC*or BBV131).mp.

16 8 or 9

17 10 or 11 or 12 or 13 or 14 or 15

18 16 or 17

19 limit 18 to yr="1980 -Current"

20 randomized controlled trial.pt.

21 controlled clinical trial.pt.

22 randomized.ab.

23 (placebo or randomly or trial or groups).ti,ab.

24 dt.fs.

25 20 or 21 or 22 or 23 or 24

26 Animals/

27 humans/

28 26 and 27

29 26 not 28

30 25 not 29

31 19 and 30

Embase OVID search strategy

1 Cholera/

2 cholera.tw,kf.

3 Vibrio cholerae/

4 1 or 2 or 3

5 Vaccine/

6 (vaccin* or immuniz* or immunis*).tw,kf.

7 5 or 6

8 4 and 7

9 Cholera Vaccine/

10 shanchol.mp.

11 Cholvax.tw.

12 (Euvichol or Dukoral).mp.

13 hillchol.mp.

14 (rBS-WC or mORC-Vax or Oravacs).mp.

15 (ORC-Vax or Biv-WC*or BBV131).mp.

16 8 or 9

17 10 or 11 or 12 or 13 or 14 or 15

18 16 or 17

19 limit 18 to yr="1980 -Current"

20 (random* or factorial* or placebo* or assign* or allocat* or crossover*).tw.

21 ((blind* or mask*) and (single or double or triple or treble)).tw.

22 crossover procedure/

23 double blind procedure/ or single blind procedure/

24 randomization/ or placebo/

25 parallel design/ or Latin square design/

26 randomized controlled trial/

27 20 or 21 or 22 or 23 or 24 or 25 or 26

28 exp ANIMAL/ or exp NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp ANIMAL MODEL/

29 exp human/

30 28 not 29

31 27 not 30

32 19 and 31

CENTRAL search strategy

#1 cholera:ti,ab,kw

#2 MeSH descriptor: [Cholera] explode all trees

#3 ((vaccin* or immuniz* or immunis*)):ti,ab,kw

#4 MeSH descriptor: [Vaccines] explode all trees

#5 #3 or #4

#6 #1 or #2

#7 #5 and #6

#8 MeSH descriptor: [Cholera Vaccines] explode all trees

#9 #7 or #8

#10 (shanchol or Cholvax or Euvichol or Dukoral or Hillchol):ti,ab,kw

#11 ((rBS-WC or mORC-Vax or Oravacs or ORC-Vax or Biv-WC*or BBV131)):ti,ab,kw

#12 #9 or #10 or #11

LILACS search strategy

cholera [Words] and vaccin$ or shanchol or Cholvax or (Euvichol or Dukoral) or Euvichol-Plus or Hillchol [Words] and randomized or controlled or trial [Words]

ClinicalTrials.gov search strategy

vaccines | Cholera

WHO ICTRP search strategy

cholera and (vaccin* or shanchol or Cholvax or Euvichol or Dukoral or Euvichol-Plus or Hillchol)

CONTRIBUTIONS OF AUTHORS

KMSUR conceptualized the systematic review and developed the protocol. KMSUR, MH, RM, and AK were involved in screening, data extraction, quality assessment, and analysis. KMSUR wrote the first draft with input from MH and RM. AK and JM critically reviewed the manuscript and made the necessary modifications. JM developed the plain language summary. All review authors reviewed and approved the final review version prior to publication.

DECLARATIONS OF INTEREST

KM Saif-Ur-Rahman: none declared

Razib Mamun: none declared

Md Hasan: none declared

James Meiring: none declared

Arifuzzaman Khan is a co-author in two included articles (Qadri 2015; Qadri 2016). He was not engaged in data extraction or assessment of the risk of bias of the included articles.

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External sources

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  Project number 300342-104

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between review and review update

This is an update of the previous Cochrane review, 'Vaccines for preventing cholera', first published in 1998 and updated in 2001 (Graves 2001). The topic of cholera vaccines was updated and split into injected (Graves 2010), and oral vaccines (Sinclair 2011). Sinclair 2011 included both killed vaccines and live attenuated vaccines.

This is a review that resulted from the splitting of Sinclair 2011, and considered only the killed cholera vaccines, as the live vaccines do not have WHO-prequalification. We considered only currently available WHO-prequalified oral killed cholera vaccines (Dukoral, Shanchol, and Euvichol/Euvichol-Plus).

We focused on the effectiveness and safety outcomes of the available WHO-prequalified oral killed cholera vaccines. The outcomes were cases of cholera, cases of severe dehydrating cholera, serious adverse events, and other adverse events.