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# Oral vaccines for preventing cholera (Review)

Sinclair D, Abba K, Zaman K, Qadri F, Graves PM

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[Intervention Review]

# Oral vaccines for preventing cholera

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**Editorial note:** This review is superseded by the published Cochrane Review, Saif-Ur-Rahman 2024 [https://doi.org/10.1002/14651858.CD014573], which considers only the oral killed vaccines because the live oral vaccines do not have World Health Organization (WHO) prequalification. Saif-Ur-Rahman 2024 also considered only currently available WHO pre-qualified oral killed cholera vaccines (Dukoral, Shanchol, and Euvichol/Euvichol-Plus).

## ABSTRACT

### Background

Cholera is a cause of acute watery diarrhoea which can cause dehydration and death if not adequately treated. It usually occurs in epidemics, and is associated with poverty and poor sanitation. Effective, cheap, and easy to administer vaccines could help prevent epidemics.

### Objectives

To assess the effectiveness and safety of oral cholera vaccines in preventing cases of cholera and deaths from cholera.

### Search methods

In October 2010, we searched the Cochrane Infectious Disease Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; LILACS; the metaRegister of Controlled Trials (mRCT), and the WHO International Clinical Trials Registry Platform (ICTRP) for relevant published and ongoing trials.

### Selection criteria

Randomized or quasi-randomized controlled trials of oral cholera vaccines in healthy adults and children.

### Data collection and analysis

Each trial was assessed for eligibility and risk of bias by two authors working independently. Data was extracted by two independent reviewers and analysed using the Review Manager 5 software. Outcomes are reported as vaccine protective efficacy (VE) with 95% confidence intervals (CIs).

### Main results

Seven large efficacy trials, four small artificial challenge studies, and 29 safety trials contributed data to this review.

Five variations of a killed whole cell vaccine have been evaluated in large scale efficacy trials (four trials, 249,935 participants). The overall vaccine efficacy during the first year was 52% (95% CI 35% to 65%), and during the second year was 62% (95% CI 51% to 62%). Protective


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efficacy was lower in children aged less than 5 years; 38% (95% CI 20% to 53%) compared to older children and adults; 66% (95% CI 57% to 73%).

One trial of a killed whole cell vaccine amongst military recruits demonstrated 86% protective efficacy (95% CI 37% to 97%) in a small epidemic occurring within 4 weeks of the 2-dose schedule (one trial, 1426 participants). Efficacy data is not available beyond two years for the currently available vaccine formulations, but based on data from older trials is unlikely to last beyond three years.

The safety data available on killed whole cell vaccines have not demonstrated any clinically significant increase in adverse events compared to placebo.

Only one live attenuated vaccine has reached Phase III clinical evaluation and was not effective (one trial, 67,508 participants). Two new candidate live attenuated vaccines have demonstrated clinical effectiveness in small artificial challenge studies, but are still in development.

**Authors' conclusions**

The currently available oral killed whole cell vaccines can prevent 50 to 60% of cholera episodes during the first two years after the primary vaccination schedule. The impact and cost-effectiveness of adopting oral cholera vaccines into the routine vaccination schedule of endemic countries will depend on the prevalence of cholera, the frequency of epidemics, and access to basic services providing rapid rehydration therapy.

## PLAIN LANGUAGE SUMMARY

### Oral vaccines for preventing cholera

*Researchers in The Cochrane Collaboration conducted a review of the effect of oral vaccines for preventing cholera. After searching for relevant studies, they identified 48 relevant articles. Their findings are summarized below.*

**What is cholera and how do vaccines work?**

Cholera is a severe form of diarrhoea. People get cholera by drinking water or eating food that has been contaminated with the bacteria (*Vibrio cholera)*. Some people only become mildly ill, but some become extremely unwell with watery diarrhoea and vomiting. These people can become dehydrated very quickly and if untreated 25% to 50% can die.

The disease spreads rapidly in poor communities, especially where there is no sanitation or a lack of clean water. In refugee camps or following natural disasters a cholera epidemic can kill many hundreds of people very quickly.

Oral cholera vaccines work by giving people a small dose of the cholera bacteria to swallow. This dose of bacteria has been killed or changed so that it does not cause diarrhoea but is still able to make the person immune to natural cholera. There are three oral cholera vaccines currently available.

**What the research says about the effects of using current oral vaccines**

Oral cholera vaccines will decrease your risk of getting cholera if you live somewhere where cholera is common, but they won't remove the risk completely

Oral cholera vaccines probably don't have any major side effects when they are taken, but rare or late complications cannot be excluded.


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## SUMMARY OF FINDINGS

### Summary of findings 1. Summary of findings table: Oral killed whole cell vaccines for preventing cholera

**Oral killed whole cell vaccines for preventing cholera**

**Patient or population:** Adults and children

**Settings:** Endemic areas

**Intervention:** Killed whole cell vaccines administered orally

**Comparison:** Placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Vaccine efficacy (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Not being vaccinated | Being vaccinated | | | | |
| How many people get cholera during the first 2 years after vaccination? | Children aged less than 5 years | | **VE 38%** (20% to 53%) | 29005 (4 studies[5]) | **high**[1,2,3,4] | Oral cholera vaccine prevents just over one third of cholera illnesses. |
| | **90 per 10,000** | **56 per 10,000** (42 to 72) | | | | |
| | Older children and adults | | **VE 66%** (57% to 73%) | 214066 (4 studies[5]) | **high**[1,2,3,4] | Oral cholera vaccine prevents two thirds of cholera illnesses |
| | **30 per 100,000** | **10 per 100,000** (8 to 13) | | | | |
| How long does the protection last? | 3rd year after vaccination; all ages | | **VE 30%** (2% to 50%) | 58184 (1 study[7]) | **moderate**[6] | Oral cholera vaccine is probably less effective in the third year |
| | **30 per 10,000** | **21 per 10,000** (15 to 29) | | | | |
| | 4th year after vaccination; all ages | | **VE -5%** (-84% to 40%) | 56613 (1 study[7]) | **moderate**[6] | Oral cholera vaccine is probably ineffective after 4 years |
| | **30 per 100,000** | **32 per 10,000** (18 to 55) | | | | |
| Are there any side effects? | All ages | | | 44,924 | **moderate**[8] | Oral cholera vaccines probably don't have more side effects than a placebo |

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*The basis for the **assumed risk** (eg the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; VE: Vaccine protective efficacy.

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] No study limitations: Clemens 1988 Bangladesh and Taylor 2000 Peru are individually randomized trials with adequate allocation concealment and blinding. Sur 2009 India is a cluster randomized study, and Trach 1997 is a quasi-randomized study without allocation concealment.
[2] No serious inconsistency: The findings from all three trials (4 comparisons) were remarkably similar and any observed differences between the vaccines is well within the bounds of random error. It should be noted that a protective effect with the most widely available vaccine (WC-rBS/Dukoral®), given in its recommended schedule of two doses, was not shown until after a booster dose at 10 months.
[3] No serious indirectness: The trials are from several endemic countries and include both adults and children. This evidence could reasonably be applied to other endemic settings where the background risk of cholera is known and used to calculate an absolute benefit with vaccination.
[4] No serious imprecision: The finding is of a statistically significant benefit with vaccination. The clinical importance will depend on the incidence of cholera in the population.
[5] Clemens 1988 Bangladesh: a 3-arm trial of WC (currently unavailable), WC-BS (currently unavailable) vs placebo, Taylor 2000 Peru; WC-rTB (Dukoral®) versus placebo, Trach 1997 Vietnam; vWC (a variant WC vaccine only available in Vietnam) vs placebo, Sur 2009 India; BivWC (Shanchol®) vs placebo.
[6] Serious indirectness: The exact vaccines used in this trial are no longer available but the current vaccines are very similar in composition. Downgraded by 1.
[7] Only Clemens 1988 Bangladesh followed participants beyond 2-years.
[8] Fourteen studies assessed for side effects during the first 2 weeks after vaccination. No individual side effect has been shown to be more common with the oral cholera vaccine than with placebo. This data cannot exclude rare or late complications. Downgraded by 1.


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# BACKGROUND

## Description of the condition

Cholera is an acute intestinal infection, caused by the bacterium *Vibrio cholerae*. Most infected persons do not become ill, although the bacteria are present in the faeces for 7 to 14 days. Over 90% of those who do become ill experience a mild diarrhoeal episode that is indistinguishable from other diarrhoeal illnesses. However, a proportion develop typical cholera symptoms, with sudden onset of profuse watery diarrhoea, usually accompanied by vomiting, which can lead to severe dehydration (WHO 2000a). If untreated, around 25% to 50% of patients with the typical cholera symptoms will die, but if given adequate rehydration treatment the deaths can be reduced to less than 1% (WHO 2000b). In 2005 there were a total of 131,943 reported cases of cholera throughout the world, including 2272 deaths (WHO 2006a). Ninety-five percent of the reported cases were in Africa, but it is likely that many more cases, both in Africa and elsewhere, went unreported.

*V. cholerae* is transmitted mainly through the ingestion of faecally contaminated water or food, and can spread rapidly especially where there is poverty, poor hygiene and lack of sanitation. It can lead to serious outbreaks; in 2005 the World Health Organization (WHO) confirmed 49 different outbreaks in 36 countries (WHO 2006a), and in vulnerable populations epidemics can be devastating; in July 1994, in the refugee camps of Goma in Zaire, there were 70,000 cases with 12,000 deaths (Sanchez 1997). More recently, large epidemics have occurred in Zimbabwe (WHO 2009), and Haiti (WHO 2010a).

*V. cholerae* colonise the gut by attaching themselves to receptors in the mucosa of the upper small intestine (Sack 2004). Pathogenicity is mediated by a toxin, composed of two subunits; A and B. The B subunit is involved in binding the bacteria to the epithelial cell surface. It has no toxic effect, but does stimulate the host's immune response. The soluble A subunit is then released into the mucosal cells and causes hypersecretion of fluids and electrolytes, which lead to the typical symptoms of the disease (Girard 2005). Colonisation of the intestine can be inhibited by host antibodies generated in response to previous infection with *V. cholerae*.

There are over two hundred distinct serological groups of *V. cholerae*, classified on the basis of the 'O' antigen present on the cell surface, of which only two are known to cause epidemics: serogroups O1 and O139. *V. cholerae* O1 can be further classified into two biotypes: classical and El Tor. These in turn can each be divided into three serotypes: Ogawa, Inaba and Hikojima (Heymann 2008). The epidemic strains currently in circulation worldwide are the El Tor biotype of *V. cholerae* O1, which was first recognised in Indonesia in 1961 and has now spread to many other countries in Asia, Europe, Africa, and Latin America; and the Bengal strain of *V. cholerae* O139 which began in 1992 in India and Bangladesh, and remains restricted to Asia (WHO 2000b). The classical biotype of *V. cholerae* O1 is also known to cause epidemics, though these are now uncommon, and non-O1/non-O139 strains occasionally cause sporadic cases of gastroenteritis (Heymann 2008).

There is evidence that persons with blood group O have overall lower risk of cholera, but increased susceptibility to severe cholera (Harris 2005). The mechanism for this effect is not known, but it should be taken into account when assessing vaccine effectiveness.

## Description of the intervention

Widespread use of cholera vaccines began in the 1960s. The vaccines then in use were composed of whole *V. cholerae* O1 cells, killed using formalin, phenol or heat, and administered by injection. In the 1970s, these injected whole cell vaccines fell out of favour (Bhadra 1994), as it was perceived that they had a low efficacy (around 50%), provided only short-term immunity (3 to 6 months), and had an unacceptable rate of side effects. A Cochrane review first published in 1998, however, found that the duration and efficacy of the whole cell injected vaccines may have been underestimated: it was 54% at seven months (based on 18 trials) and 46% at one year (based on 14 trials). Protection waned by the second year in children under five, but persisted into the third year for those over the age of five years (Graves 2010). Nevertheless, injected vaccines are no longer in use or available, and attention is now focused on vaccines administered by the oral route.

Two main types of oral vaccines have been investigated in clinical trials: inactivated vaccines (containing killed whole cells of *V. cholerae)*, and live attenuated vaccines (containing genetically modified, non-pathogenic strains of *V. cholerae*). In addition, subunit vaccines have been tested which consist only of cell components (antigens). The live attenuated vaccines are usually given as a single dose, whereas killed whole cell vaccines may require two or three doses at one week intervals to produce an adequate immunological response. Three vaccine formulations are currently available (WHO 2010b):

- **WC-rBS (Dukoral®):** A monovalent inactivated vaccine containing killed whole cells of *V. cholerae* O1 plus additional recombinant cholera toxin B subunit. Produced by SBL Vaccine/ Crucell, Sweden.
- **BivWC (Shanchol®):** A bivalent inactivated vaccine containing killed whole cells of *V. cholerae* O1 and *V. cholerae* O139. Produced by Shantha Biotechnics, India.
- **BivWC (mORCVAX®):** A bivalent inactivated vaccine containing killed whole cells of *V. cholerae* O1 and *V. cholerae* O139. Produced by VABIOTECH, Vietnam and only available in Vietnam.

However, there are many other candidate vaccines at various stages of clinical development (Girard 2005).

## How the intervention might work

Vaccines work by stimulating immunity against a pathogen which has been killed, attenuated or otherwise rendered incapable of causing disease, in order to prevent or mitigate the effects of infection with the natural pathogen if it subsequently occurs. The route of administration of a vaccine may influence its immunogenicity and acceptability. Oral vaccines have the potential to stimulate local immunity within the mucosa of the gut, preventing the colonisation and multiplication of *V. cholerae.* Since cholera is transmitted orally, oral vaccines may thus have more direct effect than injected vaccines which stimulate immunity in the blood. Oral vaccines are also potentially easier to administer, more acceptable to patients than injected vaccines, and have a reduced risk of transmitting blood borne infections (Holmgren 2005).

The cholera toxin B subunit contains similar antigens to those found in enterotoxigenic *Escherichia coli* (ETEC); an important cause of diarrhoea in many parts of the world (Huilan 1991),


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and the most common cause of diarrhoea in people travelling from industrialised to developing countries (Sack 2004). Oral cholera vaccines may therefore provide significant cross-protection against ETEC infection and the vaccine is already licensed in many countries for preventing ETEC diarrhoea in travellers. This aspect of cholera vaccine use will be covered by another Cochrane review on vaccines to prevent ETEC.

### Why it is important to do this review

Oral vaccines have been licensed in many countries and are currently used mainly by travellers (Hill 2006). However, there has not been a full review of the relative effectiveness of different types of oral vaccine, the duration of their efficacy, or their adverse effects.

These vaccines may also have an important role in preventing cholera in areas where it is endemic, or in the prevention or control of outbreaks in high risk settings. The killed whole cell vaccine (WC/rBS) has been used in crisis situations in Darfur, Sudan (WHO 2006b), and in Aceh, Indonesia in 2005 after the tsunami (WHO 2006c). It has also been evaluated in an endemic situation in Beira, Mozambique in 2003-2004 (Lucas 2005). The live CVD 103-HgR vaccine was used during a cholera outbreak in Pohnpei, Federated States of Micronesia in 2000 (Calain 2004).

This review is one of a series of three that replaces a previous Cochrane review 'Vaccines for preventing cholera', which was first published in 1998 and updated in 2001. An updated stable review of injected vaccines (Graves 2010) has now replaced the original cholera vaccines review; it will be accompanied by this review of oral vaccines and a further review assessing the effects of vaccines (including cholera vaccine) on infection with ETEC.

## OBJECTIVES

To assess the effectiveness and safety of oral cholera vaccines in preventing cases of cholera and deaths from cholera.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomized or quasi-randomized controlled trials, including cluster-randomized trials.

#### Types of participants

Well adults or children (without symptoms of cholera).

#### Types of interventions

##### *Intervention*

Any vaccine that is designed to prevent cholera and is administered by the oral route.

##### *Control*

Placebo, control vaccine, no intervention or different dose or schedule of cholera vaccine.

#### Types of outcome measures

##### *Primary outcomes*

- Cases of cholera.
- Deaths from cholera.

##### *Secondary outcomes*

- Cases of severe dehydrating diarrhoea.
- Cases of all-cause diarrhoea.
- Deaths from severe dehydrating diarrhoea.
- Deaths from all causes.
- Serious adverse events leading to hospital admission or death.
- Other adverse events.

### Search methods for identification of studies

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress). The search was conducted in January 2010 and repeated in October 2010.

#### Electronic searches

##### *Published studies*

We searched the following databases using the search terms detailed in Table 1: The Cochrane Infectious Disease Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library; MEDLINE; EMBASE; and LILACS.

##### *Ongoing studies*

We also searched the metaRegister of Controlled Trials (mRCT) and the WHO International Clinical Trials Registry Platform (ICTRP) for ongoing trials using "cholera" and "vaccin*" as search terms.

#### Searching other resources

#### Researchers, organizations, and pharmaceutical companies

We attempted to contact individual researchers working in the field for unpublished and ongoing trials.

#### Reference lists

We also checked the reference lists of all studies identified by the above methods for any additional studies relevant to this review.

### Data collection and analysis

#### Selection of studies

Two authors (PG, KA or DS) independently screened all citations and abstracts identified by the search strategy for potentially eligible studies. Full reports of those studies deemed eligible were formally assessed for inclusion in the review using a pre-designed eligibility form based on the inclusion criteria. All reports were scrutinised for evidence of dual publication.

Trials where participants were given an artificial challenge with *V. cholerae* after vaccination (i.e. by ingesting a standardized dose of bacteria), were included but assessed separately from studies assessing efficacy against natural infection. Trials reporting only safety or adverse event data were included and summarized only


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if primary outcome data (an efficacy trial) for the same vaccine was already available. Trials testing the vaccine for purposes other than safety or prevention of cholera (for example, for prevention of diarrhoea associated with ETEC, or 'traveller's diarrhoea') were excluded.

Where it was unclear whether a trial should be included we attempted to contact the authors for clarification, and resolved any differences in opinion through discussion. We obtained translated copies of those papers published in languages other than English. The studies which did not meet the criteria for inclusion, and the reasons for their exclusion, are listed in the 'Characteristics of excluded studies' table.

### Data extraction and management

For each included trial, two authors (KA, KZ or DS) independently extracted information (using a pre-tested data extraction form) on the characteristics of the trial (study design, study dates and duration, study location, setting, and source of funding); the participants (the inclusion and exclusion criteria); the intervention (the type of vaccine, type of placebo, dose and immunisation schedule); and the outcomes presented in the papers.

For individually randomized trials, two authors independently extracted the number of participants randomized to each group, and the number experiencing the outcome. Data on the number of doses received and the number of participants lost to follow-up has been calculated and recorded for each group.

For cluster-randomized trials, we recorded the number of clusters in the trial, the average (mean) size of clusters, the unit of randomization (e.g. household or institution), and reported estimates of the intracluster correlation coefficient (ICC) for each outcome. If the trial results were adjusted for clustering we extracted the point estimate and the 95% confidence interval (CI), and also the unadjusted data so that we could calculate an adjusted risk ratio to present in a meta-analysis. Where results were not adjusted for clustering, we extracted the same data as for individually randomized trials, and adjusted the results according to known estimates of the ICC.

Adverse event data has been extracted for each individual type of event wherever possible. Where adverse events were reported for more than one dose, the number of people reporting each side effect after each dose has been recorded. Where trials reported the occurrence of adverse events over time following a single dose, if possible we recorded the proportion of people affected during each time period. If the denominator or total number of people affected for each time period is not clear, then events occurring in the first time period (typically 24 hours) after each dose was recorded.

Where data was missing or incomplete we contacted the authors for clarification. In cases of disagreement we double checked the data extraction and resolved the disagreement through discussion.

### Assessment of risk of bias in included studies

Two authors (KZ, KA or DS) independently assessed the risk of bias of the individually randomized trials using the 'The Cochrane Collaboration's tool for assessing the risk of bias' (Higgins 2008). We followed this guidance to assess whether adequate steps had been taken to reduce the risk of bias across six domains: sequence generation; allocation concealment; blinding (of participants, personnel, and outcome assessors); incomplete outcome data; selective outcome reporting; and other sources of bias. For cluster-randomized trials we also considered the possible effects of particular biases which occur with this study design: recruitment bias, baseline imbalance, loss of clusters, incorrect analysis and comparability to individually randomized trials (Higgins 2008).

For sequence generation and allocation concealment we report the methods used. For blinding we describe who was blinded and the blinding method. For incomplete outcome data we report the percentage and proportion lost to follow up. For selective outcome reporting we state any discrepancies between the methods used and the results in terms of the outcomes measured or the outcomes reported. For other biases we describe any other trial features that we think could have affected the trials result (e.g. if the trial was stopped early). We also report components of study design or conduct which may have introduced any bias specific to cluster-randomized trials.

We have categorized our judgments as 'yes' (low risk of bias), 'no' (high risk of bias), or 'unclear', and this information has been used to guide the interpretation of the results. Where our judgement for efficacy trials was unclear we attempted to contact the trial authors for clarification and any differences of opinion were resolved through discussion.

The results of this assessment of the risk of bias can be seen in Figure 1.


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**Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**

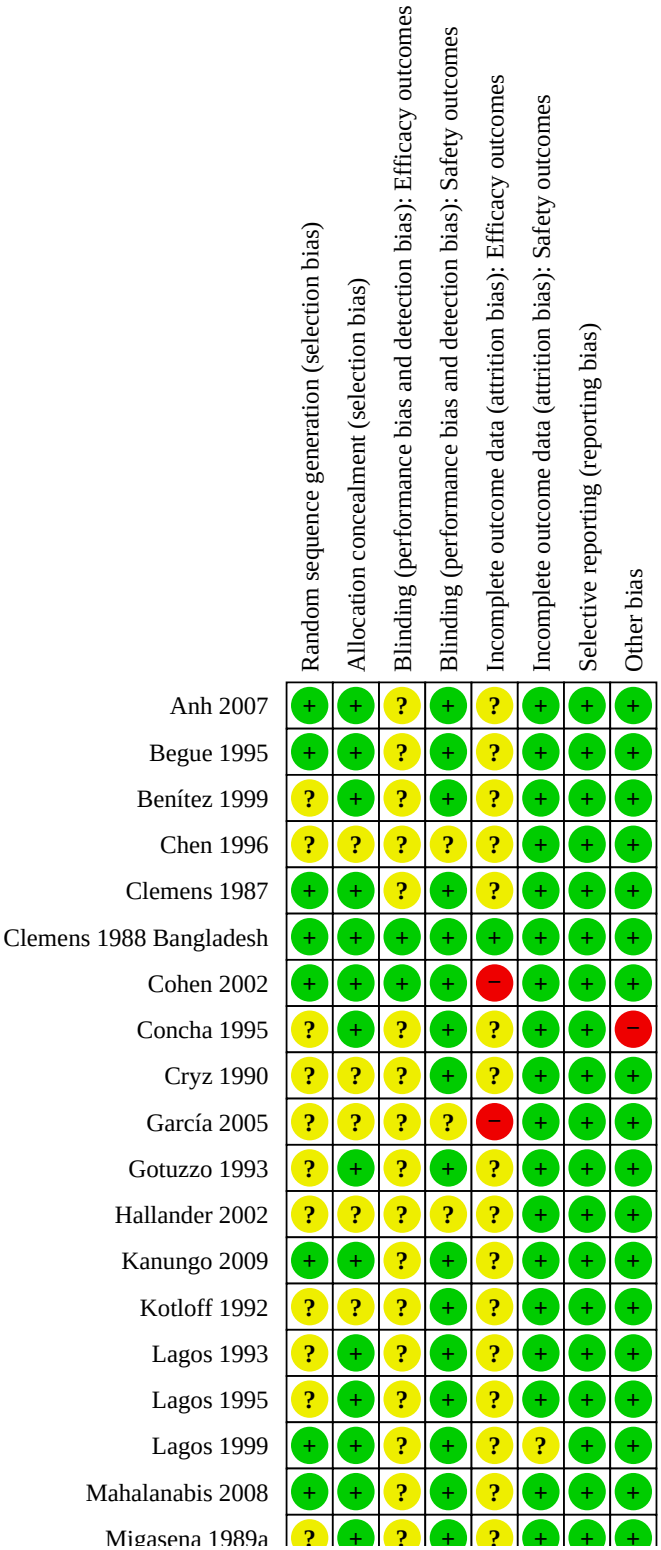



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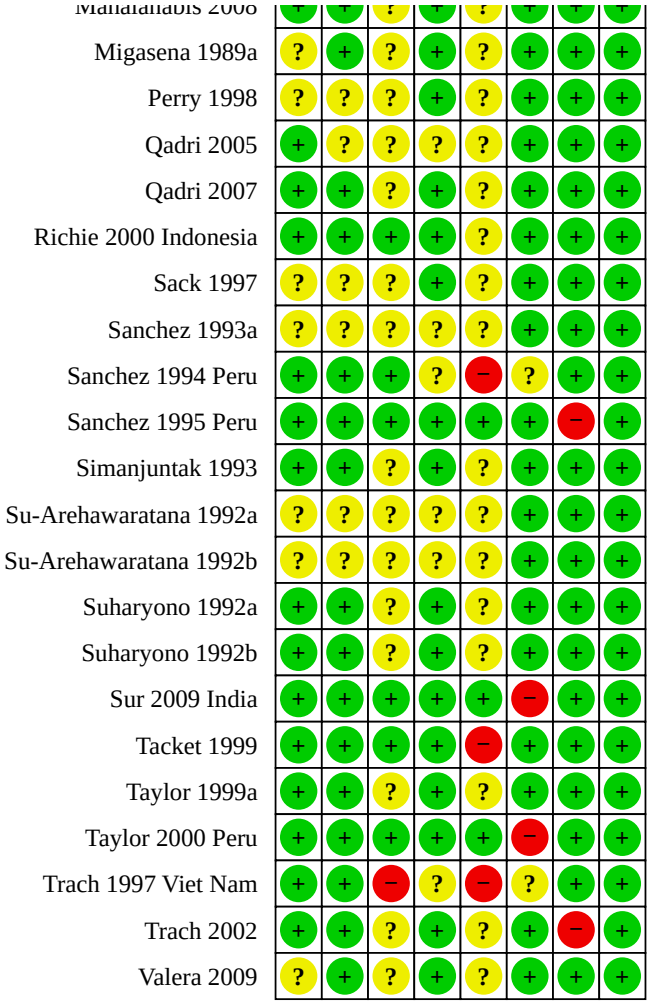
**Figure 1. (Continued)**




### Measures of treatment effect

All the pre-specified outcomes were dichotomous data and are presented as risk ratios with 95% CIs.

For the occurrence of cholera and diarrhoea cases, the overall risk ratio (RR) has been converted to vaccine efficacy (or effectiveness where intention-to-treat analysis was used) using the formula: % Vaccine Efficacy = (1-RR) x 100%.

### Unit of analysis issues

Trials including more than two comparison groups have been split and analysed as individual pair-wise comparisons. When conducting meta-analysis we have ensured that participants and cases in the placebo group were not counted more than once, by dividing the placebo cases and participants evenly between the intervention groups.

Cluster-randomized trials have only been included in the meta-analysis after appropriate adjustment for the effect of clustering. The individualized data has been reduced to the 'effective sample size' by dividing the number of events and the number of participants by the 'design effect'. The design effect was calculated as: 1 + (M-1)ICC; where M = average cluster size and ICC = intracluster correlation coefficient. We used estimates of the ICC as presented in the relevant papers.

### Dealing with missing data

If data from the trial reports were insufficient, unclear, or missing, we attempted to contact the trial authors for additional information. If we judged the missing data to render the result uninterpretable we have excluded the data from the meta-analysis and clearly stated the reason.

The primary analysis is a complete case analysis where the number of evaluable participants at each time point is used as the denominator.

### Assessment of heterogeneity

We assessed for heterogeneity between the trials by examining the forest plot to check for overlapping CIs, by using the $Chi^2$ test for heterogeneity using a 10% level of significance, and the $I^2$ statistic using a value of 50% to represent moderate levels of heterogeneity. A rough guide to interpretation of the $I^2$ statistic is given in the Cochrane Handbook section 9.5.2.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### Assessment of reporting biases

There were insufficient trials for us to assess the likelihood of small study effects, such as publication bias, by examining the funnel plot for asymmetry.

### Data synthesis

We analysed the data using Review Manager 5. Interventions are compared directly using pair-wise comparisons, and meta-analysis has been performed, where appropriate, if there was more than one trial for a particular comparison. For outcomes that are measured at different time points we have stratified the analysis by the time point.

We have combined studies using the Mantel-Haenszel method with the fixed-effect model. When we have combined the results of trials using different vaccines, or where moderate heterogeneity was detected, we have used the random-effects model. For comparisons which included both individually and cluster-randomized studies; we adjusted the data from the cluster-randomized studies to the 'effective sample size' taking into account the design effect, and then combined the data using the Mantel-Haenzel method.

If the reported results of cluster-randomized studies had not been adjusted to take into account the effects of clustering, and we were unable to make these adjustments ourselves, the results are simply reported in tables, and not included in the meta-analysis.

### Subgroup analysis and investigation of heterogeneity

We conducted the following subgroup analyses where data were available: age (adult and child, or age under 5 years and over 5 years), time period of follow up, blood group (group O versus other blood groups), type of vaccine, vaccine regimen used or doses received, and whether the challenge was artificial or natural.

### Sensitivity analysis

We intended to conduct a sensitivity analysis to evaluate the possible effects of incomplete outcome data by carrying out a best-worst case analysis, such that patients who were lost to follow up were assumed to have the event of interest in one sensitivity analysis and then were assumed to not have the event in a second sensitivity analysis. The data to reliably do this were however not available, so the presented data are a complete-case analysis and represent an assessment of vaccine efficacy, rather than effectiveness.

# RESULTS

## Description of studies

### Results of the search

The search identified 204 references, of which 46 were excluded on abstract alone. Full text copies were obtained of 158 and these were formally assessed using the pre-stated inclusion criteria. Overall, 110 were excluded for the reasons displayed in the Characteristics of excluded studies table.

### Included studies

Forty-eight individual papers have contributed to this review describing 39 separate trials. Fourteen of these describe efficacy data from seven large scale field trials, four describe small artificial challenge efficacy studies, and 29 contribute only safety data. For further details see the Characteristics of included studies table.

#### *Killed whole cell vaccines*

Six trials have evaluated the clinical efficacy of five variations of a killed whole cell vaccine (Clemens 1988 Bangladesh; Sanchez 1994 Peru; Sanchez 1995 Peru; Taylor 2000 Peru; Trach 1997 Viet Nam; Sur 2009 India).

The composition of these vaccines, the dosing schedule, and the population groups included in these trials are shown in Table 2.

The individual vaccines represent step-wise developments from the original vaccines used in Clemens 1988 Bangladesh to the three vaccines commercially available today.

Two of the field trials used a cluster-randomized design (Trach 1997 Viet Nam; Sur 2009 India). In order to include these trials in a meta analysis, we have converted the data presented in the original papers to risk ratios, and adjusted for the effect of clustering using the ICC presented in Sur 2009 India. The remaining five trials were individually randomized.

Three of these efficacy trials and 11 additional trials contribute to the safety data for these five vaccines.

#### *Live attenuated vaccines*

Only one live attenuated vaccine (CVD 103-HgR) has reached the stage of large scale field evaluation (Richie 2000 Indonesia). The protective efficacy of two other candidate vaccines: Peru 15 and VC638, has been evaluated in small randomized artificial challenge studies (Cohen 2002; García 2005). The composition, dosing schedule and population groups included in these trials are shown in Table 3.

An additional 18 trials contributed safety data only to the evaluation of these vaccines.

### Excluded studies

Eleven of the excluded trials may be eligible for inclusion in later updates of the review, as the only reason for their exclusion was that no trials assessing the clinical efficacy of these vaccines have been published; we decided to exclude these early-stage trials because data on safety and tolerability alone is of limited use in practice.

## Risk of bias in included studies

### Allocation

#### *Efficacy studies*

One cluster, quasi-randomized study (Trach 1997 Viet Nam) used alternate open allocation and three out of the six other efficacy trials did not adequately describe the process of sequence generation or allocation concealment (Richie 2000 Indonesia; Sanchez 1994 Peru; Sanchez 1995 Peru). However, as the effect of unconcealed allocation in vaccine trials is unlikely to be substantial given that all participants are well prior to enrolment, these trials were judged to be at low risk of bias for these criteria.


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***Safety (and immunogenicity) only studies***

Eleven out of the 29 trials only presenting safety data did not adequately describe the process of allocation concealment for us to make a judgement about the risk of bias.

**Blinding**

***Efficacy outcomes***

Six of the seven efficacy trials adequately blinded participants and staff involved with the trial (Clemens 1988 Bangladesh; Richie 2000 Indonesia; Taylor 2000 Peru; Sanchez 1994 Peru, Sanchez 1995 Peru; Sur 2009 India). One trial was unblinded (Trach 1997 Viet Nam).

***Safety outcomes***

Most studies used placebos which were of identical appearance to the vaccine, and could be considered at low risk of bias for safety outcomes. In nine studies the use of a placebo was not adequately described to make a judgement and so were classified as 'unclear'.

**Incomplete outcome data**

***Efficacy studies***

Three trials adequately addressed incomplete data for cases of cholera (Taylor 2000 Peru; Sanchez 1994 Peru; Sur 2009 India). In one trial it was unclear whether this had been done, but due to the large sample size and active surveillance system used, this was unlikely to have introduced significant bias (Clemens 1988 Bangladesh). In two trials it was unclear how many participants were lost to follow-up (Richie 2000 Indonesia; Trach 1997 Viet Nam).

***Safety (and immunogenicity) only studies***

Safety only studies were generally of only short duration with minimal losses to follow-up and therefore considered at low risk of bias.

**Selective reporting**

We found no evidence of selective reporting bias.

**Other potential sources of bias**

One trial had evidence of possible other bias (Concha 1995). In this trial, 620 individuals who originally consented to participate dropped out because of a political campaign against it.

## Effects of interventions

See: **Summary of findings 1** Summary of findings table: Oral killed whole cell vaccines for preventing cholera

**Killed whole cell vaccines**

***Clinical efficacy***

Six trials have evaluated the clinical efficacy of five variations of a killed whole cell vaccine (Clemens 1988 Bangladesh; Sanchez 1994 Peru; Sanchez 1995 Peru; Taylor 2000 Peru; Trach 1997 Viet Nam; Sur 2009 India).

These vaccines are similar but not identical in composition (see Table 2). Despite the variation in dosing schedules, the protective efficacy against confirmed cholera of all five vaccines is similar in both the first and second years following vaccination. It should however be noted that protective efficacy with the two-dose schedule of the WC-rBS vaccine (Dukoral) was not demonstrated in Peru until the second year following a booster dose at 10 months (Taylor 2000 Peru).

The per protocol estimates of protective efficacy as reported in the original papers are shown in Table 4. For comparative purposes we have converted all measures of efficacy to cluster adjusted RRs (Sur 2009 India used rate ratio) and presented these in a forest plot (Year 1 of follow-up: four trials, 252,887 participants: VE 52%, 95% CI 35% to 65%, $I^2$ 49%, Analysis 1.1; Year 2 of follow-up: three trials, 130,334 participants: VE 61%, 95% CI 50% to 70%, $I^2$ 0%, Analysis 1.2).

Evidence of protection for time periods of greater than two years after vaccination is only available for the WC and WC-BS vaccine formulations which are not currently available.

The protective efficacy in children aged less than 5 years was lower than that seen in adults when the data was amalgamated over the first two years of follow-up (four trials, participants; Age < 5 years: VE 38%, 95% CI 20% to 53%, Age > 5 years: VE 66%, 95% CI 57% to 73%, Analysis 1.5; Figure 2). This data was calculated by summing the number cases of cholera in the first two years, and using the number of participants completing 2-years of follow-up as the denominator. A sensitivity analysis using the number of participants completing 1-year follow-up as the denominator did not change the result (Analysis 1.6).


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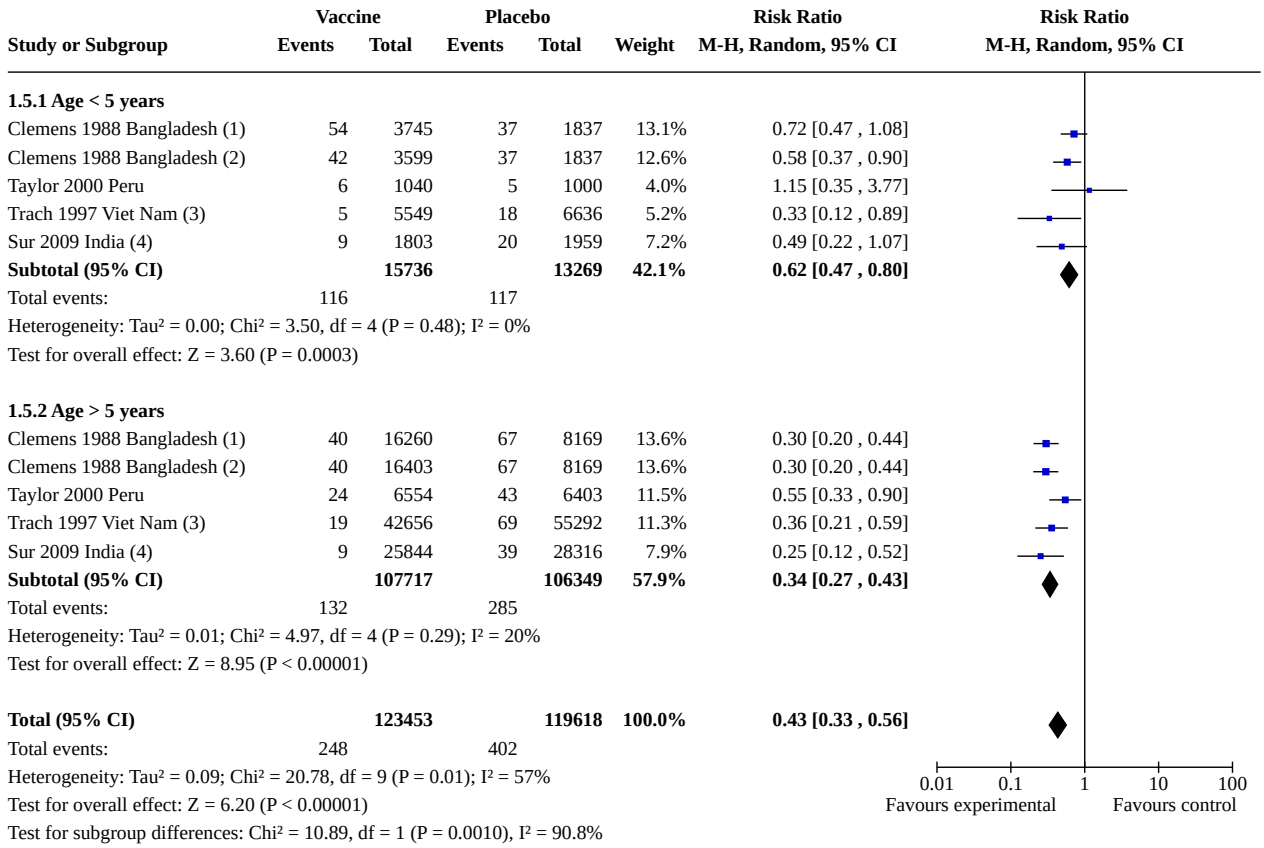
**Figure 2. Forest plot of comparison: 1 Whole cell vaccines (all types) versus placebo - Primary efficacy outcomes, outcome: 1.5 Cases of cholera by age group - First two years of follow-up.**




**Footnotes**

(1) WC vs Placebo: For the purpose of this meta analysis the events and participants in the Placebo arm of Clemens 1985 Bangladesh have been divided equally

(2) WC-BS vs Placebo: For the purpose of this meta analysis the events and participants in the Placebo arm of Clemens 1985 Bangladesh have been divided equ

(3) Trach 1997- This result has been ajusted from the crude figures given in the original paper to give the effective sample size; using an estimate of the ICC of -(

(4) Sur 2009- This result has been ajusted from the crude figures given in the original paper to give the effective sample size; using an ICC of -0.0085 and a mea

**Whole cell vaccine (WC: not currently available); three doses given 6 weeks apart**

One trial conducted in Bangladesh in 1985 (Clemens 1988 Bangladesh) compared the WC vaccine versus placebo in children aged 2 to 15 years and females aged > 15 years.

Protective efficacy against cholera episodes was established within the first 4-months after vaccination (one trial, 41,580 participants: VE 52%, 95% CI -5% to 78%, Analysis 2.1) and maintained until the third year (Year 1: VE 53%, 95% CI 34% to 66%; Year 2: VE 57%, 95% CI 38% to 70%; Year 3: VE 42%, 95% CI 11% to 62%; Year 4: VE -28%, 95% CI -137% to 31%, Analysis 2.1). Protective efficacy was lost in the fourth year of follow-up.

Vaccine efficacy appears to be lower in children age < 5 years (one trial, 41,580 participants; Year 1: Age 2 to 5 years VE 31%, 95% CI -9% to 57%; Age > 5 years VE 67%, 95% CI 44% to 80%, Analysis 2.2; Year 2: Age 2 to 5 years VE 24%, 95% CI -29% to 55%; Age > 5 years VE 73%, 95% CI 55% to 84%, Analysis 2.3). The difference between vaccine and placebo was not shown to be statistically significant at any time point in this group, although the trend was towards some protection.

There was also a statistically significant difference between vaccine and placebo in cases of severe watery diarrhoea of any cause (Year 1: VE 32%, 95% CI 7% to 51%, Analysis 2.5), any watery diarrhoea (Year 1: VE 33%, 95% CI 18% to 46%, Analysis 2.5), and diarrhoea of any cause (Year 1: VE 22%, 95% CI 8% to 35%, Analysis 2.5). There is a trend towards a protective effect against all-cause death (VE 23%, 95% CI -1% to 42%), and death from non-dysenteric diarrhoea (VE 53%, 95% CI -16% to 81%), but these did not reach statistical significance (Analysis 2.6).

**Whole cell plus B subunit vaccine (WC-BS: not currently available); three doses given 6 weeks apart**

The same study (Clemens 1988 Bangladesh) also evaluated the WC-BS vaccine.

Protective efficacy against cholera episodes was similarly demonstrated at 4-months after vaccination (one trial, 41,542 participants: VE 79%, 95% CI 38% to 93%, Analysis 3.1) but evidence of clinical efficacy was lost in the third year after vaccination (Year 1: VE 62%, 95% CI 46% to 74%; Year 2: VE 58%, 95% CI 40% to 71%; Year 3: 18%, 95% CI -21% to 44%; Year 4: 16%, 95% CI -66% to 58%, Analysis 3.1).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Vaccine efficacy again appears to be lower in children age < 5 years (one trial, 41,542 participants; Year 1: Age 2 to 5 years VE 38%, 95% CI -1% to 62%; Age > 5 years VE 78%, 95% CI 61% to 87%, Analysis 3.2; Year 2: Age 2 to 5 years VE 47%, 95% CI 3% to 71%; Age > 5 years VE 63%, 95% CI 41% to 76%, Analysis 3.3).

There was also a statistically significant difference between vaccine and placebo in cases of severe watery diarrhoea of any cause (Year 1: VE 51%, 95% CI 31% to 66%, Analysis 3.5), any watery diarrhoea (Year 1: VE 38%, 95% CI 23% to 50%, Analysis 3.5), and diarrhoea of any cause (Year 1: VE 26%, 95% CI 12% to 38%, Analysis 3.5). All-cause death and death from non-dysenteric diarrhoea were also significantly lower in the group given the vaccine (Year 1: All-cause death: VE 26%, 95% CI 3% to 44%; Deaths from non-dysenteric diarrhoea: VE 80%, 95% CI 31% to 94%, Analysis 3.6).

No statistically significant difference between WC-BS and WC was demonstrated at any time point, although there was a trend towards increased protection with WC-BS during the first 8-months after vaccination (Analysis 4.1).

#### Whole cell plus recombinant vaccine (WC-rBS: available as Dukoral®, SBL); two doses given 2 weeks apart +/- a booster dose at 10 months

One large trial in the general population (Taylor 2000 Peru), and two smaller trials in military recruits (Sanchez 1994 Peru; Sanchez 1995 Peru) have evaluated the efficacy of the WC-rBS vaccine ;

Taylor 2000 Peru did not demonstrate any significant difference between vaccine or placebo during the first year (one trial, 17,799 participants: VE -4%, 95% CI -105% to 48%, Analysis 5.1). However, following a booster dose at 10 months the vaccine was superior to placebo in the second year of follow-up (1 trial, 14,999 participants: VE 60%, 95% CI 25% to 79%, Analysis 5.2).

In the second year of follow-up the estimate of vaccine efficacy was highest in those older than 15 years, although there were very few cholera episodes in the youngest age group (one trial, 14,999 participants, Year 2: Age 2-5 years VE 52%, 95% CI -162% to 91%; Age 5 to 15 years VE 47%, 95% CI -44% to 80%; Age 16 to 65 years VE 71%, 95% CI 22% to 89%; Analysis 5.2)

Both the small trials in military recruits experienced an outbreak of cholera during or shortly after the vaccination schedule. In Sanchez 1994 Peru the outbreak occurred 2 to 4 weeks after vaccination. A vaccine efficacy of 86% (95% CI 37% to 97%) was demonstrated in those who received the full two dose schedule, but a single dose did not appear protective (one trial, 1563 participants, Analysis 5.3). In Sanchez 1995 Peru the outbreak occurred between the first and second vaccine doses, and vaccine efficacy after one dose approached statistical significance (VE 44%, 95% CI -4% to 70%, Analysis 5.3).

#### Variant whole cell vaccine (vWC: available as ORCVAX®, Vabiotech); two doses given 2 weeks apart

One cluster quasi-randomized trial evaluated the efficacy of the vWC vaccine with 1-year follow-up (Trach 1997 Viet Nam).

Two doses of vaccine were superior to placebo at preventing cholera episodes requiring in-patient care in all age groups (one trial, 119,033 participants, Age 1 to 5 years VE 68%, 95% CI 14% to 88%, Age > 5 years VE 66%, 95% CI 42% to 80%, authors own figures).

The vaccine was protective against severe and non-severe cholera episodes (one trial, 119,033 participants, Severe episodes VE 65%, 95% CI 34% to 81%, Non-severe episodes VE 56%, 95% CI 26% to 74%, authors own figures).

#### Bivalent whole cell vaccine (BivWC: available as Shanchol®, Shantha Biotechnics); two doses given 2 weeks apart

One cluster-randomized trial evaluated the efficacy of the BivWC vaccine (Sur 2009 India). Data are presented for two years of follow-up although the trial is ongoing.

The protective efficacy of the BivWC vaccine was statistically significant during the second but not the first year after vaccination (one trial, 66,900 participants in 3478 clusters: Year 1 VE 45%, 95% CI lower bound -5%, Year 2 VE 77%, 95% CI lower bound 55%, authors own figures).

Over two years follow-up the vaccine was protective in all age groups but lowest in the youngest age group (one trial, 66,900 participants: Age 1 to 4.9 years VE 49%, 95% CI lower bound 6%; Age 5 to 14.9 years VE 87%, 95% CI lower bound 54%; Age > 15 years VE 63%, 95% CI lower bound 23%; authors own figures).

### *Safety*

#### Whole cell vaccine (WC: not currently available); three doses given 6 weeks apart

Safety data were available from 613 participants. No statistically significant differences were shown between vaccine and placebo after the first or second doses (one trial, 613 participants, Analysis 6.1; Analysis 3.1)

#### Whole cell plus B subunit vaccine (WC-BS: not currently available); three doses given 6 weeks apart

Safety data were available from 631 participants. No statistically significant differences were shown between vaccine and placebo after the first or second doses (one trial, 631 participants, Analysis 6.2; Analysis 3.2)

#### Whole cell plus recombinant vaccine (WC-rBS: available as Dukoral®, SBL); two doses given 2 weeks apart +/- a booster dose at 10 months

Safety data is available on 12,121 participants who received the WC-rBS vaccine in eight placebo-controlled randomized trials (Begue 1995; Concha 1995; Hallander 2002; Sanchez 1993a; Sanchez 1995 Peru; Taylor 1999a; Taylor 2000 Peru; Trach 2002). The placebo used in seven of these studies was an oral dose of inactivated *E. coli* (K12 strain).

The largest study (Taylor 2000 Peru) collected reports of adverse events at the time of the second dose. It found very low levels of symptoms (0.2%), and only the figures for diarrhoea were presented (one study, 10,992 participants, Analysis 6.3). The remaining studies are small. The only statistically significant result was from one study (Sanchez 1995 Peru) which found a higher rate of stomach gurgling after the second dose of vaccine (seven trials, 23,870 participants, Analysis 6.3; Analysis 7.1). The symptoms most commonly reported after taking the vaccine were: stomach gurgling (14%), abdominal pain (9%), headache (5%), and these were generally described as mild.

One additional study translated from Chinese (Chen 1996) evaluated the safety of a locally formulated WC-rBS in 369


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schoolchildren and factory workers and reports no significant differences between vaccine and placebo.

#### Variant whole cell vaccine (vWC: available as ORCVAX®, Vabiotech); two doses given 2 weeks apart

There is no safety data available for this vaccine.

#### Bivalent whole cell vaccine (BivWC: available as Shanchol®, Shantha Biotechnics); two doses given 2 weeks apart

Safety data is available from 32,190 participants who received the bivalent whole cell vaccine in four randomized controlled trials (Mahalanabis 2008; Anh 2007; Kanungo 2009; Sur 2009 India). The placebo used in all four trials was an oral dose of inactivated *E. coli* (K12 strain).

The largest study (Sur 2009 India) only collected data passively, encouraging participants to present for medical care, and found very low levels of symptoms (<0.2%). It did however record 51 serious adverse events but with no differences between the vaccine and placebo groups. The remaining three studies are small. No clinically important differences between the vaccine and placebo have been shown (four trials, 67,414 participants, Analysis 6.4; Analysis 7.2). Excluding Sur 2009 India, the symptoms most commonly reported were: abdominal pain (7%), headache (7%), fever (4%), and nausea (3%). These were generally described as mild.

### Live attenuated vaccines

#### *Efficacy*

Only CVD 103-HgR has been evaluated for clinical efficacy against naturally occurring *V. cholera*. The other live attenuated vaccines listed here remain in development.

#### CVD 103-HgR (not currently available): one dose

CVD 103-HgR has not been shown to give significant clinical protection from natural cholera infection in any age group (one trial, 67,508 participants, Analysis 8.1; Analysis 8.2), however only one efficacy study has evaluated this vaccine. This study relied on passive surveillance and the number of cholera events was very low (Richie 2000 Indonesia). There was also no difference in all-cause death, or deaths related to diarrhoea (one study, 67,508 participants, Analysis 8.3; Analysis 8.4).

A small artificial challenge study in adult volunteers in the USA (Tacket 1999) did however, demonstrate a protective effect against moderate to severe diarrhoea (one trial, 51 participants: VE 91%, 95% CI 33% to 99%, Analysis 8.5) and any diarrhoea (VE 80%, 95% CI 56% to 91%, Analysis 8.6).

#### Peru 15 (in development): one dose

One artificial challenge study conducted in adult volunteers in the USA (Cohen 2002) showed a protective effect against moderate to severe diarrhoea (one trial, 36 participants: VE 95%, 95% CI 21% to 100%, Analysis 8.5) and any diarrhoea (VE 97%, 95% CI 69% to 100%, Analysis 8.6). Phase III clinical trials are necessary before conclusions on the clinical efficacy of this vaccine can be made.

#### VC638 (in development): one dose

One small artificial challenge study conducted in adult volunteers in Cuba (García 2005) demonstrated a protective effect against any diarrhoea (one trial, 21 participants: VE 99%, 95% CI 68 % to 100%, Analysis 8.6), but not severe diarrhoea (Analysis 8.5). Phase III clinical trials are necessary before conclusions on the clinical efficacy of this vaccine can be made.

#### *Safety*

#### CVD 103-HgR (not currently available): one dose

A total of 1970 participants have received CVD 103-HgR in fifteen included randomized controlled trials (Cryz 1990; Gotuzzo 1993; Kotloff 1992; Lagos 1993; Lagos 1995; Lagos 1999; Migasena 1989a; Perry 1998; Richie 2000 Indonesia; Simanjuntak 1993; Su-Arehawaratana 1992a; Su-Arehawaratana 1992b; Suharyono 1992a; Suharyono 1992b; Tacket 1999). The placebo used in 14 of these studies was an oral dose of inactivated *E. coli* (K12 strain).

No symptom was shown to be statistically more common in those given the vaccine (15 trials, 1970 participants, Analysis 9.1). The commonest reported symptoms following vaccination were: malaise (20% but only recorded in two trials), anorexia (12% but only recorded in three trials), headache (13%), abdominal pain (10%), fever (7%), diarrhoea (5%), vomiting (5%). In general these symptoms are reported to be mild. Su-Arehawaratana 1992a reports one participant developing diarrhoea after vaccination that required them to seek hospital care.

#### Peru 15 (in development): one dose

A total of 252 participants have received Peru 15 in four randomized controlled trials (Cohen 2002; Qadri 2005; Qadri 2007; Sack 1997). The placebo used in these trials was the buffer given alone.

Headache was the only symptom to be statistically more common with the vaccine (four trials, 419 participants: Headache RR 4.14, 95% CI 1.27 to 13.48, Analysis 9.2). The commonest reported symptoms during the first few days after vaccination were: nausea (18%), loss of energy (15%), loss of appetite (10%), and headache (10%). Other adverse events were uncommon, and all adverse events were described as mild.

#### VC638 (in development): one dose

A total of 90 participants have received VC638 in three randomized studies (García 2005; Benítez 1999; Valera 2009). The placebo used in these trials was the buffer given alone.

No symptom was shown to be statistically more common in those given vaccine (three trials, 137 participants, Analysis 9.3). The commonest reported symptoms during the first few days were: stomach gurgling (40%), nausea (33%), abdominal pain (32%), headache (19%), and diarrhoea (13%). Other adverse events were uncommon, and all but one adverse event (a moderate headache) were described as mild.

## DISCUSSION

### Summary of main results

#### Killed whole cell vaccines

Five variations of a killed whole cell cholera vaccine have been evaluated in large scale clinical trials. The overall vaccine efficacy during the first year was 52% (95% CI 35% to 65%), and during the second year was 61% (95% CI 50% to 70%).


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The protective efficacy over 2-years follow-up was lower in children aged less than 5 years (VE 38%, 95% CI 20% to 53%), than that seen in older age-groups (VE 66%, 95% CI 57% to 73%).

Any observed differences in vaccine efficacy between these vaccines is well within the bounds of random error.

Clinical protection against cholera with the older vaccines (WC and WC-BS) was demonstrated within 4-months of the primary schedule and persisted as long as the third year after vaccination. This cannot be reliably extrapolated to the currently available vaccines given the changes in both the immunisation schedule and the composition of the vaccines.

Of the currently available vaccines:

- A two dose regimen of WC-rBS (Dukoral®) was not shown to be clinically effective in adults in Peru until after a third booster dose was given at 10 months. One smaller trial in military recruits in Peru, did demonstrate a high protective efficacy in a small epidemic occurring within 4 weeks of the two dose schedule but extrapolation of this result beyond short term follow-up may be unreliable. Clinical efficacy in children aged less than 5 years has not been demonstrated.
- A two dose regimen of BivWC (Shanchol®) is likely to be effective during the first and second years after vaccination though this only reached statistical significance during the second year, and follow-up in this trial is ongoing. There is a trend towards protection in all age groups but this was not statistically significant in the under 5 year olds.
- The Vietnam variation of BivWC (mORCVAX®) has not been formally evaluated in published clinical trials. It contains the same elements as Shanchol but has a different manufacturing process.

#### Live attenuated vaccines

The live attenuated vaccines remain in development. The only vaccine to reach Phase III clinical trials and licensure in some countries, CVD 103-HgR, has not been shown to provide a protective effect against clinical cholera episodes; however, it has only been evaluated in one large efficacy trial in which there were few cases in either arm.

### Overall completeness and applicability of evidence

The currently available vaccines represent stepwise modifications to the original vaccines developed and studied in Bangladesh in the 1980s. Although changes have occurred in both the composition and the recommended vaccination schedule, they remain similar enough to sensibly combine in a meta-analysis, and this is confirmed by their remarkably similar efficacies. The efficacy data from these older studies and vaccines therefore remains relevant to the assessment of the WC-rBS (Dukoral®) and BivWC (Shanchol®) vaccines available today.

The current recommended schedule for WC-rBS is two doses 2 weeks apart, and three doses 2 weeks apart for children age 2 to 5 years. The two dose schedule (rather than the three doses used in the Bangladesh study) has been adopted based on immunological data, and the observation that two doses of the original WC and WC-BS vaccines were equally effective to three doses in the Bangladesh study (Clemens 1988 Bangladesh). Unfortunately we have been unable to get access to the data to confirm this finding.

The lack of protective efficacy with a two-dose schedule seen in the only large scale trial of WC-rBS (Taylor 2000 Peru) has been discussed in the literature with questions raised about the adequacy and accuracy of the cholera surveillance during the first year of follow-up (Clemens 2001; Taylor 2001). Reassuringly two doses were protective in the much smaller military trials, but the number of events was low and the period of follow-up inadequate to make conclusions for the use of the vaccine outside of an acute epidemic situation. Although the two dose schedule of BivWC has been shown to be protective in the first year (though not quite reaching statistical significance), this vaccine is sufficiently different from WC-rBS to restrict the generalisation of this result.

The primary analysis used in this review is a complete-case analysis excluding participants who received incomplete vaccine schedules. These findings will therefore tend to overestimate the effectiveness of the vaccine when given outside of trial settings, where vaccine coverage will almost always be considerably less than 100%. This factor should be taken into consideration when planning a cholera vaccination programme.

The best evidence for the use of cholera vaccines in epidemic situations, such as seen in Zimbabwe and Haiti in recent years, comes from the two trials in adult military recruits. Sanchez 1994 Peru demonstrated 86% protective efficacy (95% CI 37% to 97%) in a small epidemic occurring within 4 weeks of the two-dose schedule of WC-rBS. The reactive use of cholera vaccines once an epidemic has begun has been further evaluated through case-control studies (Anh 2011), and modelling exercises (Reyburn 2011), which are outside of the scope of this review (Ryan 2011).

### Quality of the evidence

The quality of the evidence was assessed using the GRADE methodology. Overall the quality is moderate to high, meaning that we can have a high degree of confidence in these results, and further research is unlikely to substantially alter the current estimates of protective efficacy. See Summary of findings table 1.

### Agreements and disagreements with other studies or reviews

The World Health Organization published a position paper on oral cholera vaccines in 2010 (WHO 2010b). The findings presented here are in broad agreement with this paper.

## AUTHORS' CONCLUSIONS

### Implications for practice

The currently available oral killed whole cell vaccines can prevent 50 to 60% of cholera episodes during the first 2-years after the primary vaccination schedule. Protective efficacy is unlikely to last more than 3 years and booster doses in line with the manufacturers recommendations will be required.

The impact and cost-effectiveness of adopting oral cholera vaccines into the routine vaccination schedule of endemic countries will depend on the prevalence of cholera among the community, the frequency of epidemics, and the availability or unavailability of adequate facilities to provide rapid rehydration therapy.

Athough there is currently little high quality evidence for the effect of vaccines in emergency and epidemic situations, It is likely that


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cholera vaccines would have an important impact on reducing disease in epidemics, especially where access to clean water and sanitation is difficult to achieve.

### Implications for research

The evidence from Peru suggests that countries considering routine vaccination should assess whether the two-dose primary immunization schedule is adequate in their setting.

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* Indicates the major publication for the study


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## CHARACTERISTICS OF STUDIES

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

#### Anh 2007

| ***Study characteristics*** | |
|---|---|
| Methods | Design: A randomized controlled trial (individually randomized)<br><br>Trial dates and duration: Enrollment from May to June 2005; follow-up for 28 days |
| Participants | Sample size: 153 participants enrolled<br><br>Inclusion criteria: Age 18 to 40 years, healthy male and non-pregnant females, written informed consent<br><br>Exclusion criteria: History of diarrhoea, anti-diarrhoeal or antibiotic use during the past week, history of diarrhoea and abdominal pain lasting for 2 weeks during the past 6 months |
| Interventions | Vaccine: Bivalent killed whole-cell vaccine (BivWC; mORCVAX, VABIOTECH)<br><br>Placebo: Heat-killed *E. coli* K12 strain<br><br>All participants were randomized to receive 2 doses, at an interval of 14 days. |
| Outcomes | *Included in review:*<br><br>• Serious adverse events during 28 days follow-up<br>• Adverse events within 3 days of each dose<br><br>*Not included in the review:*<br><br>• Immunological outcomes: Geometric mean-fold rise in serum vibriocidal antibody titres and proportion who develop ≥4-fold rises from baseline after one or two dose |
| Notes | Location: SonLa Province, Northwest Vietnam<br><br>Setting:<br><br>Source of funding: The Bill and Melinda Gates Foundation through the Diseases of Most Impoverished Program administered by the International Vaccine Institute, and the Swedish International Development Cooperation Agency. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: 'A randomization list was prepared by a statistician who otherwise was not involved in the study. Randomization numbers were generated in blocks of four' |
| Allocation concealment (selection bias) | Low risk | Comment: See other comments, no further description. |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: 'The reformulated vaccine and the placebo were packaged as liquid formulations in identical vials containing five 1.5-ml doses'. 'A physician who |


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**Anh 2007** *(Continued)*

| | | |
|---|---|---|
| | | was unaware of the study agent received by the subject conducted a structured interview regarding the subjects...symptoms'. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: Nine participants (5.9%) did not receive the second dose of vaccine; 5 were found ineligible and 4 lost to follow-up. |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |

**Begue 1995**

| ***Study characteristics*** | |
|---|---|
| Methods | Design: Randomized controlled trial (individual randomization)<br>Duration and dates (field work): March 1993 |
| Participants | Sample size: 624 received the first dose of vaccine, 541 received 2 doses<br>Inclusion criteria: Persons aged 2 to 65 years<br>Exclusion criteria: pregnancy |
| Interventions | Vaccine: Killed whole-cell vaccine plus recombinant cholera toxin subunit (WC-rBS; Dukoral®, SBL, Sweden)<br>Placebo: Inactived *E. coli* K12 suspension<br>Vaccine and placebo were administered along with freshly prepared antacid solution. Two doses were given two weeks apart. |
| Outcomes | *Included in the review:*<br>• Adverse events after the first dose: participants were observed for one hour and then asked about symptoms at time of the second dose<br>*Not included in the review:*<br>• Immunological outcomes: Geometric mean vibriocidal antibody, IgG antitoxin and IgA antitoxin titres pre and post vaccination. Proportion who developed ≥ 2 or ≥ 4 fold increases. |
| Notes | Location: outskirts of Lima, Peru<br>Setting: Small community of 300 families.<br>Source of funding: US Naval Medical Research and Development Command |

| ***Risk of bias*** | | |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |


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**Begue 1995** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "..administer the vaccine or placebo according to a pre-randomized list"<br><br>Comment: Unclear description but probably low risk of bias |
| Allocation concealment (selection bias) | Low risk | Comment: Not described but probably low risk of bias |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: 'Inactivated Escherichia coli K12, identical in appearance to the vaccine, was used as placebo, and was administered orally in the above antacid solution, and in a double blinded manner.' |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported as an outcome |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: No loss to follow-up |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |

**Benítez 1999**

| ***Study characteristics*** | |
|---|---|
| Methods | Design: Randomized controlled trial (individually randomized)<br><br>Duration and dates (field work): Not stated |
| Participants | Sample size: 56 (this paper describes 4 separate small trials with different doses of VC638. A total of 42 received vaccine and 14 placebo)<br><br>Inclusion criteria: Age 18 to 40 years, male students or workers, good health, informed consent.<br><br>Exclusion criteria: Recent history of diarrhoeal disease or cholera vaccination, taking medication at the time of recruitment. |
| Interventions | Vaccine: VC638 - A live attenuated strain of V. cholerae O1 El Tor Ogawa<br><br>• $2 \times 10^9$ CFU<br>• $1 \times 10^9$ CFU<br>• $2 \times 10^8$ CFU<br>• $4 \times 10^{7}$ CFU<br><br>Placebo: Buffer alone |
| Outcomes | *Included in review:*<br><br>• Adverse events (detected through inpatient observation) |


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**Benítez 1999** *(Continued)*

| | |
|---|---|
| | *Not included in the review:*<br>• Immunological outcomes: Serum vibriocidal geometric mean antibody titres on days 0, 14 and proportion who develop ≥2 or ≥4-fold rises from baseline after one dose |
| Notes | Location: La Lisa of Havana, Cuba<br>Setting: Institute of Tropical Medicine<br>Source of funding: None stated |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Comment: Not described as randomised though it seems unlikely that this was not done. |
| Allocation concealment (selection bias) | Low risk | Quote: 'The clinical investigator assigned a letter to each volunteer. The code was kept by the monitor till the end of the experiment and analysis of all samples'. |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: 'The placebo consisted of bicarbonate buffer alone and was indistinguishable from the vaccine preparation. To ensure double-blinding, identical flasks, containing either inoculum or placebo, were coded by an outside monitor'. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: No losses recorded during the monitoring of adverse events |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of any other bias |

**Chen 1996**

***Study characteristics***

| | |
|---|---|
| Methods | Design: Randomized controlled trial (individually randomized)<br>Duration and dates (field work): Jun 1993 to Jan 1994 |
| Participants | Sample size: 369<br>Inclusion criteria: Students from the primary and secondary school, and factory workers of Jiu-Fu area, Guang-Zhou. |


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**Chen 1996** *(Continued)*

| | |
|---|---|
| | Exclusion criteria: A history of cholera, or acute diarrhoea in the past 2 weeks. |
| Interventions | Vaccine 1: Killed whole-cell vaccine plus recombinant cholera toxin B subunit (locally formulated)<br>• $1x10^{10}$ vibrio cholera whole cells + 5mg rBS<br>Vaccine 1: Killed whole-cell vaccine plus recombinant cholera toxin B subunit (locally formulated)<br>• $1x10^{10}$ vibrio cholera whole cells + 1mg rBS<br>Placebo: Buffer alone |
| Outcomes | *Included in review:*<br>• Adverse events (detected through observation)<br>*Not included in the review:*<br>• Immunological outcomes |
| Notes | Location: Jiu-Fu Area in Guang-Zhou city<br>Setting:<br>Source of funding: National 638 funds and fund from the Academy of Guang-Dong Province |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Labelled as 'Randomized', no further details. |
| Allocation concealment (selection bias) | Unclear risk | None described. |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy is not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Unclear risk | Described as 'double-blind'. No further details |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy is not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | No losses to follow-up reported |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |


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**Clemens 1987**

| ***Study characteristics*** | |
|---|---|
| Methods | Design: Randomized controlled trial (individual randomization)<br>Trial dates and duration: 1984, with short-term follow-up |
| Participants | Sample size: 1,257 enrolled and took first dose of vaccine or placebo, 1051 received two doses, and 898 received third doses<br>Inclusion criteria: Children aged 2 to 15 years and women aged over 15 years.<br>Exclusion criteria: Pregnancy, people too ill to leave their beds on the day of the vaccination |
| Interventions | Vaccine 1: Killed whole cell plus purified cholera B subunit vaccine (WC-BS)<br>Vaccine 2: Killed whole cell vaccine (WC)<br>Placebo 1: Heat-inactivated *E. coli* K12 strain<br>Placebo 2: Distilled water |
| Outcomes | *Included in the review:*<br>• Adverse events for three consecutive days after each dose<br>*Not included in the review:*<br>• Immunogenicity |
| Notes | *Location:* Matlab, Bangladesh<br>Setting: Community, within a health and demographic surveillance site<br>Source of funding: United States Agency for International Development (USAID); the government of Japan; the Swedish Agency for Research Cooperation with Developing Countries, and the World Health Organization. |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "randomly assigned"<br>Comment: Unclear description but probably low risk of bias |
| Allocation concealment (selection bias) | Low risk | Quote: "Each of the agents, labelled only as W,X,Y or Z"<br>Comment: Allocation concealed |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: "..study physicians who were kept unaware of the identities of agents received by subjects.." |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |


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**Clemens 1987** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: No loss to follow-up |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |

**Clemens 1988 Bangladesh**

| ***Study characteristics*** | |
|---|---|
| Methods | Design: Randomized controlled trial (individual randomization)<br>Trial dates and duration: Vaccination January to March 1985; follow-up 5 years<br>Surveillance: Passive surveillance system at diarrhoea treatment centres serving the study population. |
| Participants | Number of participants: 89,596 received at least one dose of vaccine or placebo, 62,285 ingested three complete doses<br>Inclusion criteria: children aged 2-15 years and women over the age of 15<br>Exclusion criteria: Pregnancy, illness requiring bed rest |
| Interventions | Vaccine 1: Killed whole cell plus purified cholera B subunit vaccine (WC-BS)<br>Vaccine 2: Killed whole cell vaccine (WC)<br>Placebo: *Escherichia coli* K12 strain placebo (K12)<br>All subjects were randomized to receive three doses, at 6 week intervals. All doses were ingested with antacid. |
| Outcomes | *Included in review:*<br>• Cholera infection (faecal excretion of *V. Cholerae* 01)<br>• Symptomatic cholera infection (faecal excretion of *V. Cholerae* 01 from 48 hours before to 48 hours after a diarrhoea episode)<br>• Cases of cholera (non-bloody diarrhoea, dehydration and excretion of *V. cholerae* 01).<br>• Cases of cholera, excluding cases that are clinically atypical or associated with mixed infections.<br>• Symptomatic and asymptomatic cholera infection detected using active surveillance of among persons residing in the same courtyard as a sentinel cases detected in active surveillance. Participants were surveyed for symptoms and rectal swabs taken and cultured for *V. cholerae* 01 each day for 7 days.<br>• Cases of diarrhoea, classified according to watery and non-watery, and severe and non-severe.<br>• Deaths from cholera.<br>• All deaths.<br>• Adverse events within 3 days of first dose and within 3 days of second dose.<br>Cases of diarrhoea and cholera were only included in the analysis if they occurred at least 14 days after the third dose of vaccine or placebo.<br>*Not included in the review:*<br>• Immunological response in participants with cholera, comparing those receiving placebo and placebo. |


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**Clemens 1988 Bangladesh** *(Continued)*

- Diarrhoeal episodes associated with other *Vibrio* and *Aeromonas* species.
- Antibacterial and anti-toxic antibody responses in breast milk.
- Antibody responses following immunisation.
- Cases of cholera by neighbourhood vaccine coverage level (herd immunity).
- Diarrhoea associated with ETEC

| | |
|---|---|
| Notes | Location: Matlab, Bangladesh<br><br>Setting: Surveillance study area, served by three diarrhoea treatment centres.<br><br>Source of funding: Bill and Melinda Gates Foundation; U.S. National Institutes of Health; U.S. National Science Foundation; Swedish International Development Cooperation Agency; governments of Korea, Japan and Kuwait, USAID, Word Health Organization |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote:"After computerisation of the census, we assigned every person in the eligible age-gender categories to letters A, B or C, using simple randomisation" |
| Allocation concealment (selection bias) | Low risk | Quote: "The agents were identified only by the letters A, B and C"<br><br>Comment: Allocation concealed |
| Blinding (performance bias and detection bias) Efficacy outcomes | Low risk | Quote: "During the conduct of the study, the identities of these letter...were unknown to all persons connected with the trial in Bangladesh" |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | As above |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Low risk | Comment: Attrition between the first and third doses was high: 30.5%. The protective effect is reported as being similar in those who only received two doses, so these losses are unlikely to have introduced significant bias. |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: There was no missing data for adverse events. |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting. |
| Other bias | Low risk | No evidence of other bias. |

**Cohen 2002**

***Study characteristics***

| | |
|---|---|
| Methods | Design: Randomized controlled trial (individual randomization)<br><br>Trial dates and duration: 2000-2001 |
| Participants | Number of participants: 59 (36 included in the challenge study) |


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**Cohen 2002** *(Continued)*

| | |
|---|---|
| | Inclusion criteria: Age 18 to 40 years, informed consent, and judged likely to comply with the study requirements.<br><br>Exclusion criteria: Clinically significant abnormalities on urinalysis, full blood count, serum hepatic transaminases, glucose, creatine, urea nitrogen, electrolytes or ECG. Travel to cholera endemic areas in the previous 5 years, history of cholera or ETEC challenge, recent antibiotic use, abnormal stool pattern, regular laxative use, failure to pass psychological screening, allergy to tetracycline or ciprofloxacin, pregnant or breastfeeding, HIV-positive, hep B-positve, hep C-postive, stool culture positive for enteric pathogen. |
| Interventions | Vaccine: Peru 15 - a live attenuated strain of *V. cholerae* O1 El Tor Inaba plus 200 ml CeraVacx buffer (Cera Products, Columbia)<br><br>Placebo: 200ml CeraVacx buffer (Cera Products, Columbia)<br><br>Challenge: Three months after vaccination, willing participants were given artificial challenge with $10^5$ CFU of virulent *V. cholerae* 01 El Tor Inaba Strain N16961, prepared from a standardised frozen inoculum |
| Outcomes | *Included in the review:*<br><br>• Adverse events during the first 3 days after the dose (assessed by a self completed diary)<br><br>Participants who went on to receive artificial challenge were also monitored for diarrhoea, and positive stool culture with the challenge strain; on an inpatient basis.<br><br>• Any diarrhoea: passage of two or more unformed stools over a 48 hour period that equalled or exceeded 200 g for a single stool, or 300 g or greater in total<br>• Moderate or severe cholera: diarrhoea with passage of >3,000 g during the study period plus a positive stool culture for *V. cholerae* 01<br><br>*Not included in the review:*<br><br>• Immunological outcomes: Geometric mean inverse Inaba vibriocidal antibody titres pre and post immunisation and proportion who developed ≥4-fold rises from baseline after one dose |
| Notes | Location: USA<br><br>Setting: Volunteer study. Outpatient phase for adverse events, inpatients phase for response to artificial challenge<br><br>Sources of funding: National Institutes of Health, General Clinical Research Centres Program |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: ‘sequence generated by SAS PROC PLAN’. |
| Allocation concealment (selection bias) | Low risk | Comment: The randomization code generated off-site and study blinded until after analysis |
| Blinding (performance bias and detection bias) Efficacy outcomes | Low risk | Quote: ‘Investigators did not know the vaccine status of all volunteers until the data was locked and the code was broken after the challenge was completed’ |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: 'Volunteers were randomly assigned to groups in a double-blind manner....A study nurse who was unaware of the group assignment reviewed the (symptom) diary'. |


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**Cohen 2002** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) Efficacy outcomes | High risk | Comment: The loss of participants between randomisation and the challenge study (39%) could introduce significant bias. |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: The data was complete for the three days of adverse event monitoring |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |

**Concha 1995**

| ***Study characteristics*** | |
|---|---|
| Methods | Design: Randomized controlled trial (cluster randomized by household)<br><br>Duration: Two months, January and February 1992 |
| Participants | Sample size: 1313 received an initial dose of vaccine or placebo, 1165 received two doses.<br><br>Inclusion criteria: People between the ages of 12 months and 64 years who have resided in the study area for at least two months.<br><br>Exclusion criteria: Confirmed or possible pregnancy, illness requiring bed rest, known mental illness or incapacity to give informed consent, diarrhoea at the time either of the two vaccine doses were administered. |
| Interventions | Vaccine: Killed whole-cell vaccine plus recombinant cholera toxin subunit (WC-rBS; Dukoral®, SBL, Sweden)<br><br>Placebo: killed whole cells of *E. coli* K12.<br><br>Both vaccine and placebo were administered with a buffer solution. Two doses were given, two weeks apart. |
| Outcomes | *Included in the review:*<br><br>• Reported symptoms in the three days following ingestion of the vaccine (daily visits using pre-coded forms)<br><br>*Not included in the review:*<br><br>• Immunological outcomes: Geometric mean vibriocidal antibody, IgG antitoxin and IgA antitoxin titres pre and post vaccination. |
| Notes | Location: Los Olivios, Barraquilla, Colombia<br><br>Setting: Households in a poor neighbourhood<br><br>Source of funding: Pan American Health Organization and World Health Organization. Vaccine donated by the National Bacteriological Laboratory in Stockholm, Sweden. |

| ***Risk of bias*** | | |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |


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**Concha 1995** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Households were randomly selected to receive either vaccine or placebo"<br><br>Comment: The method of sequence generation is unclear |
| Allocation concealment (selection bias) | Low risk | Quote: "the vaccination team knew the two only as 'vaccine A and 'vaccine B' |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy is not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: "Both agents were administered double-blind; the vaccination team know the two only as "vaccine A" and "vaccine B"....nurses, who .. were unaware of how the agent were distributed..record any..symptoms" |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: No loss to follow-up |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | High risk | Comment: 620 individuals who originally consented to participate dropped out of the study because of a political campaign against it. |

**Cryz 1990**

| ***Study characteristics*** | |
|---|---|
| Methods | Design: Randomized controlled trial (individually randomized)<br><br>Trial dates and duration: Study dates not given; follow-up 21 days |
| Participants | Sample size: 50 enrolled<br><br>Inclusion criteria: Age 21 to 45 years, healthy, informed consent<br><br>Exclusion criteria: None stated |
| Interventions | Vaccine: CVD 103-HgR live attenuated vaccine containing:<br><br>• 5 x $10^8$ CFU of lyophilized genetically modified *V. cholerae* O1 Classical Inaba (569B)<br><br>Placebo: 5 x $10^8$ CFU of heat-killed *E. coli* K12 strain |
| Outcomes | *Included in review:*<br><br>• Adverse events during first 7 days after vaccination (interview on day 7) only diarrhoea and abdominal pain are reported.<br><br>*Not included in the review:* |


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**Cryz 1990** *(Continued)*

| | |
|---|---|
| | • Immunological outcome: Geometric mean serum vibriocidal antibody titres on day 0, 10 and 21, proportion who develop ≥4 fold rises in serum titres. |
| Notes | Location: Switzerland<br>Setting: Not stated<br>Source of funding: None stated |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Described as 'randomised', no further details given. |
| Allocation concealment (selection bias) | Unclear risk | None described |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: 'A coded sachet containing either vaccine or placebo was mixed with the buffer solution and immediately ingested.', 'The appearance of the placebo was identical to that of the vaccine.' |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: No losses are reported during the first week of adverse event surveillance |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |

**García 2005**

***Study characteristics***

| | |
|---|---|
| Methods | Design: Randomized controlled study with artificial challenge (Individually randomized)<br>Trial dates and duration: Dates not stated; artifical challenge took place 1 month after vaccination |
| Participants | Sample size: 45 (21 in challenge study)<br>Inclusion criteria: Age 18 to 40 years, volunteer male workers among the western scientific community, good health, informed consent.<br>Exclusion criteria: Recent history of diarrhoeal disease or cholera vaccination, taking any medication at the time of recruitment, any abnormality in clinical laboratory tests (complete blood count, chemistry panel, HIV and Hep C virus antibodies, Hep B virus antigen), stool cultures positive for an enteric pathogen, recent antibiotic use, or psychological incompatibility with accepting quarantine conditions |


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**García 2005** *(Continued)*

| | |
|---|---|
| Interventions | Vaccine: VC638 - A live attenuated strain of *V. Cholerae* O1 El Tor Ogawa<br>• 1 x $10^9$ CFU plus buffer<br>Placebo: Buffer alone<br>Artificial challenge: 7 x $10^5$ CFU of fully virulent El Tor Ogawa strain 3008 (orally). |
| Outcomes | *Included in review:*<br>• *V. cholerae* diarrhoea following oral challenge<br>• Adverse events (inpatient monitoring for 5 days)<br>*Not included in the review:*<br>• Faecal virus shedding<br>• Geometric mean vibriocidal antibody titres pre and post immunisation, LPS specific IgA, and proportion who developed ≥2-fold rises from baseline after one dose |
| Notes | Location: Havana Cuba<br>Setting: Inpatient trials unit, Institute of Tropical Medicine<br>Source of funding: None stated |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Comment: Described as 'Randomized', no further details given |
| Allocation concealment (selection bias) | Unclear risk | Comment: None described. |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Comment: Described as 'double blind', no further details given. |
| Blinding (performance bias and detection bias) Safety outcomes | Unclear risk | Comment: Described as 'double blind', no further details given. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | High risk | Comment: The loss of participants between randomisation and the challenge study (47%) could introduce significant bias. |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: The data was complete as participants for the three days of adverse event monitoring |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |


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**Gotuzzo 1993**

| ***Study characteristics*** | |
|---|---|
| Methods | Design: A randomized controlled trial (individually randomized)<br>Duration: Vaccination from Sept to Dec 1991; follow-up 28 days |
| Participants | Sample size: 241 enrolled<br>Inclusion criteria: Adults aged 18 to 38 years<br>Exclusion criteria: Pregnancy, antibiotics or diarrhoea within the previous 72 h, previous cholera vaccine. |
| Interventions | Vaccine 1: CVD 103-HgR live attenuated vaccine containing:<br>• 5 x $10^9$ lyophilized organisms of a genetically modified *V. cholerae* O1<br>Vaccine 2: CVD 103-HgR live attenuated vaccine containing:<br>• 5 x $10^8$ lyophilized organisms of a genetically modified *V. cholerae* O1<br>Placebo: 5 x $10^8$ cells of heat-killed *E. coli* K-12 strain |
| Outcomes | *Included in review:*<br>• Adverse events during the first 7 days<br>*Not included in the review:*<br>• Immunological outcomes: Geometric mean rise in vibriocidal antibody titres, and proportion who develop ≥4 fold rises in serum titres from baseline after one or two doses |
| Notes | Location: Peru<br>Setting: 2 groups: high socioeconomic group: medical students and physicians from the Facultad de Medicina, Universidad Peruana Cayetano Heredia, and a low socioeconomic group: selected from Canto Grande, a periurban slum community with poor water and sanitation.<br>Source of funding: National Institute of Allergy and Infectious Diseases (NIAID) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Comment: Described as 'randomized', no further details given. |
| Allocation concealment (selection bias) | Low risk | Quote: 'Eligible adults were administered coded preparations sequentially labelled A, B, or C, two of which contained the vaccine and the other a placebo'. |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: 'Double-blind clinical follow-up was maintained for 7 days following vaccination'. |
| Incomplete outcome data (attrition bias) | Unclear risk | Not applicable as efficacy not reported |


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**Gotuzzo 1993** *(Continued)*

| | | |
|---|---|---|
| Efficacy outcomes | | |
| Incomplete outcome data (attrition bias)<br>Safety outcomes | Low risk | Comment: No losses to follow up are reported |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |

**Hallander 2002**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Design: Randomized controlled trial (individually randomized)<br>Duration: Enrolled; follow-up 28 days |
| Participants | Sample size: 249<br>Inclusion criteria: Age 1 to 12 years, permanent resident in study area, informed consent, good health<br>Exclusion criteria: None stated |
| Interventions | Vaccine Killed whole-cell vaccine plus recombinant cholera toxin subunit (WC-rBS; Dukoral®, SBL, Sweden)<br>Placebo: heat-killed *E. coli* K-12 strain (C 600)<br>All participants were randomized to receive 2 doses, 14 days apart |
| Outcomes | *Included in review:*<br>• Serious adverse events<br>• Adverse events during the first 3 days after each dose (parental interview and diary cards for 3 days)<br>*Not included in the review:*<br>• Immunological outcomes: Geometric mean rise in vibriocidal antibody titres, and proportion who develop ≥2 fold rises in serum titres from baseline after one or two doses |
| Notes | Location: León, Nicaragua<br>Setting:<br>Source of funding: None declared<br>*This paper contained the details of three individual trials: OCV-023, OCV-024 and OCV-028. OCV-023 and OCV-024 were excluded from this review as they used a variation on this vaccine for which no primary efficacy data is available. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Comment: Described as 'randomized', no further details given. |


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**Hallander 2002** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | Comment: None described. |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Unclear risk | Comment: None described. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: No losses described |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |

**Kanungo 2009**

| ***Study characteristics*** | |
|---|---|
| Methods | Design: A randomized controlled trial (individually randomized)<br><br>Trial dates and duration: Enrollment from June to August 2007; follow-up for 28 days |
| Participants | Sample size: 160 patients stratified into adults and children<br><br>Inclusion criteria: Age 18 to 40 years for adult study, 1 to 18 years for children, healthy male and non-pregnant females, written informed consent<br><br>Exclusion criteria: Abdominal pain, loss of appetite, nausea, general ill feeling or vomiting within the past 24 h, any diarrhoea within 6 weeks of enrolment, diarrhoea or abdominal pain lasting more than 2 weeks in the past 6 months, antibiotics in the past 2 weeks, anti-diarrhoeal medication or acute disease in the past week, history of serious chronic disease or an immunocompromising condition or therapy |
| Interventions | Vaccine: Bivalent killed whole-cell vaccine (BivWC: SHanchol®, Shantha Biotechnics)<br><br>Placebo: Heat killed *E. coli* K12 strain<br><br>All subjects were randomized to receive 2 doses, at an interval of 14 days. All doses were administered via an oral syringe and offered water. |
| Outcomes | *Included in review:*<br><br>• Serious adverse events during 28 days follow-up<br>• Adverse events within 3 days of each dose<br><br>*Not included in the review:* |


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**Kanungo 2009** *(Continued)*

| | |
|---|---|
| | • Immunological outcomes: Geometric mean-fold rise in serum vibriocidal antibody titres and proportion who develop ≥4-fold rises from baseline after one or two doses |
| Notes | Location: Kolkata, India<br><br>Setting: The clinical trial unit of the National Institute of Cholera and Enteric Diseases (NICED)<br><br>Source of funding: the Bill and Melinda Gates Foundation through the Diseases of the Most Impoverished Program and the Cholera Vaccine Initiative, and the governments of Korea, Kuwait and Sweden through the International Vaccine Institute |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: 'Separate randomization lists for the two age groups were prepared by a statistician in the IVI who was otherwise not involved in the study. Randomization was performed in blocks of four using Visual Fortran 5.0 (Digital USA)'. |
| Allocation concealment (selection bias) | Low risk | Quote: 'Vials were labeled with four-letter codes... the identities of the codes were only known to Shantha staff who labeled the vials and who were otherwise not involved in the study', 'Eligible subjects were assigned to receive either vaccine or placebo according to the randomization list. Subjects were assigned sequentially to a number in the randomization list'. |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: 'Study staff and participants were unaware of the identity of the codes during the study period'. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: Five participants (3.1%) were lost to follow-up between the first and second doses. Four withdrew consent and one was found to be ineligible. |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |

**Kotloff 1992**

***Study characteristics***

| | |
|---|---|
| Methods | Design: Randomized controlled cross-over trial (individually randomized)<br><br>Duration: Study dates not given; follow-up 28 days |
| Participants | Sample size: 94 enrolled<br><br>Inclusion criteria: Age 18 to 40 years, college students, informed consent |


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**Kotloff 1992** *(Continued)*

| | |
|---|---|
| | Exclusion criteria: Previously lived in a cholera endemic area, antibiotic therapy in previous 2 weeks |
| Interventions | Vaccine: CVD 103-HgR live attenuated vaccine containing:<br>• 5 x $10^8$ CFU of lyophilized genetically modified *V. cholerae* O1 Classical Inaba (569B)<br>Placebo: 5 x $10^8$ CFU of heat-killed *E. coli* K12 strain<br>All participants were randomized to receive one dose with crossover to receive the alternative arm after 8 days. |
| Outcomes | *Included in review:*<br>• Adverse events during first 7 days after vaccination<br>*Not included in the review:*<br>• Immunological outcome: Geometric mean serum vibriocidal antibody titres, and IgG antitoxin pre and post dose, proportion who develop ≥4 fold rises in serum titres, Excretion of vaccine strain. |
| Notes | Location: Maryland, USA<br>Setting: College students<br>Source of funding: Swiss Serum and Vaccine Institute |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: 'In a double-blind fashion, subjects were randomly allocated to receive a single dose'. |
| Allocation concealment (selection bias) | Unclear risk | Comment: None described |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: 'The blind was maintained through analysis of data'. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: No losses to follow up are reported |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |


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### Lagos 1993

| ***Study characteristics*** | |
|---|---|
| Methods | Design: A randomized controlled trial (individually randomized)<br><br>Duration: Vaccination took place Nov to Dec 1991; follow-up 7 days. |
| Participants | Sample size: 81 enrolled<br><br>Inclusion criteria: Age 18 to 35 years, male conscripts of the Chilean Air Force, employees of the Roberto del Rio Hospital, and medical students of the university of Chile, informed consent<br><br>Exclusion criteria: Antibiotics or diarrhoea during the previous week, signs or symptoms of any acute disease, any type of chronic ailment |
| Interventions | Vaccine: CVD 103-HgR live attenuated vaccine containing:<br><br>• 5 x $10^9$ lyophilized organisms of a genetically modified *V. cholerae* O1<br><br>Placebo: 5 x $10^9$ heat-killed *E. coli* K12 strain (C600)<br><br>All participants were randomized to receive one dose |
| Outcomes | *Included in review:*<br><br>• Adverse events during the first 7 days after the vaccine<br><br>*Not included in the review:*<br><br>• Immunological outcomes: Geometric mean serum vibriocidal antibody titres, and IgG antitoxin pre and post dose, proportion who develop ≥4 fold rises in serum titres,<br>• Excretion of vaccine strain. |
| Notes | Location: Chile<br><br>Setting:<br><br>Source of funding: None stated |

| ***Risk of bias*** | | |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | Comment: Not described. |
| Allocation concealment (selection bias) | Low risk | Quote: 'The codes were kept in confidential archives at the Swiss Institute of Sera and Vaccines...until the end of the serological analysis'. |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: 'All observations were made using the double-blind methodology'. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |


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**Lagos 1993** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: All participants are included in the adverse event data. |
| Selective reporting (reporting bias) | Low risk | No evidence of selective outcome reporting |
| Other bias | Low risk | No other bias detected |

**Lagos 1995**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Design: Randomized controlled trial (individually randomized)<br>Duration: Study dates not given; follow-up 8 days |
| Participants | Sample size: 349 enrolled<br>Inclusion criteria: Age 5 to 9 years, from public schools in a low-socioeconomic-level community<br>Exclusion criteria: Fever, antibiotic therapy, or chronic disease |
| Interventions | Vaccine: CVD 103-HgR live attenuated vaccine containing:<br>• 5 x $10^9$ lyophilized organisms of a genetically modified *V. cholerae* O1 Classical Inaba (569B)<br>Placebo: Heat-killed *E. coli* K12 strain<br>All participants were randomized to receive one dose |
| Outcomes | *Included in review:*<br>• Adverse events during first 8 days after vaccination<br>*Not included in the review:*<br>• Immunological outcome: Geometric mean serum vibriocidal antibody titres, and IgG antitoxin pre and post dose, proportion who develop ≥4 fold rises in serum titres, Excretion of vaccine strain. |
| Notes | Location: Santiago, Chile<br>Setting:<br>Source of funding: The World Health Organization and NIAID |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Comment: Described as 'randomized', no further details given. |
| Allocation concealment (selection bias) | Low risk | Quote: 'Lyophilized vaccine and placebo were contained in randomized coded aluminum foil sachets. The code remained unbroken until the clinical study, including serology, was completed'. |


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**Lagos 1995** *(Continued)*

| | | |
|---|---|---|
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: 'Double-blind clinical follow-up to detect adverse reactions was maintained daily for 8 days after the single oral immunization'. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: No losses recorded during adverse event monitoring |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |

**Lagos 1999**

| ***Study characteristics*** | |
|---|---|
| Methods | Design: Randomized controlled trial (individually randomized)<br>Trial dates and duration: June 1995 to Nov 1997; follow-up 28 days |
| Participants | Sample size: 312 enrolled<br>Inclusion criteria: Age 3 to 17 months, normal medical history, parental consent<br>Exclusion criteria: Signs and symptoms of acute illness, antibiotic therapy or diarrhoea in previous 2 days |
| Interventions | Vaccine: CVD 103-HgR live attenuated vaccine containing:<br>• 5 x $10^9$ CFU of lyophilized organisms of a genetically modified V. cholerae O1<br>Placebo: 5 x $10^8$ CFU of heat-killed *E. coli* K12 strain<br>Participants were initially randomized to receive vaccine or placebo. After 14 days all participants in both groups received a dose of vaccine |
| Outcomes | *Included in review:*<br>• Adverse events during first 7 days after first vaccination (daily home visit and symptom enquiry),<br>*Not included in the review:*<br>• Immunological outcome: Geometric mean serum vibriocidal antibody titres, and IgG antitoxin pre and post dose, proportion who develop ≥4 fold rises in serum titres, Excretion of vaccine strain. |
| Notes | Location: Santiago, Chile<br>Setting: Well-baby clinics at a semi-rural ambulatory health centre. |


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**Lagos 1999** *(Continued)*

Source of funding: The World Health Organization and NIAID

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: 'For the first dose one-half were randomly allocated in double blind fashion to receive a dose of vaccine' |
| Allocation concealment (selection bias) | Low risk | Quote: 'The sachets of test product were packed as individual treatments consisting of two sachets labeled with the same number followed by the letter A or B, indicating the appropriate sachet for the first and second dose of the immunization regimen', 'Each subject received the treatment number matching his/her study identification number'. |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Comment: Described as 'double-blind'. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Unclear risk | Comment: All randomised participants completed the follow-up for adverse events following the first dose |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |

**Mahalanabis 2008**

***Study characteristics***

| | |
|---|---|
| Methods | Design: Randomized controlled trial (individually randomized)<br>Trial dates and duration: Enrollment from Aug to Oct 2005; follow-up for 28 days |
| Participants | Sample size: 201 participants stratified into adults and children<br>Inclusion criteria: Age 18 to 40 years for adult study, 1 to 17 years for children, healthy male and non-pregnant females, written informed consent<br>Exclusion criteria: Abdominal pain, vomiting, loss of appetite, generalized ill-feeling or nausea during the preceding 24 hours, diarrhoea or history of anti-diarrhoeal or antibiotic use during the past week, history of diarrhoea and abdominal pain lasting for more than 2 weeks during the past 6 months |
| Interventions | Vaccine: Bivalent killed whole-cell vaccine (BivWC: Shanchol®, Shantha Biotechnics)<br>Placebo: Heat-killed *E. coli* K12 strain |


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**Mahalanabis 2008** *(Continued)*

| | |
|---|---|
| | All subjects were randomized to receive 2 doses, at an interval of 14 days. All doses were administered via an oral syringe and offered water. |
| Outcomes | No evidence of other bias |
| Notes | Location: Kolkata, India<br><br>Setting: Clinical trial ward of the Infectious Diseases Hospital<br><br>Source of funding: The Bill and Melinda Gates Foundation through the Diseases of Most Impoverished Program administered by the International Vaccine Institute, and the Swedish International Development Cooperation Agency |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: 'Separate randomization lists for adults and children were prepared by a statistician in IVI who was otherwise not involved in the study. Randomization numbers were generated in blocks of 8 using the program Visual Fortran 5.0. (Digital, USA)'. |
| Allocation concealment (selection bias) | Low risk | Quote: 'Study agents were coded using 8 letters (4 for vaccine and 4 for placebo) in the adult trial and 8 different letters in the pediatric trial. Only the code letters on the vials identified the study agents as vaccine or placebo. The codes were revealed to the researchers once recruitment, data collection, and laboratory analyses were complete' |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: 'All study personnel and participants were blinded to treatment assignment during the duration of the study'. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: Three randomized participants (2.5%) were excluded from the adverse event follow-up, one who declined the first dose and two who received the wrong allocation for the second dose |
| Selective reporting (reporting bias) | Low risk | No evidence of selective outcome reporting |
| Other bias | Low risk | No evidence of other bias |

**Migasena 1989a**

***Study characteristics***

| | |
|---|---|
| Methods | Design: A randomized controlled study (individually randomized)<br><br>Duration: Datesnot given; follow-up 5 days |


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**Migasena 1989a** *(Continued)*

| | |
|---|---|
| Participants | Sample size: 24 enrolled<br>Inclusion criteria: Healthy adults age 20 to 30 years, informed consent<br>Exclusion criteria: None stated |
| Interventions | Vaccine: CVD 103-HgR live attenuated vaccine containing:<br>• 5 x $10^8$ lyophilized organisms of a genetically modified *V. cholerae* O1 Classical Inaba (569B)<br>Placebo: 5 x $10^8$ heat-killed *E. coli* K12 strain (C600)<br>On day 5 all participants began a 5-day course of tetracycline. |
| Outcomes | *Included in review:*<br>• Adverse events within 5 days of the vaccine (Daily interview)<br>*Not included in the review:*<br>• Immunological outcomes: Geometric mean serum vibriocidal antibody titres, and IgG antitoxin pre and post dose |
| Notes | Location: Thailand<br>Setting: Vaccine Trial Centre in the Faculty of Tropical Medicine.<br>Source of funding: |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Comment: Described as 'randomized', no further details given. |
| Allocation concealment (selection bias) | Low risk | Quote: 'The study was carried out in double-blind fashion without the volunteers, the nursing staff, or the clinical investigators knowing the identity of the contents of the packets. A four-letter code for the packets was employed as an extra precaution to maintain double blindness'. |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | See above |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: No losses are reported |
| Selective reporting (reporting bias) | Low risk | No evidence of selective outcome reporting |


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**Migasena 1989a** *(Continued)*

| | | |
|---|---|---|
| Other bias | Low risk | No other sources of bias identified |

**Perry 1998**

| ***Study characteristics*** | |
|---|---|
| Methods | Design: Randomized controlled cross-over trial (individually randomized)<br><br>Trial dates and duration: Dates not stated, cross-over after 12 days. |
| Participants | Number of participants: 76<br><br>Inclusion criteria: Clinically healthy commercial sex workers and students aged 18 to 50 years. Half were HIV-positive and half were age and sex matched HIV-negative.<br><br>Exclusion criteria: Pregnancy; clinical symptoms of AIDS; previous cholera vaccination; reported having previously had cholera; taken antibiotics within the previous 4 days; current diarrhoea or other acute illness |
| Interventions | vaccine: CVD 103-HgR live attenuated vaccine containing:<br><br>• 5 x $10^9$ CFU of a genetically modified *V. cholerae* O1<br><br>Placebo: Lactate and aspartame only (these are also constituents of the vaccine)<br><br>On day 12 those who initially received the placebo now received the vaccine, and vice versa. |
| Outcomes | *Included in the review:*<br><br>• Adverse events (Active surveillance; daily visits by physicians every day for 6 days and every other day for a further 6 days. Only adverse events prior to crossover are included)<br><br>*Not included in the review:*<br><br>• Rectal swabs for vaccine virus on days of inoculation, daily for 4 days and on days 6 and 12<br>• Immunological outcomes: Goemetric mean vibriocidal antibodies pre and post vaccination. Seroconversion rates (criteria not stated) |
| Notes | Location: Mali<br><br>Setting: Not clear<br><br>Source of funding:WHO Global Programme on Vaccines, National Institute of Allergy and Infectious Diseases, Centre for Vaccine Development, University of Maryland School of Medicine |

| ***Risk of bias*** | | |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | Comment: Described as 'randomized', no further details given |
| Allocation concealment (selection bias) | Unclear risk | Comment: Not described |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |


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**Perry 1998** *(Continued)*

| | | |
|---|---|---|
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: 'identically appearing placebo packets' |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: Four (6%) participants were lost to follow-up during the study |
| Selective reporting (reporting bias) | Low risk | No evidence of selective outcome reporting |
| Other bias | Low risk | No other sources of bias identified |

**Qadri 2005**

| ***Study characteristics*** | |
|---|---|
| Methods | Design: Randomized controlled trial (individually randomized)<br><br>Trial dates and duration: Dates not stated, follow-up 21 days |
| Participants | Number of participants: 70<br><br>Inclusion criteria: Age 18 to 45 years, healthy, willing to participate, informed consent<br><br>Exclusion criteria: Any chronic disease or recent illness, immunosuppressive conditions during the past 6 months, pregnancy, diarrhoeal illness in the last 6 weeks, febrile illness in the last week or antibiotics in the last 2 weeks, history of any enteric vaccine given in the last month, stool samples positive for any enteric pathogen, food handlers and those cooking for or looking after infants and young children |
| Interventions | Vaccine: Peru 15 - a live attenuated strain of *V. cholerae* 01 El Tor Inaba (AVANT Immunotherapeutics Inc, US) containing:<br><br>• 2 x $10^8$ CFU plus buffer<br><br>Placebo: Buffer only<br><br>All participants were given doxycycline for four days on day 6 to clear the vaccine strain. |
| Outcomes | *Included in the review:*<br><br>• Adverse events: reported up to 4 days after vaccination (patients were seen twice daily by a clinician or visited daily at home)<br><br>*Not included in the review:*<br><br>• Immunological outcomes: Geometric mean vibriocidal antibody titres, IgA and IgG antitoxin titres and IgA anti-lipopolysaccharide titres; on days 1, 7 and 21, and proportion who developed ≥4-fold rises from baseline after one dose |
| Notes | Location: Dhaka, Bangladesh<br><br>Setting: Participants recruited from an urban slum, close to inpatient and outpatient facilities of ICC-DR,B |


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**Qadri 2005** *(Continued)*

| | |
|---|---|
| | Source of funding: Diseases of the Most Impoverished Program, Bill and Melinda Gates Foundation, International Vaccine Institute |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: 'Randomization was performed by the International Vaccine Institute, South Korea'. |
| Allocation concealment (selection bias) | Unclear risk | Comment: None described. |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Unclear risk | Comment: Described as 'double-blind'. No further details given. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: No losses to follow-up during the 4 days of adverse event reporting |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting. |
| Other bias | Low risk | No other bias identified |

**Qadri 2007**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Trial design: Randomized controlled trial (individually randomized)<br>Trial dates and duration: Dates not stated, follow-up 21 days |
| Participants | Number of participants: 240<br>Inclusion criteria: age 9 months to 5 years, healthy, parental consent<br>Exclusion criteria: Any chronic disease; any recent illness; any illness or treatment causing immunosuppression in the last 9 months; diarrhoeal illness in the last two weeks; febrile illness in the last week; any enteric vaccine given in the last month; stool samples positive for any enteric pathogen |
| Interventions | Vaccine 1: Full dose Peru 15 - a live attenuated strain of *V. cholerae* 01 El Tor Inaba (AVANT Immunotherapeutics Inc, US)<br>• 2 x $10^8$ CFU plus buffer<br>Vaccine 2: Reduced dose Peru 15 - a live attenuated strain of *V. cholerae* 01 El Tor Inaba (AVANT Immunotherapeutics Inc, US) |


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**Qadri 2007** *(Continued)*

| | |
|---|---|
| | • 2 x $10^7$ CFU plus buffer<br><br>Placebo: Buffer only<br><br>All participants were given erythromycin for four days on day 6 to clear the vaccine strain. |
| Outcomes | *Included in the review:*<br><br>• Adverse events: reported up to 4 days after vaccination (monitored as an inpatient for 12 days then daily up to day 21, data only presented for first 4 days)<br><br>*Not included in the review:*<br><br>• Immunological outcomes: Geometric mean Inaba and Ogawa vibriocidal antibody titres on days 1 and 7 and proportion who developed ≥4-fold rises from baseline after one dose |
| Notes | Location: Dhaka, Bangladesh<br><br>Setting: Participants recruited from an urban slum, close to inpatient and outpatient facilities of ICC-DR,B<br><br>Source of funding: Bill and Melinda Gates Foundation |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: 'Randomization was carried out by the International Vaccine Institute and sent to the vaccine formulation team.' |
| Allocation concealment (selection bias) | Low risk | Quote: 'The vaccine formulation team prepared and blinded the vaccine and the placebo according to the randomization list'. |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: 'The results were analyzed sequentially in the order in which they had been completed and unblinded.' |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: Follow-up for adverse events was 100%. |
| Selective reporting (reporting bias) | Low risk | No evidence of selective outcome reporting |
| Other bias | Low risk | No other bias identified |

**Richie 2000 Indonesia**

***Study characteristics***


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**Richie 2000 Indonesia** *(Continued)*

| | |
|---|---|
| Methods | Design: Randomized controlled trial (individually randomized)<br><br>Trial dates and duration: July 1993 to Dec 1997, 4 years<br><br>Surveillance: Passive surveillance conducted through four North Jakarta hospitals distributed across the study area. |
| Participants | Sample size: 67,508<br><br>Inclusion criteria: Persons aged 2 to 41 years living in the study area.<br><br>Exclusion criteria: Pregnancy, plans to move out of the study area, diagnosis of cancer |
| Interventions | Vaccine: CVD 103-HgR live attenuated vaccine containing:<br><br>• 5 x $10^9$ lyophilized organisms of a genetically modified *V. cholerae* O1 Classical Inaba (569B)<br><br>Placebo: 5 x $10^8$ heat-killed *E. coli* K12 strain (C600) |
| Outcomes | *Included in the review:*<br><br>• Cases of cholera<br>• Deaths other than those caused by vehicular accident<br>• Adverse events reported during the three days after ingestion of the vaccine or placebo<br><br>*Not included in the review:*<br><br>• Immunological outcomes: Geometric mean vibriocidal antibody titres pre and post dose, and proportion who develop ≥4-fold rises after one dose |
| Notes | Location: 65 communities in North Jakarta, Indonesia<br><br>Setting: Poor communities with poor sanitation and relative high cholera incidences<br><br>Source of funding: World Health Organization, National Institute of Allergy and Infectious Diseases, the Swiss Serum and Vaccine Institute, Berne. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "A randomized trial"<br><br>Comment: Method of randomization unclear |
| Allocation concealment (selection bias) | Low risk | Quote: "Vaccine..and placebo ..were contained in identical, numbered packets" |
| Blinding (performance bias and detection bias) Efficacy outcomes | Low risk | Quote: "Surveillance data collected included..vaccine number. ..Patients with diarrhoea who did not state that they were participants in the study were also included in the surveillance." |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: "a double-blind nested study of adverse events was conducted.." |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Comment: No mention of the numbers of people who moved out of the area and were therefore lost of follow up. |


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**Richie 2000 Indonesia** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: No loss to follow up |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |

**Sack 1997**

| ***Study characteristics*** | |
|---|---|
| Methods | Design: Randomized controlled trial (individually randomized)<br><br>Trial dates and duration: Dates not given, 21 days follow-up |
| Participants | Number of participants: 50 in outpatient study (a smaller inpatient study is also reported but included no outcomes relevant to this review)<br><br>Inclusion criteria: Age 18 to 50 years, healthy, willing to participate, informed consent<br><br>Exclusion criteria: chronic illness, immunosuppressive condition, abnormal stool pattern, significant abnormality in screening laboratory hematology and chemistry tests, HIV +ve, hepatitis B surface antigen +ve, pregnancy, travel to a cholera endemic area within 5 years, receipt of cholera vaccine, history of cholera infection or vaccination, previous participation in a cholera or ETEC vaccine trial, use of antibiotics within 7 days of vaccination, food handlers or close contact with children under age 5 |
| Interventions | Vaccine 1: Full dose Peru 15 - a live attenuated strain of *V. cholerae* 01 El Tor Inaba<br><br>• 2 x $10^9$ CFU plus buffer<br><br>Vaccine 2: Reduced dose Peru 15 - a live attenuated strain of *V. cholerae* 01 El Tor Inaba (AVANT Immunotherapeutics Inc, US)<br><br>• 2 x $10^8$ CFU plus buffer<br><br>Placebo: Buffer only |
| Outcomes | *Included in the review:*<br><br>• Adverse events: reported up to 7 days after vaccination (using a self reported symptom diary)<br><br>*Not included in the review:*<br><br>• Immunological outcomes: Geometric mean titres of vibriocidal antibody and IgG antitoxin on days 0, 10 and 21, and proportion who developed ≥2 and ≥4-fold rises from baseline after one dose |
| Notes | Location: USA<br><br>Setting: Students or employee volunteers at John Hopkins University and Hospital<br><br>Source of funding: National Institute Health, Virus Research Institute |

| ***Risk of bias*** | | |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |


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**Sack 1997** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Comment: Described as 'Randomized'. No further details given. |
| Allocation concealment (selection bias) | Unclear risk | Comment: None described |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: 'Volunteers were randomized to receive either a $10^9$ or $10^8$ CFU or a placebo in a double-masked manner', 'To protect the masked code, some volunteers were assigned to 1 or 0.1 mL of placebo'. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: No losses are described during the adverse event monitoring. |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |

**Sanchez 1993a**

| ***Study characteristics*** | |
|---|---|
| Methods | Design:A randomized 2 x 2 factorial controlled trial (individually randomized)<br>Duration: Enrolled during October 1991; follow-up 28 days |
| Participants | Sample size: 186 enrolled and randomized to four groups*<br>Inclusion criteria: Age 18 to 44 years<br>Exclusion criteria: Pregnancy or planned pregnancy, diarrhoea or fever within the past 5 days, recent use of antimotility or antibacterial agent, foodhandler, chronic gastrointestinal disorder. |
| Interventions | Vaccine: Killed whole-cell vaccine plus recombinant cholera toxin subunit (WC-rBS; Dukoral®, SBL, Sweden)<br>Placebo: Buffer alone<br>All participants were randomized to receive 2 doses, at 11 to 16 days apart |
| Outcomes | *Included in review:*<br>• Adverse events: text summary only<br>*Not included in the review:* |


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**Sanchez 1993a** *(Continued)*

| | |
|---|---|
| | • Immunological outcomes: Geometric mean-fold rise, and proportion who develop ≥2 or ≥4-fold rises in serum titres of anti-CT IgA, anti-CT IgG, and vibriocidal antibody from baseline after one or two doses |
| Notes | Location:USA<br>Setting: Military personnel<br>Source of funding: None stated<br>* A further single arm study involving 74 participants is reported in this paper but excluded from this review |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Comment: Described as 'randomized', no further details given. |
| Allocation concealment (selection bias) | Unclear risk | Comment: None described. |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Unclear risk | Comment: None described. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: 6 participants did not receive the second dose as they were unavailable |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |

**Sanchez 1994 Peru**

***Study characteristics***

| | |
|---|---|
| Methods | Design: Randomized controlled trial (individual block randomization in groups of 10)<br>Duration: Enrolled January to March 1994, follow-up to June 1994<br>Surveillance: Passive surveillance through clinics within the military training centres where the study was conducted |
| Participants | Sample size: 1563 enrolled, 1426 received 2 doses of vaccine or placebo<br>Inclusion criteria: 17-65 years volunteers, available for three months |


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**Sanchez 1994 Peru** *(Continued)*

| | |
|---|---|
| | Exclusion criteria: Previous cholera vaccination |
| Interventions | Vaccine: Killed whole-cell vaccine plus recombinant cholera toxin subunit (WC-rBS; Dukoral®, SBL, Sweden)<br><br>Placebo: Heat -inactivated *E. coli* K12 strain<br><br>Vaccine and placebo were given with freshly prepared antacid solution. Two doses were given, 7 to 14 days apart. |
| Outcomes | *Included in the review:*<br><br>• Cases of confirmed cholera<br><br>*Not included in the review:*<br><br>• Cases of severe cholera (cholera with signs of dehydration) as the treatment group is not stated<br>• Cases subgrouped by blood group as the treatment group is not stated |
| Notes | Location: Lima, Peru<br><br>Setting: Military training centres<br><br>Source of funding: Not stated |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomization was done in blocks of 10 to ensure equal study groups"<br><br>Comment: Unclear description but probably done |
| Allocation concealment (selection bias) | Low risk | Quote: "Each bottle was identified with a unique code number; vaccine and placebo bottles were pre-coded" |
| Blinding (performance bias and detection bias) Efficacy outcomes | Low risk | Quote: "The placebo....in a concentration identical in turbidity and appearance to the vaccine preparation" Plus see above |
| Blinding (performance bias and detection bias) Safety outcomes | Unclear risk | Not applicable as safety data is not reported |
| Incomplete outcome data (attrition bias) Efficacy outcomes | High risk | Comment: Subjects lost to follow-up after the second dose were assumed to contribute half the period to the denominator analysis. Mentioned that losses to follow-up were similar in both groups.<br><br>Cases of cholera which occurred in participants between study doses were excluded from the primary analysis. |
| Incomplete outcome data (attrition bias) Safety outcomes | Unclear risk | Not applicable as safety data is not reported |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |


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### Sanchez 1995 Peru

| ***Study characteristics*** | |
|---|---|
| Methods | Design: Randomized controlled trial (individually randomized)<br><br>Trial dates and duration: February 1992, 4 weeks<br><br>Surveillance: Passive surveillance for diarrhoea was performed at the single military medical clinic, where all cases were evaluated. |
| Participants | Sample size: 346 enrolled and received first dose, 307 received two full doses<br><br>Inclusion criteria: Male Hispanics aged 17-23 years, informed consent<br><br>Exclusion criteria: Major illness at the time of vaccination, previous cholera vaccine |
| Interventions | Vaccine: Killed whole-cell vaccine plus recombinant cholera toxin subunit (WC-rBS; Dukoral®, SBL, Sweden)<br><br>Placebo: suspension of heat-inactivated *E. coli* K12 strain<br><br>Vaccines were given with a buffer solution. Two doses were given two weeks apart. |
| Outcomes | *Included in the review:*<br><br>• Cholera cases<br>• Adverse events within 24 hours of each dose (active surveillance was conducted for 3 days)<br><br>*Not included in the review:*<br><br>• Immunological outcomes: Geometric mean serum vibriocidal antibody titre pre and post vaccination, and proportion who develop ≥4 fold rises from baseline; anti-cholera toxin IgG titre pre and post vaccination, and proportion who develop ≥0.20 rises from baseline |
| Notes | Location: Ancon, Peru<br><br>Setting: Military training centre<br><br>Source of funding: US Army and Navy medical departments(?) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: 'randomly allocated'<br><br>Comment: Method of randomization not adequately described but probably done |
| Allocation concealment (selection bias) | Low risk | Quote: "Each bottle was identified with one of 2 letters; vaccine and placebo preparations were pre-coded" |
| Blinding (performance bias and detection bias) Efficacy outcomes | Low risk | Quote: 'suspension of heat-inactivated *E coli* K12 strain, with same appearance as vaccine'. |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | See above |


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**Sanchez 1995 Peru** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) Efficacy outcomes | Low risk | Comment: All participants remained in the study area and were included in the analysis. Identification of cases through passive surveillance, with clinical data collected from all participants with diarrhoea. |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: No loss to follow-up |
| Selective reporting (reporting bias) | High risk | Comment: The report states adverse event data were collected for three days after each dose but only symptoms within 24 hours are presented |
| Other bias | Low risk | No evidence of other bias |

**Simanjuntak 1993**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Trial design: Randomized controlled trial - initially randomized in pairs one to each treatment arm, later changed to individual randomization.<br><br>Trial dates and duration and dates: 1991 to 1992 |
| Participants | Number of participants: 303<br><br>Inclusion criteria: Children aged 24 to 59 months<br><br>Exclusion criteria: Chronic health problem, receiving antibiotic therapy, acute illness on the scheduled day of vaccination |
| Interventions | Vaccine: CVD 103-HgR live attenuated vaccine containing:<br><br>• 5 x $10^9$ CFU of a lyophilised genetically modified strain of *V. cholerae* O1<br><br>Placebo:<br><br>• 5 x $10^8$ CFU inactivated *E. coli* K12 (placebo)<br><br>Both were given with aspartame sweetener and a buffer. |
| Outcomes | *Included in the review:*<br><br>• Adverse events (active surveillance; daily visits by physicians to record complaints and conduct physical examination, up to day nine after vaccination<br><br>*Not included in the review:*<br><br>• Stools samples for vaccine virus on day 5<br>• Immunological outcomes: Serum vibriocidal antibody titres on days 0, 9 and 28 and proportion with a ≥4-fold rises from baseline. |
| Notes | Location: North Jakarta, Indonesia<br><br>Setting: Villages<br><br>Source of funding:Consultative group on vaccine development of the national vaccine programme, USA, National Institute of Allergy and Infectious Diseases, US Naval Medical Research and Command |
| ***Risk of bias*** | |


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**Simanjuntak 1993** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Comment: Described as randomized. Codes generated by the manufacturer. |
| Allocation concealment (selection bias) | Low risk | Quote: 'Coded preparations looked identical and were only identified by the codes ‘N’ or ‘O’' |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: 'The clinical follow-up as well as the administration of the vaccine was double-blind with neither the clinical staff, the patient or their parents knowing the identity of the preparation'. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: No losses during adverse event follow-up are noted. |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |

**Su-Arehawaratana 1992a**

| ***Study characteristics*** | |
|---|---|
| Methods | Trial design: Randomized controlled trial (individually randomized)<br>Trial dates and duration: February 1988 |
| Participants | Number of participants: 206 (in study 1),<br>Inclusion criteria: Thai soldiers aged 18 to 26, who volunteered for the study<br>Exclusion criteria: Previous parenteral inactivated whole cell vaccine |
| Interventions | Vaccine: CVD 103-HgR live attenuated vaccine containing:<br>• 5 x $10^8$ CFU of a lyophilised genetically modified strain of *V. cholerae* O1<br>Placebo: 5 x $10^8$ CFU inactivated *E. coli* K12 |
| Outcomes | *Included in the review:*<br>• Adverse events (examined every day for 7 days) although only diarrhoea is reported<br>*Not included in the review:*<br>• Immunological outcomes: Serum vibriocidal antibodies titres on days 0, 7 and 21, and the proportion who develop a ≥4-fold increase. |


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**Su-Arehawaratana 1992a** *(Continued)*

| | |
|---|---|
| Notes | Location: Thailand<br>Setting: Field study using volunteers<br>Sources of funding: National Institutes of Health, Swiss Serum and Vaccine Institute, US Agency for International Development |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Comment: Described as 'randomised', no further details |
| Allocation concealment (selection bias) | Unclear risk | Comment: None described |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Unclear risk | Comment: None described |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: No losses are reported |
| Selective reporting (reporting bias) | Low risk | No evidence of selective outcome reporting |
| Other bias | Low risk | No other bias identified |

**Su-Arehawaratana 1992b**

***Study characteristics***

| | |
|---|---|
| Methods | Trial design: Randomized controlled crossover trial.<br>Trial dates and duration: June 1991 |
| Participants | Number of participants: 120<br>Inclusion criteria: Volunteers and Thai soldiers aged 18 to 26<br>Exclusion criteria: None stated |
| Interventions | Vaccine: CVD 103-HgR live attenuated vaccine containing:<br>• 5 x $10^8$ CFU of a lyophilised genetically modified strain of *V. cholerae* O1<br>• 5 x $10^9$ CFU of a lyophilised genetically modified strain of *V. cholerae* O1 |


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**Su-Arehawaratana 1992b** *(Continued)*

| | |
|---|---|
| | Placebo: 5 x $10^8$ CFU inactivated *E. coli* K12<br><br>The trial had 6 arms with each arm crossing over to receive the alternative dose or placebo on day 7<br><br>All doses were given with buffer and aspartame sweetener |
| Outcomes | *Included in the review:*<br><br>• Adverse events (examined every day for 7 days after each dose) although only diarrhoea is reported<br><br>*Not included in the review:*<br><br>• Immunological outcomes: Serum vibriocidal antibodies titres on days 0, 7 and 21, and the proportion who develop a ≥4 fold increase. |
| Notes | Location: Thailand<br><br>Setting: Field study using volunteers<br><br>Sources of funding: National Institutes of Health, Swiss Serum and Vaccine Institute, US Agency for International Development |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Comment: Described as 'randomized', no further details |
| Allocation concealment (selection bias) | Unclear risk | Comment: None described |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Unclear risk | Comment: Described as 'double blind', no further details. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: No losses are reported |
| Selective reporting (reporting bias) | Low risk | No evidence of selective outcome reporting |
| Other bias | Low risk | No other bias identified |

**Suharyono 1992a**

***Study characteristics***

| | |
|---|---|
| Methods | Trial design: Randomized controlled trial (4 arms) |


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**Suharyono 1992a** *(Continued)*

| | |
|---|---|
| | Trial dates and duration: February to March 1990 |
| Participants | Number of participants: 274<br><br>Inclusion criteria: Children aged 5 to 9 years. Witten parental consent. Only one child per family was eligible to take part.<br><br>Exclusion criteria: Having a chronic health disorder; receiving antibiotic therapy; acute illness on the scheduled day of vaccination |
| Interventions | Vaccine: CVD 103-HgR live attenuated vaccine containing:<br><br>• 5 x $10^6$ CFU CVD 103HgR centrifuged<br>• 5 x $10^7$ CFU CVD 103HgR centrifuged<br>• 5 x $10^8$ CFU CVD 103HgR filtered<br><br>Placebo: 5 x $10^8$ CFU inactivated *E. coli* K12 strain |
| Outcomes | *Included in the review:*<br><br>• Adverse events (Active surveillance; daily visits by study staff for 9 days)<br><br>*Not included in the review:*<br><br>• Stools samples for vaccine virus on day 5<br>• Immunological outcomes: Serum vibriocidal antibodies on days 0, 9 and 28, and the proportion who develop a ≥4 fold increase. |
| Notes | Location: North Jakarta, Indonesia<br><br>Setting: Small rural village, vaccinated at village health office<br><br>Source of funding: Consultative group on vaccine development of the national vaccine programme, USA, National Institute of Allergy and Infectious Diseases, Naval Medical Research unit 2, Jakarta, United States Agency for International Development |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: 'Randomly allocated to one of the four letter-coded groups according to a computer-generated randomization sequence' |
| Allocation concealment (selection bias) | Low risk | Quote: 'Vaccine and placebo packets indistinguishable and identified only by a colour-coded letter'. |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: 'The clinical follow-up as well as the administration of the vaccine was double-blind with neither the clinical staff, the patient or their parents knowing the identity of the preparation'. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) | Low risk | Comment: No losses reported. |


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**Suharyono 1992a** *(Continued)*
Safety outcomes

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |

**Suharyono 1992b**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Trial design: Randomized controlled trial (individually randomized)<br>Trial dates and duration: Sept to Oct 1990 |
| Participants | Number of participants: 140<br>Inclusion criteria: As for Suharyono 1992a<br>Exclusion criteria: As for Suharyono 1992a |
| Interventions | Vaccine: CVD 103-HgR live attenuated vaccine containing:<br>• 5 x $10^9$ CFU CVD 103HgR centrifuged<br>• 5 x $10^{10}$ CFU CVD 103HgR centrifuged<br>• 5 x $10^9$ CFU CVD 103HgR filtered<br>• 5 x $10^{10}$ CFU CVD 103HgR filtered<br>• Half of the children in each of these groups were randomized to also receive an extra half dose of buffer<br>Placebo: 5 x $10^8$ CFU inactivated *E. coli* K12 strain |
| Outcomes | As for Suharyono 1992a |
| Notes | Location: As for Suharyono 1992a<br>Setting:<br>Source of funding: As for Suharyono 1992a |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: 'the child was allocated to receive one of the nine treatment groups, according to a randomised sequence'<br>Comment: Study A in the same paper used a computer to generate the sequence. |
| Allocation concealment (selection bias) | Low risk | Comment: Only clearly described for study A but probably done. |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |


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**Suharyono 1992b** *(Continued)*

| | | |
|---|---|---|
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: 'The clinical follow-up as well as the administration of the vaccine was double-blind with neither the clinical staff, the patient or their parents knowing the identity of the preparation'. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: No losses to follow up are reported |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |

**Sur 2009 India**

| ***Study characteristics*** | |
|---|---|
| Methods | Design: Randomized controlled trial (cluster randomization)<br><br>Dates and duration: Vaccination July to September 2006; An interim analysis after 2 years of follow-up<br><br>Surveillance: Passive surveillance through nine diarrhoea clinics established in the study area, two hospitals serving the study area, and encouragement to private medical practitioners to refer to the treatment centres.<br><br>Method of adjustment for clustering: Robust sandwich variance estimates |
| Participants | Sample size: 3933 clusters (107,774 individuals) were randomized. 69,328 individuals received at least one dose of vaccine or placebo. The primary analysis includes 66,900 participants who received 2 doses of the vaccine.<br><br>Inclusion criteria: Age > 1 year, written informed consent<br><br>Exclusion criteria: Pregnancy |
| Interventions | Vaccine: Bivalent killed whole-cell vaccine (BivWC: Shanchol®, Shantha Biotechnics)<br><br>Placebo: Heat killed *E. coli* K12 strain<br><br>All subjects were randomized to receive 2 doses, at a minimum interval of 14 days. All doses were administered via an oral syringe. |
| Outcomes | *Included in review:*<br><br>• First symptomatic cholera episode detected using a passive surveillance system with confirmation of faecal excretion of *V. Cholerae* 01 during a non-bloody diarrhoeal episode.<br>• All-cause death<br>• Serious adverse events within 14 days of vaccination<br>• Adverse events within 14 days of each dose.<br><br>*Not included in the review:* |
| Notes | Location: Kolkata, India |


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**Sur 2009 India** *(Continued)*

| | |
|---|---|
| | Setting: Surveillance study area, served by 9 study clinics, private practitioners and 2 hospitals.<br><br>Source of funding: Bill and Melinda Gates Foundation; Swedish International Development Cooperation Agency; governments of South Korea, Sweden and Kuwait |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: 'An external statistician, who was masked to the identities of the codes, used an SAS version 9.1 computer algorithm to randomly assign dwellings to the four codes in a 1:1:1:1 ratio within each of the strata'. |
| Allocation concealment (selection bias) | Low risk | Quote: 'The vials were labelled with one of four letters, two each for vaccine and placebo. Project staff and study participants were unaware of the identities of the codes'. |
| Blinding (performance bias and detection bias) Efficacy outcomes | Low risk | Quote: 'The vaccine and placebo were identical in appearance' |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | See above |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Low risk | Comment: Attrition between the first and second doses of vaccine were low: 3.6% vaccine group vs 3.4% placebo group. |
| Incomplete outcome data (attrition bias) Safety outcomes | High risk | Comment: Safety data was collected passively with participants requested to present to medical services. Consequently the incidence of adverse event reporting is very low and likely to be an underestimate. |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |

**Tacket 1999**

***Study characteristics***

| | |
|---|---|
| Methods | Design: Randomized controlled trial (individually randomized) with challenge study<br><br>Trial dates and duration: Dates not stated; challenge study was undertaken 3 months after vaccination |
| Participants | Sample size: 85 (51 included in challenge study)<br><br>Inclusion criteria: Age 18 to 40, healthy, informed consent.<br><br>Exclusion criteria: clinically significant abnormalities on urinalysis, complete blood count, serum hepatic transaminases, glucose, creatinine, blood urea nitrogen, electrolytes, or electrocardiogram, travel to a cholera endemic area in the previous 5 years, abnormal stool pattern or regular use of laxatives, failure to pass a psychological examination, allergy to tetracycline or ciprofloxacin, history of cholera or enterotoxigenic E. coli challenge, history of recent antibiotic use, pregnancy or nursing, positive serology for HIV, hepatitis B antigen, or hepatitis B, stool culture positive for an enteric pathogen |


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**Tacket 1999** *(Continued)*

| | |
|---|---|
| Interventions | Vaccine: CVD 103-HgR live attenuated vaccine containing:<br>• 2 to 8 x $10^8$ CFU of lyophilized organisms of a genetically modified strain of *V. cholerae* O1 plus buffer<br>Placebo: heat-inactivated *E. coli* K12 plus buffer<br>Challenge: $10^5$ organisms of *V. cholerae* O1 El Tor Inaba (N16961) |
| Outcomes | *Included in review:*<br>• Adverse events following vaccine (symptom diary for 3 days)<br>• Any diarrhoea following artificial challenge<br>• Moderate or severe cholera diarrhoea following artificial challenge<br>*Not included in the review:*<br>• Immunological outcomes: Geometric mean serum vibriocidal antibody titre pre and post vaccination, and proportion who develop ≥4 fold rises from baseline; anti-cholera toxin IgG titre pre and post vaccination, and proportion who develop ≥0.20 rises from baseline |
| Notes | Location: Baltimore and Cincinatti, USA<br>Setting: Hospital<br>Source of funding: National Institute of Allergy and Infectious Diseases, and the Swiss Serum and Vaccine Institute |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: 'For those of blood group O and non-O within each clinical center, subjects were randomized in blocks of four (two to receive vaccine and two to receive placebo) by using SAS PROC PLAN'. |
| Allocation concealment (selection bias) | Low risk | Quote: 'The code was held by the study sponsor until the database was complete and unalterable'. |
| Blinding (performance bias and detection bias) Efficacy outcomes | Low risk | Quote: 'When suspended in the buffer solution, the placebo was identical in appearance to the vaccine suspension'. |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: 'When suspended in the buffer solution, the placebo was identical in appearance to the vaccine suspension'. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | High risk | Comment: The artificial challenge study included only 60% of those given the vaccine. |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: No participants were lost to follow-up or excluded during the initial 3 days. |
| Selective reporting (reporting bias) | Low risk | No evidence of selective outcome reporting |
| Other bias | Low risk | No other bias identified. |


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### Taylor 1999a

| ***Study characteristics*** | |
|---|---|
| Methods | Design: Randomized controlled trial (individually randomized)<br>Duration: Enrollment from Jan to Feb 1995; follow-up for 28 days |
| Participants | Sample size: 216 enrolled<br>Inclusion criteria: Age 2 to 64 years and residing in the study area, informed consent<br>Exclusion criteria: None stated. |
| Interventions | Vaccine: Killed whole-cell vaccine plus recombinant cholera toxin subunit (WC-rBS; Dukoral®, SBL, Sweden)<br>Placebo: Heat killed *E. coli* K12 strain<br>All participants were randomized to receive 2 doses, at a minimum interval of 14 days. All doses were administered via pumps designed to deliver the correct dose |
| Outcomes | *Included in review:*<br>• Adverse events within 3 days of each dose<br>*Not included in the review:*<br>• Immunological outcomes: Geometric mean serum vibriocidal antibody titre, proportion who develop ≥2 or ≥4-fold rises from baseline after one or two doses |
| Notes | Location: Flores de Villa, southern Lima<br>Setting:<br>Source of funding: The U.S. Army Medical Material and Development Command. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: 'Vaccination teams were assigned to a section of households using pre-randomized forms to enter adults and children in the study'. |
| Allocation concealment (selection bias) | Low risk | Quote: 'Each bottle was identified with a unique number; vaccine and placebo preparations were pre-coded'. |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: 'The participants and the persons who assessed side effects were blinded to the vaccine code'. 'The placebo consisted of a suspension of heat-inactivated E. coli K12 strain (SBL Vaccin AB) in a concentration that matched the turbidity and appearance of the vaccine preparation'. |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |


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**Taylor 1999a** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: 12 participants were lost to follow-up between doses. Reasons for drop-out were not given but follow-up in the 3 days after each dose was complete. |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of any other bias |

**Taylor 2000 Peru**

| ***Study characteristics*** | |
|---|---|
| Methods | Design: Randomized controlled trial (individually randomized)<br>Duration: 1993 to 1995<br>Surveillance: Active surveillance in the community through twice weekly visits to each household |
| Participants | Sample size: 21,924 received the first dose, 17,799 received the second dose, and 14,997 received the booster dose.<br>Inclusion criteria: Aged 2 to 65 years old and residing in the vaccine trial area.<br>Exclusion criteria: None stated. |
| Interventions | Vaccine: Killed whole-cell vaccine plus recombinant cholera toxin subunit (WC-rBS; Dukoral®, SBL, Sweden)<br>Placebo: Heat-inactivated *E. coli* K12 strain<br>Vaccine or placebo were given as two doses two weeks apart, followed by a third dose 10 months later. |
| Outcomes | *Included in the review:*<br>• Cases of cholera identified through active household surveillance. Rectal swabs were collected from participants with diarrhoea and cultured to test for *V. cholerae.*<br>• Cases of cholera identified through passive surveillance at the health post and hospital serving the area.<br>• Level of dehydration in participants with cholera; using WHO definitions of mild, moderate or severe.<br>• Adverse events after the first dose: Symptom enquiry at time of second dose<br>*Not included in the review:*<br>• Immunological outcomes: Plasma vibriocidal and anti-cholera toxin antibodies at day 14 after the second dose. |
| Notes | Location: Pampas de San Juan de Miraflores, in the southern outskirts of Lima, Peru.<br>Setting: 36 poor marginal neighbourhoods, with a nearby hospital, 4 health posts and 40 neighbourhood rehydration units.<br>Source of funding: US Army Medical Materiel and Development Command, Fort Detrick, Maryland |

| ***Risk of bias*** | | |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |


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**Taylor 2000 Peru** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "The trial area was divided into 4 quadrants (A to D), and every eligible person was randomly assigned a vaccine code of 1 or 9 to give a total of 8 possible codes"<br><br>Comment: Sequence generation unclear but probably low risk |
| Allocation concealment (selection bias) | Low risk | Quote:"During the study, the vaccine codes were kept locked by.. who was not involved in the study; the codes were not known to any person conducting the trial" |
| Blinding (performance bias and detection bias) Efficacy outcomes | Low risk | Quote: "Suspension of heat-inactivated *Escherichia coli* K12 strain in a concentration that matched the turbidity and appearance of the vaccine preparation." plus see above |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | See above |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Low risk | Comment: Attrition between the first and second doses was high: 18.8% overall. As well as the per protocol analysis, the authors conducted an intention to treat analysis which did not significantly alter the result |
| Incomplete outcome data (attrition bias) Safety outcomes | High risk | Comment: Adverse events from the first dose were recorded only for those attending for a second dose. This method is likely to underestimate the true incidence of adverse events if those experiencing a significant event after the first dose are more likely to drop-out. |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of other bias |

**Trach 1997 Viet Nam**

| ***Study characteristics*** | |
|---|---|
| Methods | Design: Quasi-randomized controlled trial (alternate allocation, clustered by household)<br><br>Duration: Vaccination started December 1992, follow-up to December 1993<br><br>Surveillance: Passive surveillance through community health centres, polyclinics and hospitals serving the study area<br><br>Method of adjustment for clustering: Logistic regression models with generalised estimating equations |
| Participants | Sample size: 134,453 individuals, 22,653 households<br><br>Inclusion criteria: Residents aged one year or older<br><br>Exclusion criteria: None |
| Interventions | Vaccine: Variant killed whole cell vaccine (vWC; National Institute of Hygiene and Epidemiology, Vietnam)<br><br>Control: No vaccine<br><br>Two doses were given with a two week interval between them. |


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**Trach 1997 Viet Nam** *(Continued)*

| | |
|---|---|
| Outcomes | *Included in the review:*<br>• Cases of cholera requiring inpatient care in hospital or polyclinic (faecal sample yields *V. cholerae* 01)<br>• Deaths from cholera<br>• Visits to community health centres, polyclinics and hospitals for treatment of diarrhoea |
| Notes | Location: Hue, central Vietnam<br>Setting: city community served by 19 health centres, four polyclinics and one regional hospital.<br>Sources of funding: Ministry of Health Vietnam, Swedish Agency for Research Cooperation, World Health Organization, USA National Institute of Child Health and Human Development |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: 'Each household.. was given a serial number. Even-numbered households were assigned the vaccine, and odd numbered households were assigned no vaccine'.<br>Comment: Alternate allocation is unlikely to significantly bias a vaccine trial |
| Allocation concealment (selection bias) | Low risk | Comment: Alternate allocation, concealment not possible, but unlikely to introduce significant bias. |
| Blinding (performance bias and detection bias) Efficacy outcomes | High risk | Quote: 'open field trial' |
| Blinding (performance bias and detection bias) Safety outcomes | Unclear risk | Not applicable - not included as an outcome |
| Incomplete outcome data (attrition bias) Efficacy outcomes | High risk | Comment: No mention of the participants who may have moved out of the area and therefore been lost to follow up. Cases identified through passive surveillance at the polyclinics and hospitals. |
| Incomplete outcome data (attrition bias) Safety outcomes | Unclear risk | Not applicable as safety data not reported |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of any other bias |

**Trach 2002**

***Study characteristics***

| | |
|---|---|
| Methods | Design: A 3-arm randomized controlled trial (individually randomized)<br>Trial dates and duration: Dates not stated, follow-up 28 days |
| Participants | Sample size: 71 in adult study, 70 in child study (from included study arms) |


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**Trach 2002** *(Continued)*

| | |
|---|---|
| | Inclusion criteria: Adult study: Age 17 to 25 years, Hanoi residents. Child study: Age 1-12 years, attending an elementary school or day care centre in Hanoi<br><br>Exclusion criteria: Diarrhoea during the preceding week, chronic or recurrent abdominal pain or diarrhoea, pregnancy, steroids or other immunosuppressive medications, antibiotics, or known to have HIV or another immunosuppressive condition |
| Interventions | Vaccine 1: Killed whole-cell vaccine plus recombinant cholera toxin subunit (WC-rBS; Dukoral®, SBL, Sweden)<br><br>Vaccine 2: A bivalent vaccine containing: 5 x $10^{10}$ formalin-killed *V. cholerae* 01 Inaba, El Tor biotype cells (strain Phil 6973); 2.5 x $10^{10}$ heat-killed *V. cholerae* O1 Ogawa, classical biotype cells (strain Cairo 50); 2.5 x $10^{10}$ formalin-killed *V. cholerae* O1 Inaba, classical biotype cells (strain 569B); 2.5 x $10^{10}$ heat-killed *V. cholerae* O1 Inaba, classical biotype cells (strain Cairo 48);and 5 x $10^{10}$ formalin-killed *V. cholerae* O139 (strainAI4456): This arm was excluded as the included strains are different from both the vWC vaccine and the BivWC vaccines with efficacy data<br><br>Placebo: heat-killed *E. coli* K12 strain |
| Outcomes | *Included in review:*<br><br>• Adverse events (visited for three consecutive days to ask about AE plus an interview at day 14)<br>• Serious adverse events<br><br>*Not included in the review:*<br><br>• Immunological outcomes: Geometric mean vibriocidal antibody titres pre and post vaccination, and proportion who develop a ≥ 4 fold increase. |
| Notes | Location: Hanoi, Vietnam<br><br>Setting:<br><br>Source of funding: Swedish Agency for Cooperation with Developing Countries; the National Institute of Child Health and Human Development, National Institutes ofHealth, USA; the World Health Organization; and the Diseases of the Most Impoverished Programme, funded by the Bill and Melinda Gates Foundation. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: 'Consenting eligible subjects in blocks of eight were randomly allocated'<br><br>Comment: Description is unclear but probably done |
| Allocation concealment (selection bias) | Low risk | Quote: 'The vials with the agent for each group were labelled with one of two code letters'. 'The codes were kept secret from all persons involved in the study until freezing of the data set.' |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy outcomes are not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Quote: 'The two vaccines and the placebo were packaged as liquid formulations in identical vials'. |
| Incomplete outcome data (attrition bias) | Unclear risk | Not applicable as efficacy outcomes are not reported |


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**Trach 2002** *(Continued)*
Efficacy outcomes

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias)<br>Safety outcomes | Low risk | Comment: Only three participants were lost to follow-up between doses, although the reasons are not stated. |
| Selective reporting (reporting bias) | High risk | Comment: Nausea was not assessed in the children's study |
| Other bias | Low risk | No other source of bias identified |

**Valera 2009**

| ***Study characteristics*** | |
|---|---|
| Methods | Design: Randomized controlled trial (individually randomized)<br>Duration and dates (field work): |
| Participants | Sample size: 36<br>Inclusion criteria: Age 18 to 40 years, volunteers working in the scientific community, healthy, informed consent.<br>Exclusion criteria: Previous history of clinically significant diarrhoea or cholera vaccination, receiving medication at the time of recruitment. |
| Interventions | Vaccine: VC638 - A live attenuated strain of *V. cholerae* O1 El Tor Ogawa (Final Institute, Havana)<br>• 1 x $10^9$ CFU plus buffer<br>Placebo: Buffer alone<br>All participants received 300mg of doxycycline on day 5. |
| Outcomes | *Included in review:*<br>• Adverse events (active surveillance for 5 days, then passive up to day 30)<br>*Not included in the review:*<br>• Immunological outcomes: Geometric mean serum vibriocidal antibody titres on day 0 and 14, and proportion who develop ≥4-fold rises from baseline after one dose |
| Notes | Location: Havana, Cuba<br>Setting: Unit for Isolation of Biological Risks at Tropical Medicine Institute<br>Source of funding: None stated |

| ***Risk of bias*** | | |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | Comment: Described as 'randomized', no further details given. |


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**Valera 2009** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | Quote: 'Vaccine and placebo vials were packaged and coded at random with identical appearance. The code remained unbroken until the end of the study' |
| Blinding (performance bias and detection bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Blinding (performance bias and detection bias) Safety outcomes | Low risk | Comment: See above |
| Incomplete outcome data (attrition bias) Efficacy outcomes | Unclear risk | Not applicable as efficacy not reported |
| Incomplete outcome data (attrition bias) Safety outcomes | Low risk | Comment: No losses during the adverse event monitoring stage |
| Selective reporting (reporting bias) | Low risk | No evidence of selective reporting |
| Other bias | Low risk | No evidence of any other bias |

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

| Study | Reason for exclusion |
|---|---|
| Ahmed 2006 | Non-cholera vaccine, no cholera outcomes (abstract) |
| Ahren 1993 | Non-comparative study. |
| Albert 2003 | A non-comparative study, all children received the same vaccine (abstract) |
| Ali 2005 | Relates to Clemens 1988 Bangladesh. No additional data relevant to this review. |
| Ali 2008 | Relates to Clemens 1988 Bangladesh. No additional data relevant to this review. |
| Anonymous 1968 | Injectable vaccine |
| Anonymous 1973a | Injectable vaccine |
| Anonymous 1973b | Injectable vaccine |
| Azurin 1967 | Injectable cholera vaccine |
| Azurin 1971 | Injectable cholera vaccine |
| Benenson 1968a | Injectable cholera vaccine |
| Benenson 1968b | Injectable cholera vaccine |
| Bergquist 1997 | Intranasal vaccination (abstract) |


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| Study | Reason for exclusion |
|---|---|
| Black 1986 | Non-randomized study |
| Black 1987 | Non-randomized study |
| Burgasov 1976 | Injectable cholera vaccine |
| Bwanga 1984 | Not randomized |
| Cash 1974 | Non-randomized study |
| Cavailler 2006 | Non-randomized study |
| Chaicumpa 1998 | Non-randomized, immunological outcomes only |
| Chongsa-nguan 1988 | Safety data presented but no trials assess the efficacy of this type of vaccine (lipopolysaccharide) |
| Chongsa-nguan 1991 | Compared two new vaccine candidates for which efficacy data is not currently available |
| Ciznar 1989 | Not a human study (abstract) |
| Clemens 1986 | Immunological outcomes only |
| Clemens 1988 | Relates to Clemens 1988 Bangladesh. No additional data relevant to this review. |
| Clemens 1989a | Relates to Clemens 1988 Bangladesh. No additional data relevant to this review. |
| Clemens 1989b | Relates to Clemens 1988 Bangladesh. No additional data relevant to this review. |
| Clemens 1990 | Relates to Clemens 1988 Bangladesh. No additional data relevant to this review. |
| Clemens 1991 | Relates to Clemens 1988 Bangladesh. No additional data relevant to this review. |
| Clemens 1992a | Refers to Clemens 1988, no new data relevant to this review |
| Clemens 1992b | Relates to Clemens 1988 Bangladesh. No additional data relevant to this review. |
| Clemens 1995 | Relates to Clemens 1988 Bangladesh. No additional data relevant to this review. |
| Cohen 1999 | No vaccine was given (abstract) |
| Cohen 2000 | Non-cholera vaccine, no cholera outcomes |
| Cooper 2000 | Non-comparative study, all participants received the same vaccine |
| Cooper 2001 | Non-comparative study, all participants received the same vaccine |
| Coster 1995 | The paper contains two very small studies. Study 1 is excluded as it has no placebo group. Study 2 is excluded as it was not randomized. |
| Cryz 1992 | No control group. |
| Cryz 1995 | No efficacy data for this vaccine (CVD 103-HgR-Ty21a) |
| Das 1967 | Injectable cholera vaccine |


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| Study | Reason for exclusion |
|---|---|
| Dearlove 1992 | Non-cholera vaccine (abstract) |
| Durham 1998 | Relates to Clemens 1988 Bangladesh. No additional data relevant to this review. |
| Emch 2006 | Relates to Clemens 1988 Bangladesh. No additional data relevant to this review. |
| Emch 2007 | Relates to Clemens 1988 Bangladesh. No additional data relevant to this review. |
| Emch 2009 | Relates to Clemens 1988 Bangladesh. No additional data relevant to this review. |
| Forrest 1991 | A new vaccine candidate for which efficacy data is not currently available |
| Ganguly 1975 | Immunological outcomes only |
| Gateff 1975 | Injectable cholera vaccine |
| Glass 1989 | Immunological outcomes only |
| Glenn 2007 | Non-cholera vaccine, no cholera outcomes (abstract) |
| Graves 2000 | A Cochrane Review (abstract) |
| Gray 1989 | Not relevant (abstract) |
| Gupta 1998 | Injectable cholera vaccine |
| Hall 2001 | Non-cholera vaccine, no cholera outcomes (abstract) |
| Holmgren 1989 | Relates to Clemens 1988 Bangladesh. No additional data relevant to this review. |
| Holmgren 1992 | Relates to Clemens 1988 Bangladesh. No additional data relevant to this review. |
| Hotomi 1998 | Intranasal vaccination (abstract) |
| Islam 2008 | Not an RCT; a willingness to pay study |
| Jertborn 1984 | Not randomized |
| Jertborn 1986 | Retrospective, non-comparative study. |
| Jertborn 1988 | Retrospective study. |
| Jertborn 1992 | This small study (41 participants) compared the safety and immunogenicity of the WC-BS and WC-rBS vaccines. As there was no placebo group we could not include the data. |
| Jertborn 1993 | Immunogenicity data only |
| Jertborn 1994 | Not randomized |
| Jertborn 1996 | Non-randomised study. |
| Jertborn 1998 | Non-cholera vaccine, no cholera outcomes |
| Jertborn 2001 | Not cholera vaccine |


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| Study | Reason for exclusion |
|---|---|
| Johansson 2001 | Nasal and intravaginal vaccination (abstract) |
| Johansson 2004 | Nasal and intravaginal vaccination (abstract) |
| Jones 2004 | A summary of included studies |
| Karlsen 2003 | All participants received the same vaccine (abstract) |
| Kenner 1995 | Not randomized |
| Kilhamn 1998 | All participants received the same vaccine (abstract) |
| Kim 2008 | A willingness to pay study (abstract) |
| Kirk 2005 | A case-control study (abstract) |
| Koenig 1998 | Non-cholera vaccine, no cholera outcomes (abstract) |
| Kollaritsch 1996 | No efficacy data for this vaccine (CVD 103-HgR-Ty21a) |
| Kollaritsch 1997 | All participants received the same vaccine (abstract) |
| Kozlowski 1999 | Not a relevant comparison. Randomized to oral, intranasal and vaginal vaccination. (abstract) |
| Langevin-Perriat 1988 | Immunological data only |
| Lastre 2002 | Immunological outcomes only |
| Lelikov 1974 | Injectable cholera vaccine |
| Levine 1984 | Not randomized |
| Levine 1988a | Not randomized |
| Levine 1988b | Not randomized |
| Lewis 1993 | Not randomized (on abstract) |
| Leyten 2005 | No relevant outcomes |
| Lopez 2008 | Not an RCT. A review (abstract) |
| Losonsky 1993 | Not randomized |
| Losonsky 1996 | Not randomized |
| Lucas 2005 | A case-control study |
| Lucas 2007 | A willingness to pay study (abstract) |
| Mahalanabis 2009 | No efficacy data for this vaccine (VA1.3) |
| Martell 2009 | Non-cholera vaccine, no cholera outcomes |


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| Study | Reason for exclusion |
|---|---|
| María Garcia 2005 | This paper describes multiple small comparative studies (9 volunteers in each treatment arm) with different modifications and dosing of potential vaccine strains including VC638. We were unable to incorporate any of this data. |
| McCormack 1969 | Injectable vaccine |
| Migasena 1988 | Non-randomized study |
| Migasena 1989b | Contains only safety and immunogenicity data. Excluded as no group received placebo. |
| Migasena 1989c | No efficacy study available for these vaccines |
| Mitra 1990 | No cholera vaccine was given. (Abstract) |
| Mosley 1968 | Injectable vaccine |
| Mosley 1969a | Injectable vaccine |
| Mosley 1969b | Injectable vaccine |
| Mosley 1970 | Injectable vaccine |
| Mosley 1972 | Injectable vaccine |
| Mosley 1973 | Injectable vaccine |
| Nimbkar 1975 | Immunological outcomes only |
| Olsson 2006 | Not an RCT (abstract) |
| Oseasohn 1965 | Injectable vaccine |
| Paineau 2008 | No vaccine given (abstract) |
| Pal 1980 | Injectable vaccine |
| Peltola 1977 | Intracutaneous vaccine (abstract) |
| Peltola 1989 | Trial assesses oral cholera vaccine for preventing travellers diarrhoea, not cholera. |
| Peltola 1991 | No cholera outcomes relevant to this review |
| Philippines 1965 | Injectable cholera vaccine |
| Pitisuttithum 2001 | No cholera vaccine was given. A study to validate an artificial cholera challenge model |
| Qadri 2003 | Not cholera vaccine |
| Qadri 2004 | All participants received the same vaccine |
| Qadri 2006 | Non-cholera vaccine, no cholera outcomes (abstract) |
| Quiding-Jarbrink 2001 | All participants received the same vaccine |
| Rao 2002 | Not an RCT (Abstract) |


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| Study | Reason for exclusion |
|---|---|
| Rudin 1998 | Not an appropriate comparison group; oral versus nasal vaccination (abstract) |
| Rudin 1999 | Not an appropriate comparison group; oral versus nasal vaccination (abstract) |
| Sack 1991 | Relates to Clemens 1988 Bangladesh. No additional data relevant to this review. |
| Sack 2007 | Refers to Clemens 1988, no new data relevant to this review |
| Sanchez 1993b | Data on adverse effects not presented in usable form. |
| Sanchez 1994 | A preliminary report from Taylor 2000 Peru. Contains no additional data. |
| Saroso 1978 | Injectable cholera vaccine |
| Savarino 1998 | Non-cholera vaccine, no cholera outcomes |
| Savarino 1999 | Non-cholera vaccine, no cholera outcomes |
| Savarino 2002 | Non-cholera vaccine, no cholera outcomes |
| Sommer 1973 | Randomized controlled study, but vaccine given after exposure to cholera in family members |
| SonLa 2007 | Non-comparative study |
| Stellfeld 2004 | A review article. Not an RCT |
| Sumarokov 1974 | Injectable vaccine (abstract) |
| Sumarokov 1978 | No clinical efficacy data is available for this vaccine. Oral tablet containing choleragen toxoid, Ogawa and Inaba O-antigens and *Vibrio cholerae* exoenzymes. |
| Sumarokov 1990 | No clinical efficacy data is available for this vaccine. Oral tablet containing choleragen toxoid, Ogawa and Inaba O-antigens and *Vibrio cholerae* exoenzymes. |
| Sumarokov 1991 | No clinical efficacy data is available for this vaccine. Oral tablet containing choleragen toxoid, Ogawa and Inaba O-antigens and *Vibrio cholerae* exoenzymes. |
| Sumarokov 1993 | No clinical efficacy data is available for this vaccine. Oral tablet containing choleragen toxoid, Ogawa and Inaba O-antigens and *Vibrio cholerae* exoenzymes. |
| Suntharasamai 1992 | No vaccine given |
| Svennerholm 1981 | No cholera vaccine given (abstract) |
| Svennerholm 1984 | No efficacy data for this vaccine (B subunit alone) |
| Tacket 1992 | Not randomized |
| Tacket 1995a | No vaccine given |
| Tacket 1995b | No efficacy data for this vaccine (CVD 112) |
| Tacket 1998 | No efficacy data for this vaccine (CVD 112) |
| Taylor 1994 | No efficacy data for these vaccines (Peru 14, Peru 5, Peru 3) |


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| Study | Reason for exclusion |
|---|---|
| Taylor 1997 | No efficacy data for this vaccine (CVD 103-HgR/CVD112) |
| Taylor 1999b | No efficacy data for this vaccine (CVD 103-HgR/CVD112) |
| Thiem 2006 | Case control study |
| Von Seidlein 2007 | A study of a fingerprint recognition system used during a cholera vaccine trial. Contains no relevant outcomes. |
| Wassen 2005 | Vaginal vaccination (abstract) |
| Wassen 2006 | Vaginal vaccination (abstract) |
| Wasserman 1993 | Immunogenicity data only |
| Wassén 1996 | Intravaginal vaccination (abstract) |
| Wiedermann 2000 | Non cholera vaccine, no cholera outcomes |

## DATA AND ANALYSES

### Comparison 1. Whole cell vaccines (all types) versus placebo - Primary efficacy outcomes

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.1 Cases of cholera - 1st year of follow up (with meta analysis) | 4 | 249935 | Risk Ratio (M-H, Random, 95% CI) | 0.48 [0.35, 0.65] |
| 1.1.1 Whole cell vaccine (WC); 3 doses, 6 weeks apart | 1 | 31162 | Risk Ratio (M-H, Random, 95% CI) | 0.47 [0.33, 0.69] |
| 1.1.2 Whole cell plus B subunit vaccine (WC-BS); 3 doses, 6 weeks apart | 1 | 31124 | Risk Ratio (M-H, Random, 95% CI) | 0.38 [0.25, 0.56] |
| 1.1.3 Whole cell plus recombinant B subunit vaccine (WC-rBS); 2 doses, 2 weeks apart | 1 | 17799 | Risk Ratio (M-H, Random, 95% CI) | 1.04 [0.52, 2.05] |
| 1.1.4 Variant whole cell vaccine (vWC); 2 doses, 2 weeks apart | 1 | 111928 | Risk Ratio (M-H, Random, 95% CI) | 0.36 [0.23, 0.56] |
| 1.1.5 Bivalent whole cell vaccine (BivWC); 2 doses, 2 weeks apart | 1 | 57922 | Risk Ratio (M-H, Random, 95% CI) | 0.55 [0.26, 1.17] |
| 1.2 Cases of cholera - 2nd year of follow up (with meta analysis) | 3 | 130334 | Risk Ratio (M-H, Random, 95% CI) | 0.39 [0.30, 0.50] |
| 1.2.1 Whole cell vaccine (WC); 3 doses, 6 weeks apart | 1 | 30011 | Risk Ratio (M-H, Random, 95% CI) | 0.43 [0.28, 0.65] |


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| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.2.2 Whole cell plus B subunit vaccine (WC-BS); 3 doses, 6 weeks apart | 1 | 30008 | Risk Ratio (M-H, Random, 95% CI) | 0.42 [0.28, 0.63] |
| 1.2.3 Whole cell plus recombinant B subunit vaccine (WC-rBS); 2 doses, 2 weeks apart plus booster at 10 months | 1 | 14997 | Risk Ratio (M-H, Random, 95% CI) | 0.40 [0.21, 0.75] |
| 1.2.4 Variant whole cell vaccine (vWC); 2 doses, 2 weeks apart | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 1.2.5 Bivalent whole cell vaccine (BivWC); 2 doses, 2 weeks apart | 1 | 55318 | Risk Ratio (M-H, Random, 95% CI) | 0.22 [0.11, 0.48] |
| 1.3 Cases of cholera - 3rd year of follow up (with meta analysis) | 1 | 58174 | Risk Ratio (M-H, Random, 95% CI) | 0.70 [0.50, 0.98] |
| 1.3.1 Whole cell vaccine (WC); 3 doses, 6 weeks apart | 1 | 29114 | Risk Ratio (M-H, Random, 95% CI) | 0.59 [0.36, 0.97] |
| 1.3.2 Whole cell plus B subunit vaccine (WC-BS); 3 doses, 6 weeks apart | 1 | 29060 | Risk Ratio (M-H, Random, 95% CI) | 0.81 [0.51, 1.29] |
| 1.3.3 Whole cell plus recombinant B subunit vaccine (WC-rBS); 2 doses, 2 weeks apart plus booster at 10 months | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 1.3.4 Variant whole cell vaccine (vWC); 2 doses, 2 weeks apart | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 1.3.5 Bivalent whole cell vaccine (BivWC); 2 doses, 2 weeks apart | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 1.4 Cases of cholera - 4th year of follow up (with meta analysis) | 1 | 56613 | Risk Ratio (M-H, Random, 95% CI) | 1.05 [0.60, 1.84] |
| 1.4.1 Whole cell vaccine (WC); 3 doses, 6 weeks apart | 1 | 28357 | Risk Ratio (M-H, Random, 95% CI) | 1.28 [0.59, 2.76] |
| 1.4.2 Whole cell plus B subunit vaccine (WC-BS); 3 doses, 6 weeks apart | 1 | 28256 | Risk Ratio (M-H, Random, 95% CI) | 0.84 [0.37, 1.91] |
| 1.4.3 Whole cell plus recombinant B subunit vaccine (WC-rBS); 2 doses, 2 weeks apart plus booster at 10 months | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 1.4.4 Variant whole cell vaccine (vWC); 2 doses, 2 weeks apart | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 1.4.5 Bivalent whole cell vaccine (BivWC); 2 doses, 2 weeks apart | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 1.5 Cases of cholera by age group - First two years of follow-up | 4 | 243071 | Risk Ratio (M-H, Random, 95% CI) | 0.43 [0.33, 0.56] |


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| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.5.1 Age < 5 years | 4 | 29005 | Risk Ratio (M-H, Random, 95% CI) | 0.62 [0.47, 0.80] |
| 1.5.2 Age > 5 years | 4 | 214066 | Risk Ratio (M-H, Random, 95% CI) | 0.34 [0.27, 0.43] |
| 1.6 Cases of cholera by age group - First two years of follow-up (sensitivity analysis) | 4 | 248140 | Risk Ratio (M-H, Random, 95% CI) | 0.43 [0.33, 0.56] |
| 1.6.1 Age < 5 years | 4 | 29773 | Risk Ratio (M-H, Random, 95% CI) | 0.62 [0.47, 0.80] |
| 1.6.2 Age > 5 years | 4 | 218367 | Risk Ratio (M-H, Random, 95% CI) | 0.34 [0.27, 0.43] |


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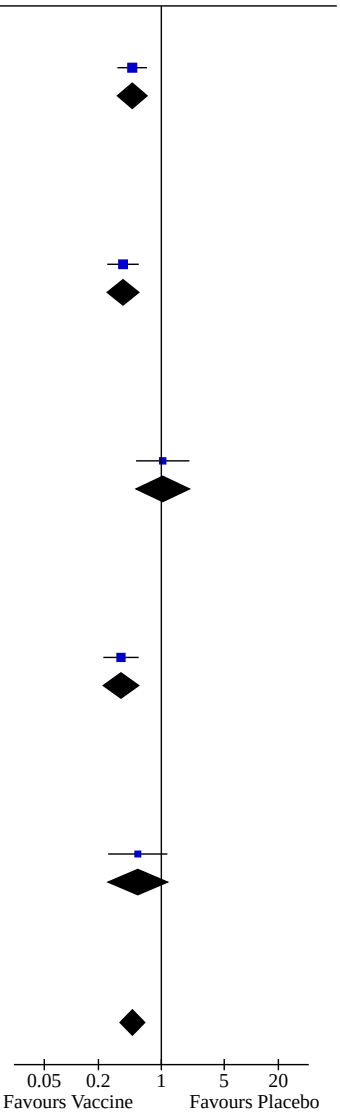
## Analysis 1.1. Comparison 1: Whole cell vaccines (all types) versus placebo - Primary efficacy outcomes, Outcome 1: Cases of cholera - 1st year of follow up (with meta analysis)

| Study or Subgroup | Vaccine Events | Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.1.1 Whole cell vaccine (WC); 3 doses, 6 weeks apart** | | | | | | |
| Clemens 1988 Bangladesh (1) | 52 | 20743 | 55 | 10419 | 26.2% | 0.47 [0.33 , 0.69] |
| **Subtotal (95% CI)** | | **20743** | | **10419** | **26.2%** | **0.47 [0.33 , 0.69]** |
| Total events: | 52 | | 55 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 3.86 (P = 0.0001) | | | | | | |
| **1.1.2 Whole cell plus B subunit vaccine (WC-BS); 3 doses, 6 weeks apart** | | | | | | |
| Clemens 1988 Bangladesh | 41 | 20705 | 55 | 10419 | 24.9% | 0.38 [0.25 , 0.56] |
| **Subtotal (95% CI)** | | **20705** | | **10419** | **24.9%** | **0.38 [0.25 , 0.56]** |
| Total events: | 41 | | 55 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 4.76 (P < 0.00001) | | | | | | |
| **1.1.3 Whole cell plus recombinant B subunit vaccine (WC-rBS); 2 doses, 2 weeks apart** | | | | | | |
| Taylor 2000 Peru | 17 | 9012 | 16 | 8787 | 14.1% | 1.04 [0.52 , 2.05] |
| **Subtotal (95% CI)** | | **9012** | | **8787** | **14.1%** | **1.04 [0.52 , 2.05]** |
| Total events: | 17 | | 16 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.10 (P = 0.92) | | | | | | |
| **1.1.4 Variant whole cell vaccine (vWC); 2 doses, 2 weeks apart** | | | | | | |
| Trach 1997 Viet Nam (2) | 24 | 48873 | 87 | 63055 | 22.6% | 0.36 [0.23 , 0.56] |
| **Subtotal (95% CI)** | | **48873** | | **63055** | **22.6%** | **0.36 [0.23 , 0.56]** |
| Total events: | 24 | | 87 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 4.48 (P < 0.00001) | | | | | | |
| **1.1.5 Bivalent whole cell vaccine (BivWC); 2 doses, 2 weeks apart** | | | | | | |
| Sur 2009 India (3) | 10 | 27647 | 20 | 30275 | 12.2% | 0.55 [0.26 , 1.17] |
| **Subtotal (95% CI)** | | **27647** | | **30275** | **12.2%** | **0.55 [0.26 , 1.17]** |
| Total events: | 10 | | 20 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.56 (P = 0.12) | | | | | | |
| **Total (95% CI)** | | **126980** | | **122955** | **100.0%** | **0.48 [0.35 , 0.65]** |
| Total events: | 144 | | 233 | | | |
| Heterogeneity: Tau² = 0.06; Chi² = 7.89, df = 4 (P = 0.10); I² = 49% | | | | | | |
| Test for overall effect: Z = 4.61 (P < 0.00001) | | | | | | |
| Test for subgroup differences: Chi² = 7.88, df = 4 (P = 0.10), I² = 49.3% | | | | | | |




**Footnotes**

(1) For the purpose of this meta analysis the events and participants in the Placebo arm of Clemens 1985 Bangladesh have been divided equally between the two

(2) Trach 1997- This result has been ajusted from the crude figures given in the original paper to give the effective sample size; using an estimate of the ICC of -(

(3) Sur 2009- This result has been ajusted from the crude figures given in the original paper to give the effective sample size; using an ICC of -0.0085 and a mear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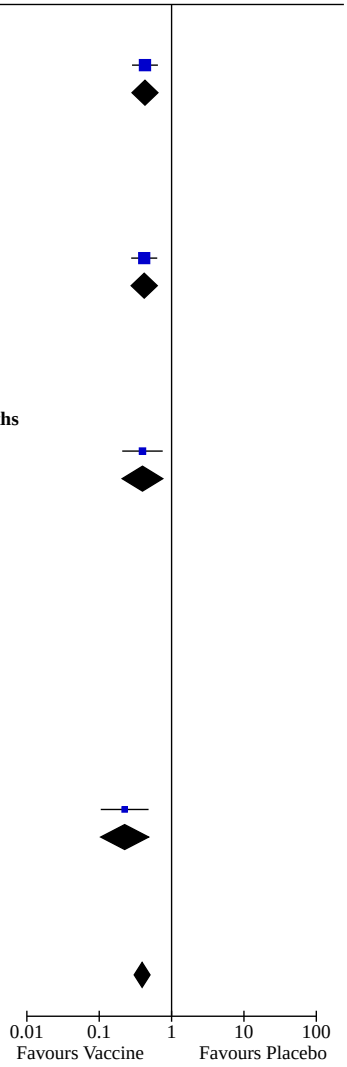
## Analysis 1.2. Comparison 1: Whole cell vaccines (all types) versus placebo - Primary efficacy outcomes, Outcome 2: Cases of cholera - 2nd year of follow up (with meta analysis)

| Study or Subgroup | Whole cell vaccine Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.2.1 Whole cell vaccine (WC); 3 doses, 6 weeks apart** | | | | | | |
| Clemens 1988 Bangladesh (1) | 42 | 20005 | 49 | 10006 | 37.2% | 0.43 [0.28 , 0.65] |
| **Subtotal (95% CI)** | | **20005** | | **10006** | **37.2%** | **0.43 [0.28 , 0.65]** |
| Total events: | 42 | | 49 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 4.03 (P < 0.0001) | | | | | | |
| **1.2.2 Whole cell plus B subunit vaccine (WC-BS); 3 doses, 6 weeks apart** | | | | | | |
| Clemens 1988 Bangladesh | 41 | 20002 | 49 | 10006 | 36.7% | 0.42 [0.28 , 0.63] |
| **Subtotal (95% CI)** | | **20002** | | **10006** | **36.7%** | **0.42 [0.28 , 0.63]** |
| Total events: | 41 | | 49 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 4.12 (P < 0.0001) | | | | | | |
| **1.2.3 Whole cell plus recombinant B subunit vaccine (WC-rBS); 2 doses, 2 weeks apart plus booster at 10 months** | | | | | | |
| Taylor 2000 Peru | 13 | 7594 | 32 | 7403 | 15.2% | 0.40 [0.21 , 0.75] |
| **Subtotal (95% CI)** | | **7594** | | **7403** | **15.2%** | **0.40 [0.21 , 0.75]** |
| Total events: | 13 | | 32 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.82 (P = 0.005) | | | | | | |
| **1.2.4 Variant whole cell vaccine (vWC); 2 doses, 2 weeks apart** | | | | | | |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **1.2.5 Bivalent whole cell vaccine (BivWC); 2 doses, 2 weeks apart** | | | | | | |
| Sur 2009 India (2) | 8 | 26403 | 39 | 28915 | 10.9% | 0.22 [0.11 , 0.48] |
| **Subtotal (95% CI)** | | **26403** | | **28915** | **10.9%** | **0.22 [0.11 , 0.48]** |
| Total events: | 8 | | 39 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 3.85 (P = 0.0001) | | | | | | |
| **Total (95% CI)** | | **74004** | | **56330** | **100.0%** | **0.39 [0.30 , 0.50]** |
| Total events: | 104 | | 169 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 2.37, df = 3 (P = 0.50); I² = 0% | | | | | | |
| Test for overall effect: Z = 7.33 (P < 0.00001) | | | | | | |
| Test for subgroup differences: Chi² = 2.34, df = 3 (P = 0.51), I² = 0% | | | | | | |




**Footnotes**

(1) For the purpose of this meta analysis the events and participants in the Placebo arm of Clemens 1985 Bangladesh have been divided equally between the two int

(2) Sur 2009- This result has been ajusted from the crude figures given in the original paper to give the effective sample size; using an ICC of -0.0085 and a mean cl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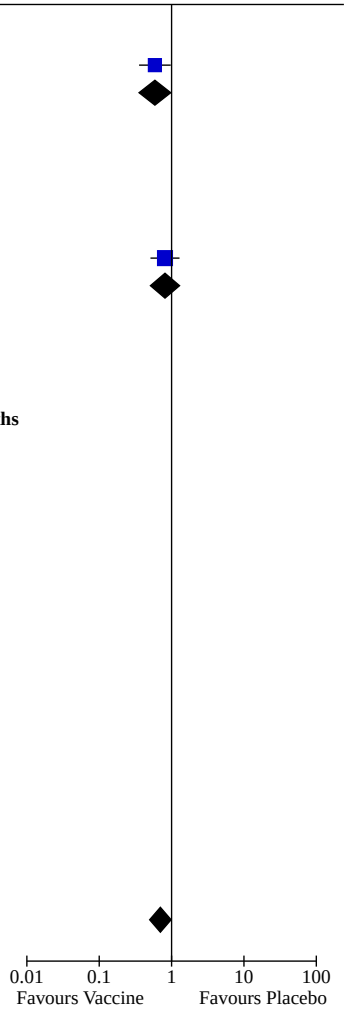
## Analysis 1.3. Comparison 1: Whole cell vaccines (all types) versus placebo - Primary efficacy outcomes, Outcome 3: Cases of cholera - 3rd year of follow up (with meta analysis)

| Study or Subgroup | Whole cell vaccine Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.3.1 Whole cell vaccine (WC); 3 doses, 6 weeks apart** | | | | | | |
| Clemens 1988 Bangladesh | 33 | 19424 | 28 | 9690 | 45.8% | 0.59 [0.36 , 0.97] |
| **Subtotal (95% CI)** | | **19424** | | **9690** | **45.8%** | **0.59 [0.36 , 0.97]** |
| Total events: | 33 | | 28 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.07 (P = 0.04) | | | | | | |
| **1.3.2 Whole cell plus B subunit vaccine (WC-BS); 3 doses, 6 weeks apart** | | | | | | |
| Clemens 1988 Bangladesh | 47 | 19370 | 29 | 9690 | 54.2% | 0.81 [0.51 , 1.29] |
| **Subtotal (95% CI)** | | **19370** | | **9690** | **54.2%** | **0.81 [0.51 , 1.29]** |
| Total events: | 47 | | 29 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.89 (P = 0.37) | | | | | | |
| **1.3.3 Whole cell plus recombinant B subunit vaccine (WC-rBS); 2 doses, 2 weeks apart plus booster at 10 months** | | | | | | |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **1.3.4 Variant whole cell vaccine (vWC); 2 doses, 2 weeks apart** | | | | | | |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **1.3.5 Bivalent whole cell vaccine (BivWC); 2 doses, 2 weeks apart** | | | | | | |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **Total (95% CI)** | | **38794** | | **19380** | **100.0%** | **0.70 [0.50 , 0.98]** |
| Total events: | 80 | | 57 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 1 (P = 0.36); I² = 0% | | | | | | |
| Test for overall effect: Z = 2.06 (P = 0.04) | | | | | | |
| Test for subgroup differences: Chi² = 0.85, df = 1 (P = 0.36), I² = 0% | | | | | | |





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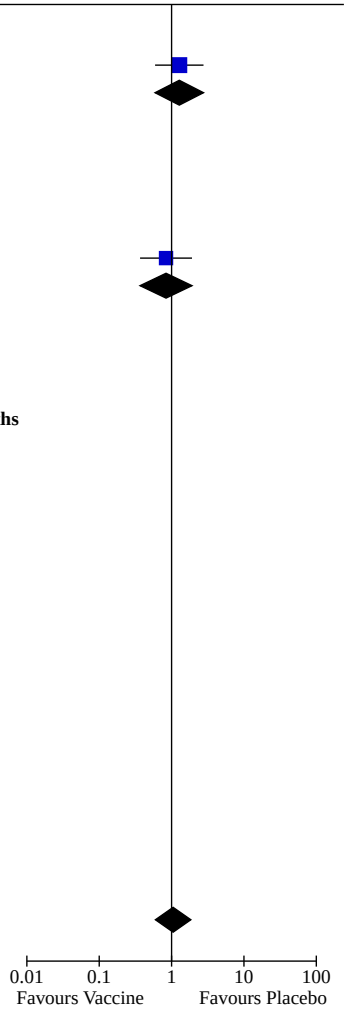
## Analysis 1.4. Comparison 1: Whole cell vaccines (all types) versus placebo - Primary efficacy outcomes, Outcome 4: Cases of cholera - 4th year of follow up (with meta analysis)

| Study or Subgroup | Whole cell vaccine Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.4.1 Whole cell vaccine (WC); 3 doses, 6 weeks apart** | | | | | | |
| Clemens 1988 Bangladesh | 23 | 18905 | 9 | 9452 | 53.5% | 1.28 [0.59 , 2.76] |
| **Subtotal (95% CI)** | | **18905** | | **9452** | **53.5%** | **1.28 [0.59 , 2.76]** |
| Total events: | 23 | | 9 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.62 (P = 0.53) | | | | | | |
| **1.4.2 Whole cell plus B subunit vaccine (WC-BS); 3 doses, 6 weeks apart** | | | | | | |
| Clemens 1988 Bangladesh | 15 | 18803 | 9 | 9453 | 46.5% | 0.84 [0.37 , 1.91] |
| **Subtotal (95% CI)** | | **18803** | | **9453** | **46.5%** | **0.84 [0.37 , 1.91]** |
| Total events: | 15 | | 9 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.42 (P = 0.67) | | | | | | |
| **1.4.3 Whole cell plus recombinant B subunit vaccine (WC-rBS); 2 doses, 2 weeks apart plus booster at 10 months** | | | | | | |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **1.4.4 Variant whole cell vaccine (vWC); 2 doses, 2 weeks apart** | | | | | | |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **1.4.5 Bivalent whole cell vaccine (BivWC); 2 doses, 2 weeks apart** | | | | | | |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **Total (95% CI)** | | **37708** | | **18905** | **100.0%** | **1.05 [0.60 , 1.84]** |
| Total events: | 38 | | 18 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 1 (P = 0.46); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.17 (P = 0.87) | | | | | | |
| Test for subgroup differences: Chi² = 0.54, df = 1 (P = 0.46), I² = 0% | | | | | | |





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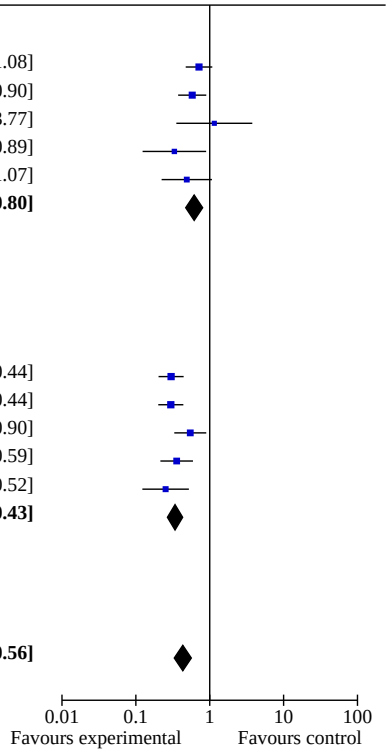
## Analysis 1.5. Comparison 1: Whole cell vaccines (all types) versus placebo - Primary efficacy outcomes, Outcome 5: Cases of cholera by age group - First two years of follow-up

| Study or Subgroup | Vaccine Events | Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.5.1 Age < 5 years** | | | | | | |
| Clemens 1988 Bangladesh (1) | 54 | 3745 | 37 | 1837 | 13.1% | 0.72 [0.47 , 1.08] |
| Clemens 1988 Bangladesh (2) | 42 | 3599 | 37 | 1837 | 12.6% | 0.58 [0.37 , 0.90] |
| Taylor 2000 Peru | 6 | 1040 | 5 | 1000 | 4.0% | 1.15 [0.35 , 3.77] |
| Trach 1997 Viet Nam (3) | 5 | 5549 | 18 | 6636 | 5.2% | 0.33 [0.12 , 0.89] |
| Sur 2009 India (4) | 9 | 1803 | 20 | 1959 | 7.2% | 0.49 [0.22 , 1.07] |
| **Subtotal (95% CI)** | | **15736** | | **13269** | **42.1%** | **0.62 [0.47 , 0.80]** |
| Total events: | 116 | | 117 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 3.50, df = 4 (P = 0.48); I² = 0% | | | | | | |
| Test for overall effect: Z = 3.60 (P = 0.0003) | | | | | | |
| **1.5.2 Age > 5 years** | | | | | | |
| Clemens 1988 Bangladesh (1) | 40 | 16260 | 67 | 8169 | 13.6% | 0.30 [0.20 , 0.44] |
| Clemens 1988 Bangladesh (2) | 40 | 16403 | 67 | 8169 | 13.6% | 0.30 [0.20 , 0.44] |
| Taylor 2000 Peru | 24 | 6554 | 43 | 6403 | 11.5% | 0.55 [0.33 , 0.90] |
| Trach 1997 Viet Nam (3) | 19 | 42656 | 69 | 55292 | 11.3% | 0.36 [0.21 , 0.59] |
| Sur 2009 India (4) | 9 | 25844 | 39 | 28316 | 7.9% | 0.25 [0.12 , 0.52] |
| **Subtotal (95% CI)** | | **107717** | | **106349** | **57.9%** | **0.34 [0.27 , 0.43]** |
| Total events: | 132 | | 285 | | | |
| Heterogeneity: Tau² = 0.01; Chi² = 4.97, df = 4 (P = 0.29); I² = 20% | | | | | | |
| Test for overall effect: Z = 8.95 (P < 0.00001) | | | | | | |
| **Total (95% CI)** | | **123453** | | **119618** | **100.0%** | **0.43 [0.33 , 0.56]** |
| Total events: | 248 | | 402 | | | |
| Heterogeneity: Tau² = 0.09; Chi² = 20.78, df = 9 (P = 0.01); I² = 57% | | | | | | |
| Test for overall effect: Z = 6.20 (P < 0.00001) | | | | | | |
| Test for subgroup differences: Chi² = 10.89, df = 1 (P = 0.0010), I² = 90.8% | | | | | | |




**Footnotes**

(1) WC vs Placebo: For the purpose of this meta analysis the events and participants in the Placebo arm of Clemens 1985 Bangladesh have been divided equally

(2) WC-BS vs Placebo: For the purpose of this meta analysis the events and participants in the Placebo arm of Clemens 1985 Bangladesh have been divided equa

(3) Trach 1997- This result has been ajusted from the crude figures given in the original paper to give the effective sample size; using an estimate of the ICC of -(

(4) Sur 2009- This result has been ajusted from the crude figures given in the original paper to give the effective sample size; using an ICC of -0.0085 and a mea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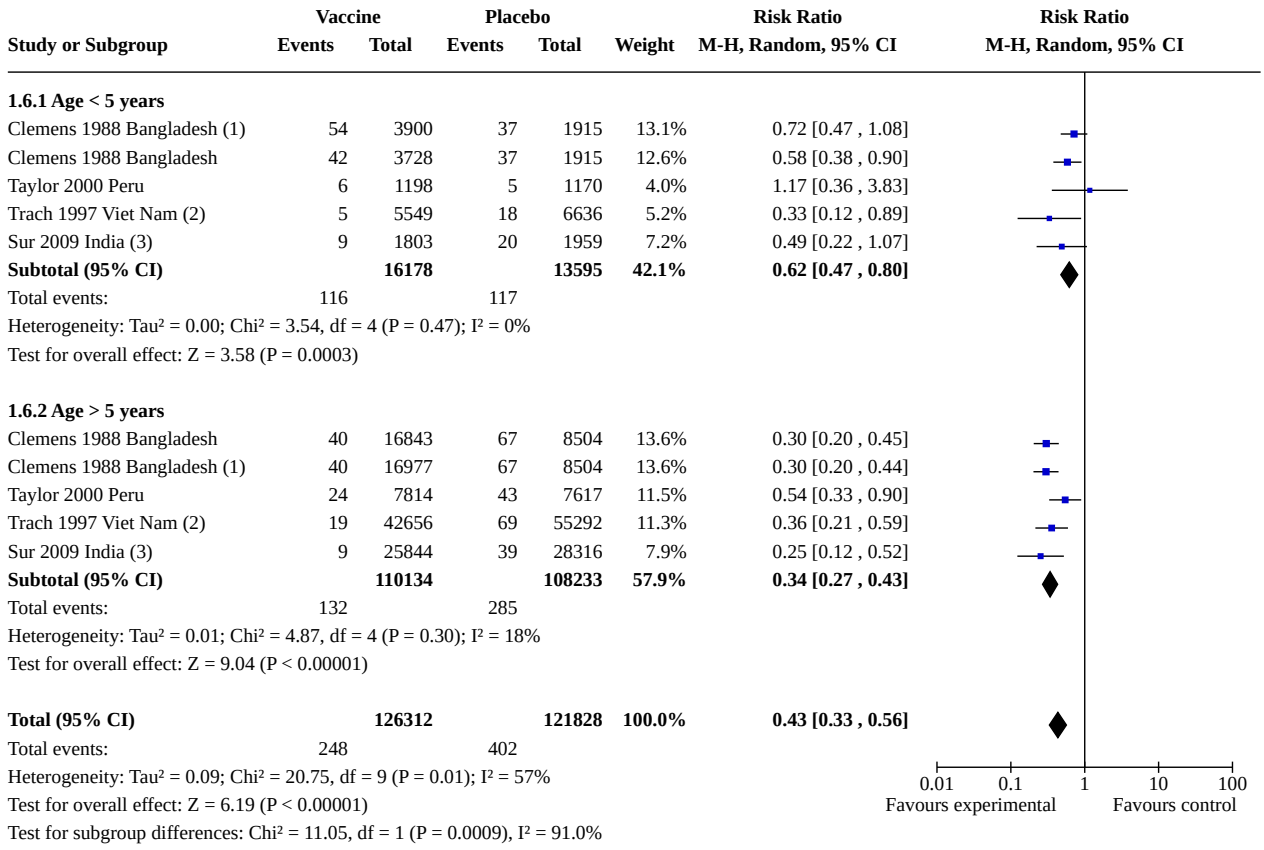
**Analysis 1.6. Comparison 1: Whole cell vaccines (all types) versus placebo - Primary efficacy outcomes, Outcome 6: Cases of cholera by age group - First two years of follow-up (sensitivity analysis)**




**Footnotes**

(1) For the purpose of this meta analysis the events and participants in the Placebo arm of Clemens 1985 Bangladesh have been divided equally between the two

(2) Trach 1997- This result has been ajusted from the crude figures given in the original paper to give the effective sample size; using an estimate of the ICC of -(

(3) Sur 2009- This result has been ajusted from the crude figures given in the original paper to give the effective sample size; using an ICC of -0.0085 and a mea

## Comparison 2. Whole cell vaccine (WC) versus placebo - Subgroup analysis

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.1 Cases of cholera by time of follow-up (3-dose recipients) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.1.1 First four months after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.1.2 First year after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.1.3 Second year after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.1.4 Third year after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |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| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.1.5 Fourth year after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.2 Cases of cholera by age-group - 1st year of follow-up (3-dose recipients) | 1 | 41580 | Risk Ratio (M-H, Random, 95% CI) | 0.48 [0.23, 0.98] |
| 2.2.1 Age 2 to 5 years | 1 | 7730 | Risk Ratio (M-H, Random, 95% CI) | 0.69 [0.43, 1.09] |
| 2.2.2 Age > 5 years | 1 | 33850 | Risk Ratio (M-H, Random, 95% CI) | 0.33 [0.20, 0.54] |
| 2.3 Cases of cholera by age-group - 2nd year of follow-up (3-dose recipients) | 1 | 40017 | Risk Ratio (M-H, Random, 95% CI) | 0.45 [0.16, 1.25] |
| 2.3.1 Age 2 to 5 years | 1 | 7419 | Risk Ratio (M-H, Random, 95% CI) | 0.76 [0.45, 1.29] |
| 2.3.2 Age > 5 years | 1 | 32598 | Risk Ratio (M-H, Random, 95% CI) | 0.27 [0.16, 0.45] |
| 2.4 Cases of cholera by blood group - First 2 years of follow-up (3-dose recipients) | 1 | 41580 | Risk Ratio (M-H, Fixed, 95% CI) | 0.45 [0.36, 0.58] |
| 2.4.1 Blood Group O | 1 | 13465 | Risk Ratio (M-H, Fixed, 95% CI) | 0.53 [0.37, 0.76] |
| 2.4.2 All other blood groups | 1 | 28115 | Risk Ratio (M-H, Fixed, 95% CI) | 0.41 [0.29, 0.56] |
| 2.5 Cases of all cause diarrhoea - 1st year of follow-up (3-dose recipients) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.5.1 Severe watery diarrhoea | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.5.2 Any watery diarrhoea | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.5.3 Any diarrhoea | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.6 Deaths - 1st year of follow-up (3-dose recipients) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.6.1 All cause deaths | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.6.2 Deaths from non-dysenteric diarrhoea (adult females only) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |


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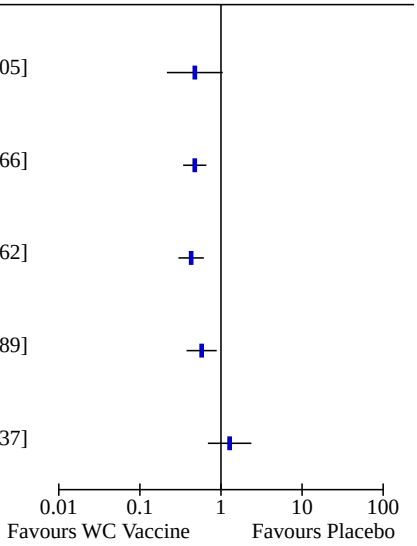
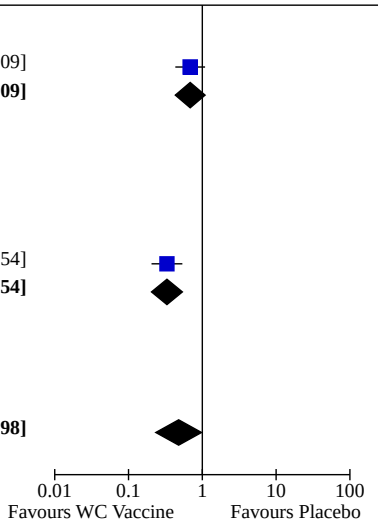
## Analysis 2.1. Comparison 2: Whole cell vaccine (WC) versus placebo - Subgroup analysis, Outcome 1: Cases of cholera by time of follow-up (3-dose recipients)

| Study or Subgroup | WC Vaccine Events | WC Vaccine Total | Placebo Events | Placebo Total | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **2.1.1 First four months after vaccination** | | | | | |
| Clemens 1988 Bangladesh | 9 | 20743 | 19 | 20837 | 0.48 [0.22 , 1.05] |
| **2.1.2 First year after vaccination** | | | | | |
| Clemens 1988 Bangladesh | 52 | 20743 | 110 | 20837 | 0.47 [0.34 , 0.66] |
| **2.1.3 Second year after vaccination** | | | | | |
| Clemens 1988 Bangladesh | 42 | 20005 | 98 | 20012 | 0.43 [0.30 , 0.62] |
| **2.1.4 Third year after vaccination** | | | | | |
| Clemens 1988 Bangladesh | 33 | 19424 | 57 | 19380 | 0.58 [0.38 , 0.89] |
| **2.1.5 Fourth year after vaccination** | | | | | |
| Clemens 1988 Bangladesh | 23 | 18905 | 18 | 18905 | 1.28 [0.69 , 2.37] |




## Analysis 2.2. Comparison 2: Whole cell vaccine (WC) versus placebo - Subgroup analysis, Outcome 2: Cases of cholera by age-group - 1st year of follow-up (3-dose recipients)

| Study or Subgroup | WC Vaccine Events | WC Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **2.2.1 Age 2 to 5 years** | | | | | | |
| Clemens 1988 Bangladesh | 30 | 3900 | 43 | 3830 | 50.4% | 0.69 [0.43 , 1.09] |
| **Subtotal (95% CI)** | | **3900** | | **3830** | **50.4%** | **0.69 [0.43 , 1.09]** |
| Total events: | 30 | | 43 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.60 (P = 0.11) | | | | | | |
| **2.2.2 Age > 5 years** | | | | | | |
| Clemens 1988 Bangladesh | 22 | 16843 | 67 | 17007 | 49.6% | 0.33 [0.20 , 0.54] |
| **Subtotal (95% CI)** | | **16843** | | **17007** | **49.6%** | **0.33 [0.20 , 0.54]** |
| Total events: | 22 | | 67 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 4.50 (P < 0.00001) | | | | | | |
| **Total (95% CI)** | | **20743** | | **20837** | **100.0%** | **0.48 [0.23 , 0.98]** |
| Total events: | 52 | | 110 | | | |
| Heterogeneity: Tau² = 0.21; Chi² = 4.55, df = 1 (P = 0.03); I² = 78% | | | | | | |
| Test for overall effect: Z = 2.03 (P = 0.04) | | | | | | |
| Test for subgroup differences: Chi² = 4.53, df = 1 (P = 0.03), I² = 77.9% | | | | | | |





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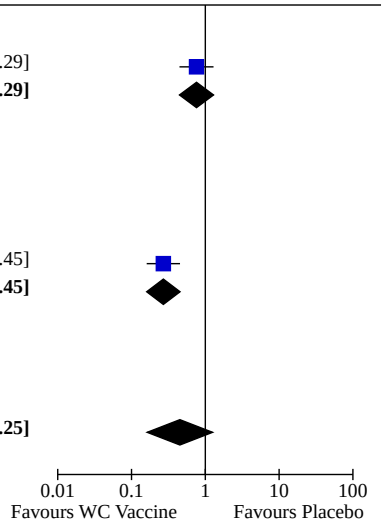
## Analysis 2.3. Comparison 2: Whole cell vaccine (WC) versus placebo - Subgroup analysis, Outcome 3: Cases of cholera by age-group - 2nd year of follow-up (3-dose recipients)

| Study or Subgroup | WC Vaccine Events | WC Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **2.3.1 Age 2 to 5 years** | | | | | | |
| Clemens 1988 Bangladesh (1) | 24 | 3745 | 31 | 3674 | 49.9% | 0.76 [0.45 , 1.29] |
| **Subtotal (95% CI)** | | **3745** | | **3674** | **49.9%** | **0.76 [0.45 , 1.29]** |
| Total events: | 24 | | 31 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.02 (P = 0.31) | | | | | | |
| **2.3.2 Age > 5 years** | | | | | | |
| Clemens 1988 Bangladesh (1) | 18 | 16260 | 67 | 16338 | 50.1% | 0.27 [0.16 , 0.45] |
| **Subtotal (95% CI)** | | **16260** | | **16338** | **50.1%** | **0.27 [0.16 , 0.45]** |
| Total events: | 18 | | 67 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 4.94 (P < 0.00001) | | | | | | |
| **Total (95% CI)** | | **20005** | | **20012** | **100.0%** | **0.45 [0.16 , 1.25]** |
| Total events: | 42 | | 98 | | | |
| Heterogeneity: Tau² = 0.47; Chi² = 7.51, df = 1 (P = 0.006); I² = 87% | | | | | | |
| Test for overall effect: Z = 1.53 (P = 0.13) | | | | | | |
| Test for subgroup differences: Chi² = 7.44, df = 1 (P = 0.006), I² = 86.6% | | | | | | |

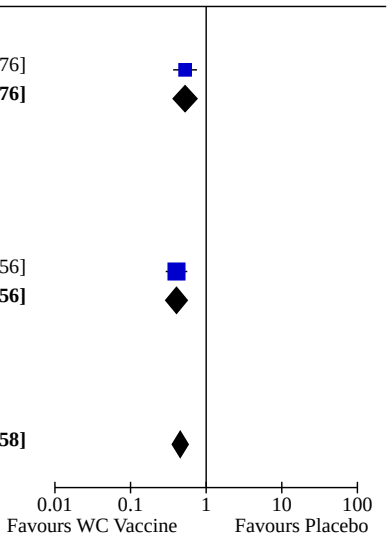



**Footnotes**

(1) For the purpose of this meta analysis the events and participants in the Placebo arm of Clemens 1985 Bangladesh have been divided equally between the two

## Analysis 2.4. Comparison 2: Whole cell vaccine (WC) versus placebo - Subgroup analysis, Outcome 4: Cases of cholera by blood group - First 2 years of follow-up (3-dose recipients)

| Study or Subgroup | WC Vaccine Events | WC Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **2.4.1 Blood Group O** | | | | | | |
| Clemens 1988 Bangladesh | 44 | 6717 | 84 | 6748 | 40.4% | 0.53 [0.37 , 0.76] |
| **Subtotal (95% CI)** | | **6717** | | **6748** | **40.4%** | **0.53 [0.37 , 0.76]** |
| Total events: | 44 | | 84 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 3.46 (P = 0.0005) | | | | | | |
| **2.4.2 All other blood groups** | | | | | | |
| Clemens 1988 Bangladesh | 50 | 14026 | 124 | 14089 | 59.6% | 0.41 [0.29 , 0.56] |
| **Subtotal (95% CI)** | | **14026** | | **14089** | **59.6%** | **0.41 [0.29 , 0.56]** |
| Total events: | 50 | | 124 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 5.41 (P < 0.00001) | | | | | | |
| **Total (95% CI)** | | **20743** | | **20837** | **100.0%** | **0.45 [0.36 , 0.58]** |
| Total events: | 94 | | 208 | | | |
| Heterogeneity: Chi² = 1.10, df = 1 (P = 0.29); I² = 9% | | | | | | |
| Test for overall effect: Z = 6.38 (P < 0.00001) | | | | | | |
| Test for subgroup differences: Chi² = 1.10, df = 1 (P = 0.29), I² = 9.1% | | | | | | |





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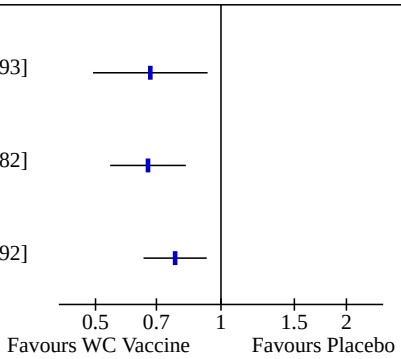
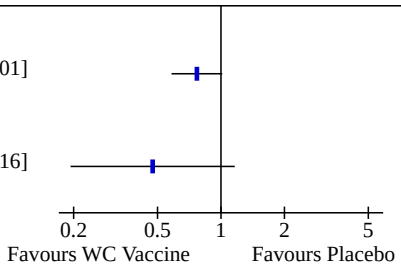
**Analysis 2.5. Comparison 2: Whole cell vaccine (WC) versus placebo - Subgroup analysis, Outcome 5: Cases of all cause diarrhoea - 1st year of follow-up (3-dose recipients)**

| Study or Subgroup | WC Vaccine Events | WC Vaccine Total | Placebo Events | Placebo Total | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **2.5.1 Severe watery diarrhoea** | | | | | |
| Clemens 1988 Bangladesh | 64 | 20743 | 95 | 20837 | 0.68 [0.49 , 0.93] |
| **2.5.2 Any watery diarrhoea** | | | | | |
| Clemens 1988 Bangladesh | 145 | 20743 | 218 | 20837 | 0.67 [0.54 , 0.82] |
| **2.5.3 Any diarrhoea** | | | | | |
| Clemens 1988 Bangladesh | 221 | 20743 | 286 | 20837 | 0.78 [0.65 , 0.92] |




**Analysis 2.6. Comparison 2: Whole cell vaccine (WC) versus placebo - Subgroup analysis, Outcome 6: Deaths - 1st year of follow-up (3-dose recipients)**

| Study or Subgroup | WC Vaccine Events | WC Vaccine Total | Placebo Events | Placebo Total | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **2.6.1 All cause deaths** | | | | | |
| Clemens 1988 Bangladesh | 88 | 20743 | 115 | 20837 | 0.77 [0.58 , 1.01] |
| **2.6.2 Deaths from non-dysenteric diarrhoea (adult females only)** | | | | | |
| Clemens 1988 Bangladesh | 7 | 7794 | 15 | 7918 | 0.47 [0.19 , 1.16] |




**Comparison 3. Whole cell vaccine plus B subunit (WC-BS) versus placebo - Subgroup analysis**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 3.1 Cases of cholera by time of follow-up (3-dose recipients) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 3.1.1 First four months after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 3.1.2 First year after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 3.1.3 Second year after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 3.1.4 Third year after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |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| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 3.1.5 Fourth year after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 3.2 Cases of cholera by age-group - 1st year of follow-up (3-dose recipients) | 1 | 41542 | Risk Ratio (M-H, Random, 95% CI) | 0.38 [0.14, 1.03] |
| 3.2.1 Age 2 to 5 years | 1 | 7558 | Risk Ratio (M-H, Random, 95% CI) | 0.62 [0.38, 1.01] |
| 3.2.2 Age > 5 years | 1 | 33984 | Risk Ratio (M-H, Random, 95% CI) | 0.22 [0.13, 0.39] |
| 3.3 Cases of cholera by age-group - 2nd year of follow-up (3-dose recipients) | 1 | 40014 | Risk Ratio (M-H, Fixed, 95% CI) | 0.42 [0.29, 0.60] |
| 3.3.1 Age 2 to 5 years | 1 | 7273 | Risk Ratio (M-H, Fixed, 95% CI) | 0.53 [0.29, 0.96] |
| 3.3.2 Age > 5 years | 1 | 32741 | Risk Ratio (M-H, Fixed, 95% CI) | 0.37 [0.23, 0.59] |
| 3.4 Cases of cholera by blood group - First 2 years of follow-up (3-dose recipients) | 1 | 41542 | Risk Ratio (M-H, Fixed, 95% CI) | 0.40 [0.31, 0.51] |
| 3.4.1 Blood Group O | 1 | 13453 | Risk Ratio (M-H, Fixed, 95% CI) | 0.48 [0.33, 0.70] |
| 3.4.2 All other blood groups | 1 | 28089 | Risk Ratio (M-H, Fixed, 95% CI) | 0.34 [0.24, 0.48] |
| 3.5 Cases of all cause diarrhoea - 1st year of follow-up (3-dose recipients) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 3.5.1 Severe watery diarrhoea | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 3.5.2 Any watery diarrhoea | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 3.5.3 Any diarrhoea | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 3.6 Deaths - 1st year of follow-up (3-dose recipients) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 3.6.1 All cause deaths | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 3.6.2 Deaths from non-dysenteric diarrhoea (adult females only) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |


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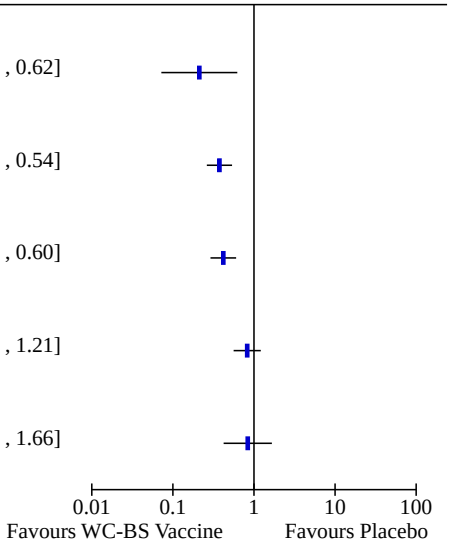
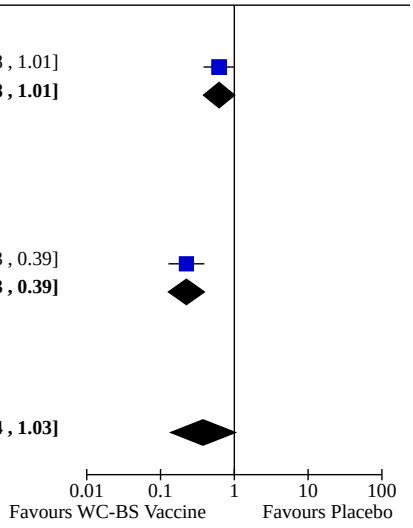
### Analysis 3.1. Comparison 3: Whole cell vaccine plus B subunit (WC-BS) versus placebo - Subgroup analysis, Outcome 1: Cases of cholera by time of follow-up (3-dose recipients)

| Study or Subgroup | WC-BS Vaccine Events | WC-BS Vaccine Total | Placebo Events | Placebo Total | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **3.1.1 First four months after vaccination** | | | | | |
| Clemens 1988 Bangladesh | 4 | 20705 | 19 | 20837 | 0.21 [0.07 , 0.62] |
| **3.1.2 First year after vaccination** | | | | | |
| Clemens 1988 Bangladesh | 41 | 20705 | 110 | 20837 | 0.38 [0.26 , 0.54] |
| **3.1.3 Second year after vaccination** | | | | | |
| Clemens 1988 Bangladesh | 41 | 20002 | 98 | 20012 | 0.42 [0.29 , 0.60] |
| **3.1.4 Third year after vaccination** | | | | | |
| Clemens 1988 Bangladesh | 47 | 19370 | 57 | 19380 | 0.82 [0.56 , 1.21] |
| **3.1.5 Fourth year after vaccination** | | | | | |
| Clemens 1988 Bangladesh | 15 | 18803 | 18 | 18905 | 0.84 [0.42 , 1.66] |




### Analysis 3.2. Comparison 3: Whole cell vaccine plus B subunit (WC-BS) versus placebo - Subgroup analysis, Outcome 2: Cases of cholera by age-group - 1st year of follow-up (3-dose recipients)

| Study or Subgroup | WC-BS Vaccine Events | WC-BS Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **3.2.1 Age 2 to 5 years** | | | | | | |
| Clemens 1988 Bangladesh | 26 | 3728 | 43 | 3830 | 51.0% | 0.62 [0.38 , 1.01] |
| **Subtotal (95% CI)** | | **3728** | | **3830** | **51.0%** | **0.62 [0.38 , 1.01]** |
| Total events: | 26 | | 43 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.92 (P = 0.05) | | | | | | |
| **3.2.2 Age > 5 years** | | | | | | |
| Clemens 1988 Bangladesh | 15 | 16977 | 67 | 17007 | 49.0% | 0.22 [0.13 , 0.39] |
| **Subtotal (95% CI)** | | **16977** | | **17007** | **49.0%** | **0.22 [0.13 , 0.39]** |
| Total events: | 15 | | 67 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 5.24 (P < 0.00001) | | | | | | |
| **Total (95% CI)** | | **20705** | | **20837** | **100.0%** | **0.38 [0.14 , 1.03]** |
| Total events: | 41 | | 110 | | | |
| Heterogeneity: Tau² = 0.45; Chi² = 7.38, df = 1 (P = 0.007); I² = 86% | | | | | | |
| Test for overall effect: Z = 1.90 (P = 0.06) | | | | | | |
| Test for subgroup differences: Chi² = 7.28, df = 1 (P = 0.007), I² = 86.3% | | | | | | |





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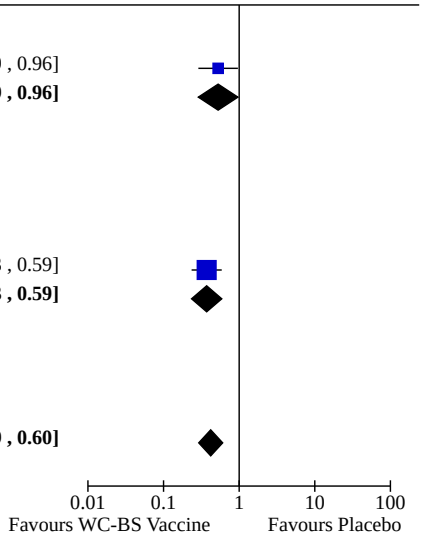
## Analysis 3.3. Comparison 3: Whole cell vaccine plus B subunit (WC-BS) versus placebo - Subgroup analysis, Outcome 3: Cases of cholera by age-group - 2nd year of follow-up (3-dose recipients)

| Study or Subgroup | WC-BS Vaccine Events | WC-BS Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **3.3.1 Age 2 to 5 years** | | | | | | |
| Clemens 1988 Bangladesh (1) | 16 | 3599 | 31 | 3674 | 31.4% | 0.53 [0.29 , 0.96] |
| **Subtotal (95% CI)** | | **3599** | | **3674** | **31.4%** | **0.53 [0.29 , 0.96]** |
| Total events: | 16 | | 31 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.09 (P = 0.04) | | | | | | |
| **3.3.2 Age > 5 years** | | | | | | |
| Clemens 1988 Bangladesh (1) | 25 | 16403 | 67 | 16338 | 68.6% | 0.37 [0.23 , 0.59] |
| **Subtotal (95% CI)** | | **16403** | | **16338** | **68.6%** | **0.37 [0.23 , 0.59]** |
| Total events: | 25 | | 67 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 4.23 (P < 0.0001) | | | | | | |
| **Total (95% CI)** | | **20002** | | **20012** | **100.0%** | **0.42 [0.29 , 0.60]** |
| Total events: | 41 | | 98 | | | |
| Heterogeneity: Chi² = 0.82, df = 1 (P = 0.37); I² = 0% | | | | | | |
| Test for overall effect: Z = 4.67 (P < 0.00001) | | | | | | |
| Test for subgroup differences: Chi² = 0.82, df = 1 (P = 0.37), I² = 0% | | | | | | |

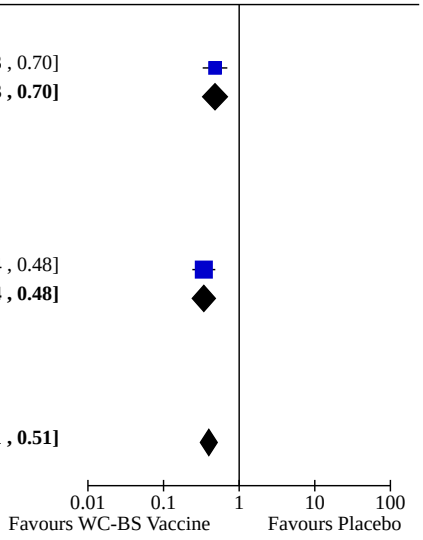



**Footnotes**

(1) For the purpose of this meta analysis the events and participants in the Placebo arm of Clemens 1985 Bangladesh have been divided equally between the t

## Analysis 3.4. Comparison 3: Whole cell vaccine plus B subunit (WC-BS) versus placebo - Subgroup analysis, Outcome 4: Cases of cholera by blood group - First 2 years of follow-up (3-dose recipients)

| Study or Subgroup | WC-BS Vaccine Events | WC-BS Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **3.4.1 Blood Group O** | | | | | | |
| Clemens 1988 Bangladesh | 40 | 6705 | 84 | 6748 | 40.4% | 0.48 [0.33 , 0.70] |
| **Subtotal (95% CI)** | | **6705** | | **6748** | **40.4%** | **0.48 [0.33 , 0.70]** |
| Total events: | 40 | | 84 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 3.84 (P = 0.0001) | | | | | | |
| **3.4.2 All other blood groups** | | | | | | |
| Clemens 1988 Bangladesh | 42 | 14000 | 124 | 14089 | 59.6% | 0.34 [0.24 , 0.48] |
| **Subtotal (95% CI)** | | **14000** | | **14089** | **59.6%** | **0.34 [0.24 , 0.48]** |
| Total events: | 42 | | 124 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 6.04 (P < 0.00001) | | | | | | |
| **Total (95% CI)** | | **20705** | | **20837** | **100.0%** | **0.40 [0.31 , 0.51]** |
| Total events: | 82 | | 208 | | | |
| Heterogeneity: Chi² = 1.70, df = 1 (P = 0.19); I² = 41% | | | | | | |
| Test for overall effect: Z = 7.11 (P < 0.00001) | | | | | | |
| Test for subgroup differences: Chi² = 1.70, df = 1 (P = 0.19), I² = 41.1% | | | | | | |





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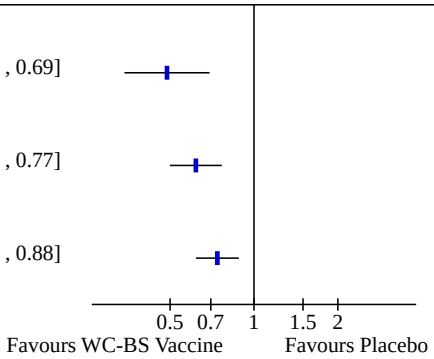
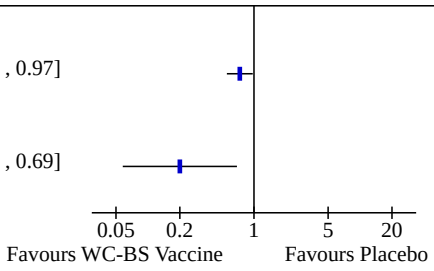
**Analysis 3.5. Comparison 3: Whole cell vaccine plus B subunit (WC-BS) versus placebo - Subgroup analysis, Outcome 5: Cases of all cause diarrhoea - 1st year of follow-up (3-dose recipients)**

| Study or Subgroup | WC-BS Vaccine Events | WC-BS Vaccine Total | Placebo Events | Placebo Total | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **3.5.1 Severe watery diarrhoea** | | | | | |
| Clemens 1988 Bangladesh | 46 | 20705 | 95 | 20837 | 0.49 [0.34 , 0.69] |
| **3.5.2 Any watery diarrhoea** | | | | | |
| Clemens 1988 Bangladesh | 134 | 20705 | 218 | 20837 | 0.62 [0.50 , 0.77] |
| **3.5.3 Any diarrhoea** | | | | | |
| Clemens 1988 Bangladesh | 210 | 20705 | 286 | 20837 | 0.74 [0.62 , 0.88] |




**Analysis 3.6. Comparison 3: Whole cell vaccine plus B subunit (WC-BS) versus placebo - Subgroup analysis, Outcome 6: Deaths - 1st year of follow-up (3-dose recipients)**

| Study or Subgroup | WC-BS Vaccine Events | WC-BS Vaccine Total | Placebo Events | Placebo Total | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **3.6.1 All cause deaths** | | | | | |
| Clemens 1988 Bangladesh | 84 | 20705 | 115 | 20837 | 0.74 [0.56 , 0.97] |
| **3.6.2 Deaths from non-dysenteric diarrhoea (adult females only)** | | | | | |
| Clemens 1988 Bangladesh | 3 | 7916 | 15 | 7918 | 0.20 [0.06 , 0.69] |




**Comparison 4. Whole cell vaccine (WC) versus Whole cell vaccine plus B subunit (WC-BS) - Subgroup analysis**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 4.1 Cases of confirmed cholera by time of follow-up (3-dose recipients) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 4.1.1 First four months after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 4.1.2 Four to eight months after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 4.1.3 First year after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 4.1.4 Second year after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |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| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 4.1.5 Third year after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 4.1.6 Fourth year after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 4.2 Cases of cholera by age-group - 1st year of follow-up (3-dose recipients) | 1 | 82085 | Risk Ratio (M-H, Fixed, 95% CI) | 1.12 [0.80, 1.55] |
| 4.2.1 Age 2 to 5 years | 1 | 7628 | Risk Ratio (M-H, Fixed, 95% CI) | 1.10 [0.65, 1.86] |
| 4.2.2 Age > 5 years | 1 | 33820 | Risk Ratio (M-H, Fixed, 95% CI) | 1.48 [0.77, 2.85] |
| 4.2.3 Eight to 12 months after vaccination | 1 | 40637 | Risk Ratio (M-H, Fixed, 95% CI) | 0.92 [0.53, 1.60] |
| 4.3 Cases of cholera by age-group - 2nd year of follow-up (3-dose recipients) | 1 | 40007 | Risk Ratio (M-H, Fixed, 95% CI) | 1.01 [0.66, 1.55] |
| 4.3.1 Age 2 to 5 years | 1 | 7344 | Risk Ratio (M-H, Fixed, 95% CI) | 1.44 [0.77, 2.71] |
| 4.3.2 Age > 5 years | 1 | 32663 | Risk Ratio (M-H, Fixed, 95% CI) | 0.73 [0.40, 1.33] |
| 4.4 Cases of cholera by blood group, First 2 years of follow-up (3-dose recipients) | 1 | 41448 | Risk Ratio (M-H, Fixed, 95% CI) | 1.14 [0.85, 1.54] |
| 4.4.1 Blood group O | 1 | 13422 | Risk Ratio (M-H, Fixed, 95% CI) | 1.10 [0.72, 1.68] |
| 4.4.2 Any other blood group | 1 | 28026 | Risk Ratio (M-H, Fixed, 95% CI) | 1.19 [0.79, 1.79] |
| 4.5 Cases of all cause diarrhoea - 1st year of follow-up (3-dose recipients) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 4.5.1 Severe watery diarrhoea | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 4.5.2 Any watery diarrhoea | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 4.5.3 Any diarrhoea | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 4.6 Deaths - 1st year of follow-up (3-dose recipients) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |


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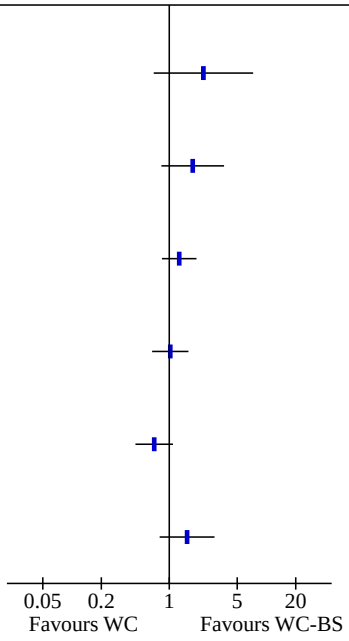
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 4.6.1 All cause deaths | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 4.6.2 Deaths from non-dysenteric diarrhoea (adult females only) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |

**Analysis 4.1. Comparison 4: Whole cell vaccine (WC) versus Whole cell vaccine plus B subunit (WC-BS) - Subgroup analysis, Outcome 1: Cases of confirmed cholera by time of follow-up (3-dose recipients)**

| Study or Subgroup | WC Vaccine Events | WC Vaccine Total | WC-BS Vaccine Events | WC-BS Vaccine Total | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **4.1.1 First four months after vaccination** | | | | | |
| Clemens 1988 Bangladesh | 9 | 20743 | 4 | 20705 | 2.25 [0.69 , 7.29] |
| **4.1.2 Four to eight months after vaccination** | | | | | |
| Clemens 1988 Bangladesh | 19 | 20333 | 11 | 20515 | 1.74 [0.83 , 3.66] |
| **4.1.3 First year after vaccination** | | | | | |
| Clemens 1988 Bangladesh | 52 | 20743 | 41 | 20705 | 1.27 [0.84 , 1.91] |
| **4.1.4 Second year after vaccination** | | | | | |
| Clemens 1988 Bangladesh | 42 | 20005 | 41 | 20002 | 1.02 [0.67 , 1.57] |
| **4.1.5 Third year after vaccination** | | | | | |
| Clemens 1988 Bangladesh | 33 | 19424 | 47 | 19370 | 0.70 [0.45 , 1.09] |
| **4.1.6 Fourth year after vaccination** | | | | | |
| Clemens 1988 Bangladesh | 23 | 18905 | 15 | 18803 | 1.53 [0.80 , 2.92] |





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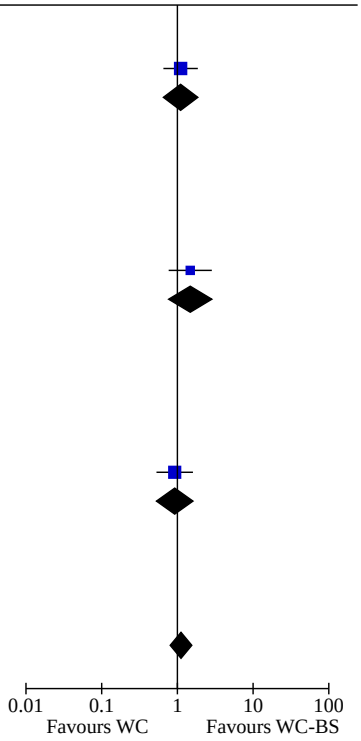
## Analysis 4.2. Comparison 4: Whole cell vaccine (WC) versus Whole cell vaccine plus B subunit (WC-BS) - Subgroup analysis, Outcome 2: Cases of cholera by age-group - 1st year of follow-up (3-dose recipients)

| Study or Subgroup | WC Vaccine Events | WC Vaccine Total | WC-BS Vaccine Events | WC-BS Vaccine Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **4.2.1 Age 2 to 5 years** | | | | | | |
| Clemens 1988 Bangladesh (1) | 30 | 3900 | 26 | 3728 | 39.4% | 1.10 [0.65 , 1.86] |
| **Subtotal (95% CI)** | | **3900** | | **3728** | **39.4%** | **1.10 [0.65 , 1.86]** |
| Total events: | 30 | | 26 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.37 (P = 0.71) | | | | | | |
| **4.2.2 Age > 5 years** | | | | | | |
| Clemens 1988 Bangladesh (1) | 22 | 16843 | 15 | 16977 | 22.1% | 1.48 [0.77 , 2.85] |
| **Subtotal (95% CI)** | | **16843** | | **16977** | **22.1%** | **1.48 [0.77 , 2.85]** |
| Total events: | 22 | | 15 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.17 (P = 0.24) | | | | | | |
| **4.2.3 Eight to 12 months after vaccination** | | | | | | |
| Clemens 1988 Bangladesh | 24 | 20333 | 26 | 20304 | 38.5% | 0.92 [0.53 , 1.60] |
| **Subtotal (95% CI)** | | **20333** | | **20304** | **38.5%** | **0.92 [0.53 , 1.60]** |
| Total events: | 24 | | 26 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.29 (P = 0.77) | | | | | | |
| **Total (95% CI)** | | **41076** | | **41009** | **100.0%** | **1.12 [0.80 , 1.55]** |
| Total events: | 76 | | 67 | | | |
| Heterogeneity: Chi² = 1.16, df = 2 (P = 0.56); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.66 (P = 0.51) | | | | | | |
| Test for subgroup differences: Chi² = 1.16, df = 2 (P = 0.56), I² = 0% | | | | | | |




**Footnotes**

(1) For the purpose of this meta analysis the events and participants in the Placebo arm of Clemens 1985 Bangladesh have been divided equally between the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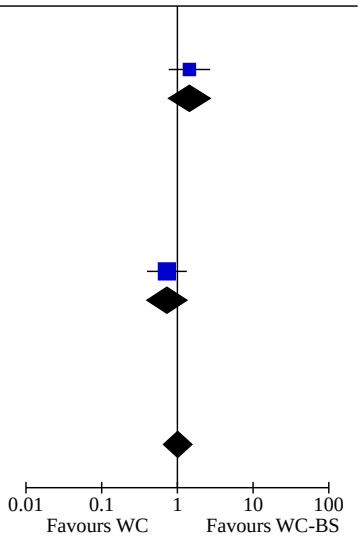
## Analysis 4.3. Comparison 4: Whole cell vaccine (WC) versus Whole cell vaccine plus B subunit (WC-BS) - Subgroup analysis, Outcome 3: Cases of cholera by age-group - 2nd year of follow-up (3-dose recipients)

| Study or Subgroup | WC Vaccine Events | WC Vaccine Total | WC-BS Vaccine Events | WC-BS Vaccine Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **4.3.1 Age 2 to 5 years** | | | | | | |
| Clemens 1988 Bangladesh (1) | 24 | 3745 | 16 | 3599 | 39.6% | 1.44 [0.77 , 2.71] |
| **Subtotal (95% CI)** | | **3745** | | **3599** | **39.6%** | **1.44 [0.77 , 2.71]** |
| Total events: | 24 | | 16 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.14 (P = 0.26) | | | | | | |
| **4.3.2 Age > 5 years** | | | | | | |
| Clemens 1988 Bangladesh (1) | 18 | 16260 | 25 | 16403 | 60.4% | 0.73 [0.40 , 1.33] |
| **Subtotal (95% CI)** | | **16260** | | **16403** | **60.4%** | **0.73 [0.40 , 1.33]** |
| Total events: | 18 | | 25 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.04 (P = 0.30) | | | | | | |
| **Total (95% CI)** | | **20005** | | **20002** | **100.0%** | **1.01 [0.66 , 1.55]** |
| Total events: | 42 | | 41 | | | |
| Heterogeneity: Chi² = 2.36, df = 1 (P = 0.12); I² = 58% | | | | | | |
| Test for overall effect: Z = 0.04 (P = 0.97) | | | | | | |
| Test for subgroup differences: Chi² = 2.36, df = 1 (P = 0.12), I² = 57.6% | | | | | | |

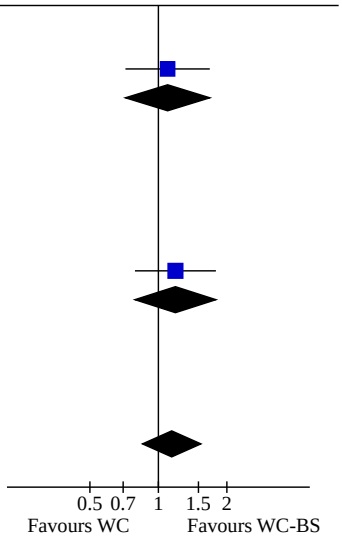



**Footnotes**

(1) For the purpose of this meta analysis the events and participants in the Placebo arm of Clemens 1985 Bangladesh have been divided equally between the

## Analysis 4.4. Comparison 4: Whole cell vaccine (WC) versus Whole cell vaccine plus B subunit (WC-BS) - Subgroup analysis, Outcome 4: Cases of cholera by blood group, First 2 years of follow-up (3-dose recipients)

| Study or Subgroup | WC Vaccine Events | WC Vaccine Total | WC-BS Vaccine Events | WC-BS Vaccine Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **4.4.1 Blood group O** | | | | | | |
| Clemens 1988 Bangladesh | 44 | 6717 | 40 | 6705 | 48.8% | 1.10 [0.72 , 1.68] |
| **Subtotal (95% CI)** | | **6717** | | **6705** | **48.8%** | **1.10 [0.72 , 1.68]** |
| Total events: | 44 | | 40 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.43 (P = 0.67) | | | | | | |
| **4.4.2 Any other blood group** | | | | | | |
| Clemens 1988 Bangladesh | 50 | 14026 | 42 | 14000 | 51.2% | 1.19 [0.79 , 1.79] |
| **Subtotal (95% CI)** | | **14026** | | **14000** | **51.2%** | **1.19 [0.79 , 1.79]** |
| Total events: | 50 | | 42 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.83 (P = 0.41) | | | | | | |
| **Total (95% CI)** | | **20743** | | **20705** | **100.0%** | **1.14 [0.85 , 1.54]** |
| Total events: | 94 | | 82 | | | |
| Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.89 (P = 0.37) | | | | | | |
| Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0% | | | | | | |





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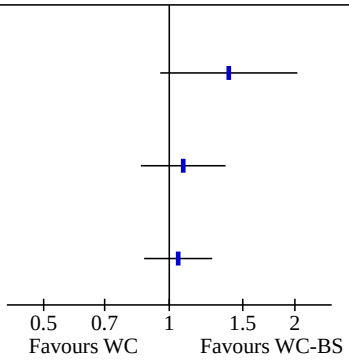
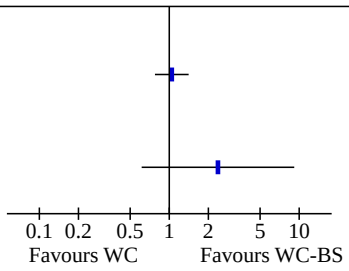
**Analysis 4.5. Comparison 4: Whole cell vaccine (WC) versus Whole cell vaccine plus B subunit (WC-BS) - Subgroup analysis, Outcome 5: Cases of all cause diarrhoea - 1st year of follow-up (3-dose recipients)**

| Study or Subgroup | WC Vaccine Events | WC Vaccine Total | WC-BS Vaccine Events | WC-BS Vaccine Total | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **4.5.1 Severe watery diarrhoea** | | | | | |
| Clemens 1988 Bangladesh | 64 | 20743 | 46 | 20705 | 1.39 [0.95 , 2.03] |
| **4.5.2 Any watery diarrhoea** | | | | | |
| Clemens 1988 Bangladesh | 145 | 20743 | 134 | 20705 | 1.08 [0.85 , 1.36] |
| **4.5.3 Any diarrhoea** | | | | | |
| Clemens 1988 Bangladesh | 221 | 20743 | 210 | 20705 | 1.05 [0.87 , 1.27] |




**Analysis 4.6. Comparison 4: Whole cell vaccine (WC) versus Whole cell vaccine plus B subunit (WC-BS) - Subgroup analysis, Outcome 6: Deaths - 1st year of follow-up (3-dose recipients)**

| Study or Subgroup | WC Vaccine Events | WC Vaccine Total | WC-BS Vaccine Events | WC-BS Vaccine Total | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **4.6.1 All cause deaths** | | | | | |
| Clemens 1988 Bangladesh | 88 | 20743 | 84 | 20705 | 1.05 [0.78 , 1.41] |
| **4.6.2 Deaths from non-dysenteric diarrhoea (adult females only)** | | | | | |
| Clemens 1988 Bangladesh | 7 | 7794 | 3 | 7916 | 2.37 [0.61 , 9.16] |




**Comparison 5. Whole cell plus recombinant B subunit vaccine (WC-rBS) versus placebo - Subgroup analysis**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 5.1 Cases of cholera by age group - 1st year of follow-up (2 doses) | 1 | 17799 | Risk Ratio (M-H, Fixed, 95% CI) | 1.04 [0.52, 2.05] |
| 5.1.1 Age 2 to 5 years | 1 | 2368 | Risk Ratio (M-H, Fixed, 95% CI) | 3.91 [0.44, 34.90] |
| 5.1.2 Age 6 to 15 years | 1 | 6782 | Risk Ratio (M-H, Fixed, 95% CI) | 0.70 [0.22, 2.19] |
| 5.1.3 Age 16 to 65 years | 1 | 8649 | Risk Ratio (M-H, Fixed, 95% CI) | 0.98 [0.37, 2.60] |
| 5.2 Cases of cholera by age group - 2nd year of follow-up (2 doses plus booster) | 1 | 14997 | Risk Ratio (M-H, Fixed, 95% CI) | 0.40 [0.21, 0.75] |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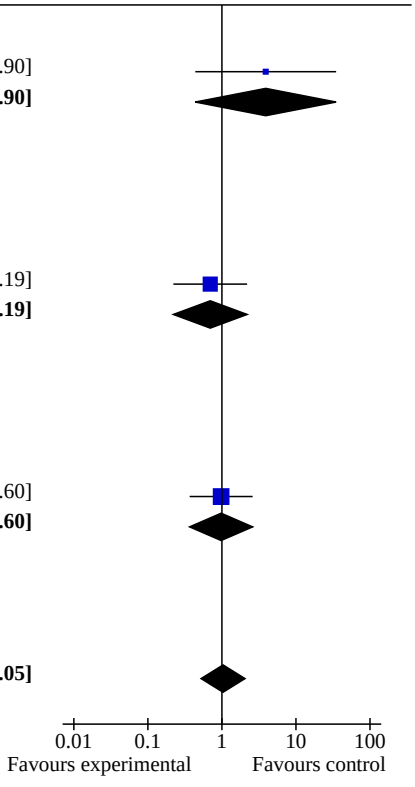
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 5.2.1 Age 2 to 5 years | 1 | 2040 | Risk Ratio (M-H, Fixed, 95% CI) | 0.48 [0.09, 2.62] |
| 5.2.2 Age 6 to 15 years | 1 | 6049 | Risk Ratio (M-H, Fixed, 95% CI) | 0.53 [0.20, 1.44] |
| 5.2.3 Age 16 to 65 years | 1 | 6908 | Risk Ratio (M-H, Fixed, 95% CI) | 0.29 [0.11, 0.78] |
| 5.3 Cases of cholera in military recruits, 4 to 18 weeks follow-up | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 5.3.1 Cases of cholera - Occurring after the second dose | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 5.3.2 Cases of cholera - Occurring between the first and second dose | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |

**Analysis 5.1. Comparison 5: Whole cell plus recombinant B subunit vaccine (WC-rBS) versus placebo - Subgroup analysis, Outcome 1: Cases of cholera by age group - 1st year of follow-up (2 doses)**

| Study or Subgroup | Vaccine Events | Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **5.1.1 Age 2 to 5 years** | | | | | | |
| Taylor 2000 Peru | 4 | 1198 | 1 | 1170 | 6.2% | 3.91 [0.44 , 34.90] |
| **Subtotal (95% CI)** | | **1198** | | **1170** | **6.2%** | **3.91 [0.44 , 34.90]** |
| Total events: | 4 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.22 (P = 0.22) | | | | | | |
| **5.1.2 Age 6 to 15 years** | | | | | | |
| Taylor 2000 Peru | 5 | 3436 | 7 | 3346 | 43.8% | 0.70 [0.22 , 2.19] |
| **Subtotal (95% CI)** | | **3436** | | **3346** | **43.8%** | **0.70 [0.22 , 2.19]** |
| Total events: | 5 | | 7 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.62 (P = 0.53) | | | | | | |
| **5.1.3 Age 16 to 65 years** | | | | | | |
| Taylor 2000 Peru | 8 | 4378 | 8 | 4271 | 50.0% | 0.98 [0.37 , 2.60] |
| **Subtotal (95% CI)** | | **4378** | | **4271** | **50.0%** | **0.98 [0.37 , 2.60]** |
| Total events: | 8 | | 8 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.05 (P = 0.96) | | | | | | |
| **Total (95% CI)** | | **9012** | | **8787** | **100.0%** | **1.04 [0.52 , 2.05]** |
| Total events: | 17 | | 16 | | | |
| Heterogeneity: Chi² = 1.89, df = 2 (P = 0.39); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.10 (P = 0.92) | | | | | | |
| Test for subgroup differences: Chi² = 1.87, df = 2 (P = 0.39), I² = 0% | | | | | | |





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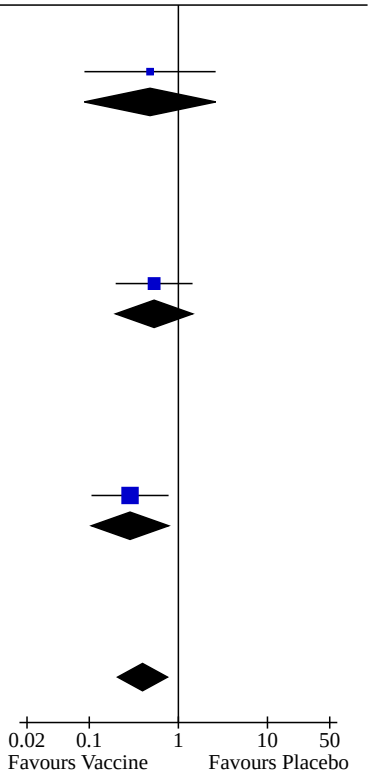
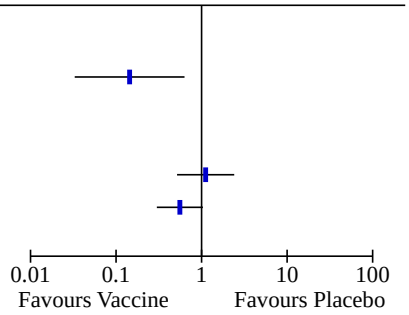
## Analysis 5.2. Comparison 5: Whole cell plus recombinant B subunit vaccine (WC-rBS) versus placebo - Subgroup analysis, Outcome 2: Cases of cholera by age group - 2nd year of follow-up (2 doses plus booster)

| Study or Subgroup | Vaccine Events | Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **5.2.1 Age 2 to 5 years** | | | | | | |
| Taylor 2000 Peru | 2 | 1040 | 4 | 1000 | 12.6% | 0.48 [0.09 , 2.62] |
| **Subtotal (95% CI)** | | **1040** | | **1000** | **12.6%** | **0.48 [0.09 , 2.62]** |
| Total events: | 2 | | 4 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.85 (P = 0.40) | | | | | | |
| **5.2.2 Age 6 to 15 years** | | | | | | |
| Taylor 2000 Peru | 6 | 3056 | 11 | 2993 | 34.3% | 0.53 [0.20 , 1.44] |
| **Subtotal (95% CI)** | | **3056** | | **2993** | **34.3%** | **0.53 [0.20 , 1.44]** |
| Total events: | 6 | | 11 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.24 (P = 0.22) | | | | | | |
| **5.2.3 Age 16 to 65 years** | | | | | | |
| Taylor 2000 Peru | 5 | 3498 | 17 | 3410 | 53.1% | 0.29 [0.11 , 0.78] |
| **Subtotal (95% CI)** | | **3498** | | **3410** | **53.1%** | **0.29 [0.11 , 0.78]** |
| Total events: | 5 | | 17 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.46 (P = 0.01) | | | | | | |
| **Total (95% CI)** | | **7594** | | **7403** | **100.0%** | **0.40 [0.21 , 0.75]** |
| Total events: | 13 | | 32 | | | |
| Heterogeneity: $Chi^2$ = 0.80, df = 2 (P = 0.67); $I^2$ = 0% | | | | | | |
| Test for overall effect: Z = 2.82 (P = 0.005) | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.80, df = 2 (P = 0.67), $I^2$ = 0% | | | | | | |




## Analysis 5.3. Comparison 5: Whole cell plus recombinant B subunit vaccine (WC-rBS) versus placebo - Subgroup analysis, Outcome 3: Cases of cholera in military recruits, 4 to 18 weeks follow-up

| Study or Subgroup | Vaccine Events | Vaccine Total | Placebo Events | Placebo Total | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **5.3.1 Cases of cholera - Occurring after the second dose** | | | | | |
| Sanchez 1994 Peru (1) | 2 | 710 | 14 | 716 | 0.14 [0.03 , 0.63] |
| **5.3.2 Cases of cholera - Occurring between the first and second dose** | | | | | |
| Sanchez 1994 Peru | 12 | 71 | 10 | 66 | 1.12 [0.52 , 2.41] |
| Sanchez 1995 Peru | 14 | 157 | 24 | 150 | 0.56 [0.30 , 1.04] |




**Footnotes**

(1) 18 weeks follow-up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**Comparison 6. Whole cell vaccines (all types) versus placebo - Safety outcomes (first dose)**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 6.1 Adverse events - Whole cell (WC) versus placebo | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 6.1.1 Abdominal pain | 1 | 613 | Risk Ratio (M-H, Fixed, 95% CI) | 1.17 [0.80, 1.70] |
| 6.1.2 Severe abdominal pain | 1 | 613 | Risk Ratio (M-H, Fixed, 95% CI) | 0.51 [0.09, 2.77] |
| 6.1.3 Diarrhoea | 1 | 613 | Risk Ratio (M-H, Fixed, 95% CI) | 1.50 [0.95, 2.36] |
| 6.1.4 Watery diarrhoea | 1 | 613 | Risk Ratio (M-H, Fixed, 95% CI) | 1.46 [0.75, 2.84] |
| 6.1.5 Subjective fever | 1 | 613 | Risk Ratio (M-H, Fixed, 95% CI) | 1.77 [0.86, 3.65] |
| 6.1.6 Nausea | 1 | 613 | Risk Ratio (M-H, Fixed, 95% CI) | 1.92 [0.83, 4.46] |
| 6.1.7 Vomiting | 1 | 613 | Risk Ratio (M-H, Fixed, 95% CI) | 2.39 [0.62, 9.15] |
| 6.1.8 Other symptoms requiring bedrest | 1 | 613 | Risk Ratio (M-H, Fixed, 95% CI) | 1.02 [0.06, 16.28] |
| 6.2 Adverse events - Whole cell plus B subunit (WC-BS) versus placebo | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 6.2.1 Abdominal pain or stomach cramps | 1 | 631 | Risk Ratio (M-H, Fixed, 95% CI) | 1.17 [0.80, 1.70] |
| 6.2.2 Severe abdominal pain | 1 | 631 | Risk Ratio (M-H, Fixed, 95% CI) | 0.48 [0.09, 2.62] |
| 6.2.3 Diarrhoea | 1 | 631 | Risk Ratio (M-H, Fixed, 95% CI) | 1.35 [0.85, 2.13] |
| 6.2.4 Watery diarrhoea | 1 | 631 | Risk Ratio (M-H, Fixed, 95% CI) | 1.31 [0.67, 2.57] |
| 6.2.5 Subjective fever | 1 | 631 | Risk Ratio (M-H, Fixed, 95% CI) | 1.14 [0.52, 2.51] |
| 6.2.6 Nausea | 1 | 631 | Risk Ratio (M-H, Fixed, 95% CI) | 1.45 [0.60, 3.50] |
| 6.2.7 Vomiting | 1 | 624 | Risk Ratio (M-H, Fixed, 95% CI) | 1.21 [0.46, 3.22] |
| 6.2.8 Other symptoms requiring bedrest | 1 | 631 | Risk Ratio (M-H, Fixed, 95% CI) | 0.97 [0.06, 15.37] |
| 6.3 Adverse events - Whole cell plus recombinant B subunit (WC-rBS) versus placebo | 7 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 6.3.1 Abdominal pain or stomach cramps | 6 | 2878 | Risk Ratio (M-H, Random, 95% CI) | 1.11 [0.70, 1.74] |
| 6.3.2 Stomach gurgling | 3 | 1219 | Risk Ratio (M-H, Random, 95% CI) | 1.16 [0.90, 1.49] |


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| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 6.3.3 Diarrhoea | 7 | 23870 | Risk Ratio (M-H, Random, 95% CI) | 1.04 [0.73, 1.49] |
| 6.3.4 Fever | 4 | 941 | Risk Ratio (M-H, Random, 95% CI) | 0.31 [0.08, 1.26] |
| 6.3.5 Nausea | 4 | 2213 | Risk Ratio (M-H, Random, 95% CI) | 1.41 [0.32, 6.13] |
| 6.3.6 Vomiting | 4 | 2049 | Risk Ratio (M-H, Random, 95% CI) | 1.46 [0.40, 5.33] |
| 6.3.7 Headache | 4 | 2488 | Risk Ratio (M-H, Random, 95% CI) | 0.72 [0.37, 1.40] |
| 6.3.8 Loss of appetite | 2 | 390 | Risk Ratio (M-H, Random, 95% CI) | 0.74 [0.17, 3.18] |
| 6.3.9 Dizziness | 1 | 1313 | Risk Ratio (M-H, Random, 95% CI) | 1.04 [0.41, 2.69] |
| 6.3.10 Any adverse event | 2 | 21616 | Risk Ratio (M-H, Random, 95% CI) | 0.95 [0.71, 1.28] |
| 6.3.11 Any serious adverse event | 2 | 21133 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 6.3.12 Other | 1 | 624 | Risk Ratio (M-H, Random, 95% CI) | 0.89 [0.35, 2.29] |
| 6.4 Adverse events - Bivalent whole cell (BivWC) versus placebo | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 6.4.1 Diarrhoea | 4 | 67414 | Risk Ratio (M-H, Fixed, 95% CI) | 0.80 [0.42, 1.55] |
| 6.4.2 Abdo pain | 4 | 67414 | Risk Ratio (M-H, Fixed, 95% CI) | 1.09 [0.63, 1.88] |
| 6.4.3 Gas | 1 | 160 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.19, 2.22] |
| 6.4.4 Loss of appetite | 3 | 514 | Risk Ratio (M-H, Fixed, 95% CI) | 1.20 [0.35, 4.13] |
| 6.4.5 Nausea | 4 | 67414 | Risk Ratio (M-H, Fixed, 95% CI) | 0.80 [0.38, 1.67] |
| 6.4.6 Vomiting | 4 | 67414 | Risk Ratio (M-H, Fixed, 95% CI) | 1.12 [0.57, 2.21] |
| 6.4.7 Fever | 4 | 67414 | Risk Ratio (M-H, Fixed, 95% CI) | 1.62 [0.84, 3.10] |
| 6.4.8 Headache | 3 | 514 | Risk Ratio (M-H, Fixed, 95% CI) | 0.98 [0.55, 1.75] |
| 6.4.9 General ill feeling | 3 | 514 | Risk Ratio (M-H, Fixed, 95% CI) | 1.70 [0.61, 4.77] |
| 6.4.10 Rash | 1 | 66900 | Risk Ratio (M-H, Fixed, 95% CI) | 1.64 [0.27, 9.83] |
| 6.4.11 Weakness | 1 | 66900 | Risk Ratio (M-H, Fixed, 95% CI) | 0.27 [0.03, 2.45] |
| 6.4.12 Itch | 1 | 66900 | Risk Ratio (M-H, Fixed, 95% CI) | 3.29 [0.34, 31.58] |
| 6.4.13 Cough | 1 | 66900 | Risk Ratio (M-H, Fixed, 95% CI) | 1.10 [0.15, 7.77] |
| 6.4.14 Dizziness | 1 | 66900 | Risk Ratio (M-H, Fixed, 95% CI) | 1.10 [0.07, 17.51] |


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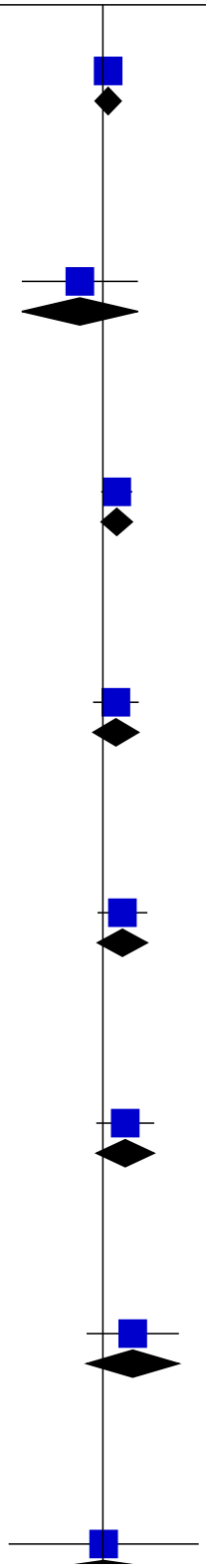
**Analysis 6.1. Comparison 6: Whole cell vaccines (all types) versus placebo - Safety outcomes (first dose), Outcome 1: Adverse events - Whole cell (WC) versus placebo**

| Study or Subgroup | Vaccine Events | Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **6.1.1 Abdominal pain** | | | | | | |
| Clemens 1987 | 49 | 303 | 43 | 310 | 100.0% | 1.17 [0.80 , 1.70] |
| **Subtotal (95% CI)** | | **303** | | **310** | **100.0%** | **1.17 [0.80 , 1.70]** |
| Total events: | 49 | | 43 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.80 (P = 0.43) | | | | | | |
| **6.1.2 Severe abdominal pain** | | | | | | |
| Clemens 1987 | 2 | 303 | 4 | 310 | 100.0% | 0.51 [0.09 , 2.77] |
| **Subtotal (95% CI)** | | **303** | | **310** | **100.0%** | **0.51 [0.09 , 2.77]** |
| Total events: | 2 | | 4 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.78 (P = 0.44) | | | | | | |
| **6.1.3 Diarrhoea** | | | | | | |
| Clemens 1987 | 41 | 303 | 28 | 310 | 100.0% | 1.50 [0.95 , 2.36] |
| **Subtotal (95% CI)** | | **303** | | **310** | **100.0%** | **1.50 [0.95 , 2.36]** |
| Total events: | 41 | | 28 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.75 (P = 0.08) | | | | | | |
| **6.1.4 Watery diarrhoea** | | | | | | |
| Clemens 1987 | 20 | 303 | 14 | 310 | 100.0% | 1.46 [0.75 , 2.84] |
| **Subtotal (95% CI)** | | **303** | | **310** | **100.0%** | **1.46 [0.75 , 2.84]** |
| Total events: | 20 | | 14 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.12 (P = 0.26) | | | | | | |
| **6.1.5 Subjective fever** | | | | | | |
| Clemens 1987 | 19 | 303 | 11 | 310 | 100.0% | 1.77 [0.86 , 3.65] |
| **Subtotal (95% CI)** | | **303** | | **310** | **100.0%** | **1.77 [0.86 , 3.65]** |
| Total events: | 19 | | 11 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.54 (P = 0.12) | | | | | | |
| **6.1.6 Nausea** | | | | | | |
| Clemens 1987 | 15 | 303 | 8 | 310 | 100.0% | 1.92 [0.83 , 4.46] |
| **Subtotal (95% CI)** | | **303** | | **310** | **100.0%** | **1.92 [0.83 , 4.46]** |
| Total events: | 15 | | 8 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.51 (P = 0.13) | | | | | | |
| **6.1.7 Vomiting** | | | | | | |
| Clemens 1987 | 7 | 303 | 3 | 310 | 100.0% | 2.39 [0.62 , 9.15] |
| **Subtotal (95% CI)** | | **303** | | **310** | **100.0%** | **2.39 [0.62 , 9.15]** |
| Total events: | 7 | | 3 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.27 (P = 0.20) | | | | | | |
| **6.1.8 Other symptoms requiring bedrest** | | | | | | |
| Clemens 1987 | 1 | 303 | 1 | 310 | 100.0% | 1.02 [0.06 , 16.28] |

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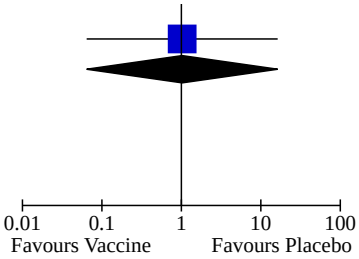
## Analysis 6.1. (Continued)

| | | | | | | |
|---|---|---|---|---|---|---|
| **6.1.8 Other symptoms requiring bedrest** | | | | | | |
| Clemens 1987 | 1 | 303 | 1 | 310 | 100.0% | 1.02 [0.06 , 16.28] |
| **Subtotal (95% CI)** | | **303** | | **310** | **100.0%** | **1.02 [0.06 , 16.28]** |
| Total events: | 1 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.02 (P = 0.99) | | | | | | |





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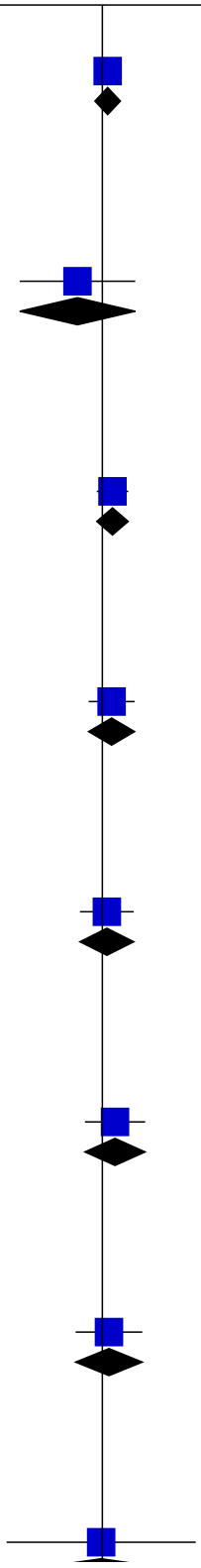
**Analysis 6.2. Comparison 6: Whole cell vaccines (all types) versus placebo - Safety outcomes (first dose), Outcome 2: Adverse events - Whole cell plus B subunit (WC-BS) versus placebo**

| Study or Subgroup | Vaccine Events | Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **6.2.1 Abdominal pain or stomach cramps** | | | | | | |
| Clemens 1987 | 52 | 321 | 43 | 310 | 100.0% | 1.17 [0.80 , 1.70] |
| **Subtotal (95% CI)** | | **321** | | **310** | **100.0%** | **1.17 [0.80 , 1.70]** |
| Total events: | 52 | | 43 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.82 (P = 0.41) | | | | | | |
| **6.2.2 Severe abdominal pain** | | | | | | |
| Clemens 1987 | 2 | 321 | 4 | 310 | 100.0% | 0.48 [0.09 , 2.62] |
| **Subtotal (95% CI)** | | **321** | | **310** | **100.0%** | **0.48 [0.09 , 2.62]** |
| Total events: | 2 | | 4 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.84 (P = 0.40) | | | | | | |
| **6.2.3 Diarrhoea** | | | | | | |
| Clemens 1987 | 39 | 321 | 28 | 310 | 100.0% | 1.35 [0.85 , 2.13] |
| **Subtotal (95% CI)** | | **321** | | **310** | **100.0%** | **1.35 [0.85 , 2.13]** |
| Total events: | 39 | | 28 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.26 (P = 0.21) | | | | | | |
| **6.2.4 Watery diarrhoea** | | | | | | |
| Clemens 1987 | 19 | 321 | 14 | 310 | 100.0% | 1.31 [0.67 , 2.57] |
| **Subtotal (95% CI)** | | **321** | | **310** | **100.0%** | **1.31 [0.67 , 2.57]** |
| Total events: | 19 | | 14 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.79 (P = 0.43) | | | | | | |
| **6.2.5 Subjective fever** | | | | | | |
| Clemens 1987 | 13 | 321 | 11 | 310 | 100.0% | 1.14 [0.52 , 2.51] |
| **Subtotal (95% CI)** | | **321** | | **310** | **100.0%** | **1.14 [0.52 , 2.51]** |
| Total events: | 13 | | 11 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.33 (P = 0.74) | | | | | | |
| **6.2.6 Nausea** | | | | | | |
| Clemens 1987 | 12 | 321 | 8 | 310 | 100.0% | 1.45 [0.60 , 3.50] |
| **Subtotal (95% CI)** | | **321** | | **310** | **100.0%** | **1.45 [0.60 , 3.50]** |
| Total events: | 12 | | 8 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.82 (P = 0.41) | | | | | | |
| **6.2.7 Vomiting** | | | | | | |
| Clemens 1987 | 9 | 321 | 7 | 303 | 100.0% | 1.21 [0.46 , 3.22] |
| **Subtotal (95% CI)** | | **321** | | **303** | **100.0%** | **1.21 [0.46 , 3.22]** |
| Total events: | 9 | | 7 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.39 (P = 0.70) | | | | | | |
| **6.2.8 Other symptoms requiring bedrest** | | | | | | |
| Clemens 1987 | 1 | 321 | 1 | 310 | 100.0% | 0.97 [0.06 , 15.37] |

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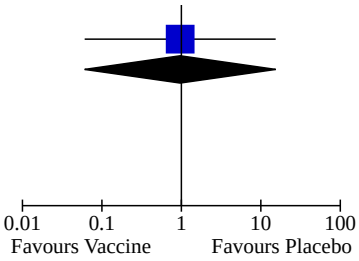
## Analysis 6.2. (Continued)

| | | | | | | |
|---|---|---|---|---|---|---|
| **6.2.8 Other symptoms requiring bedrest** | | | | | | |
| Clemens 1987 | 1 | 321 | 1 | 310 | 100.0% | 0.97 [0.06 , 15.37] |
| **Subtotal (95% CI)** | | **321** | | **310** | **100.0%** | **0.97 [0.06 , 15.37]** |
| Total events: | 1 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.02 (P = 0.98) | | | | | | |





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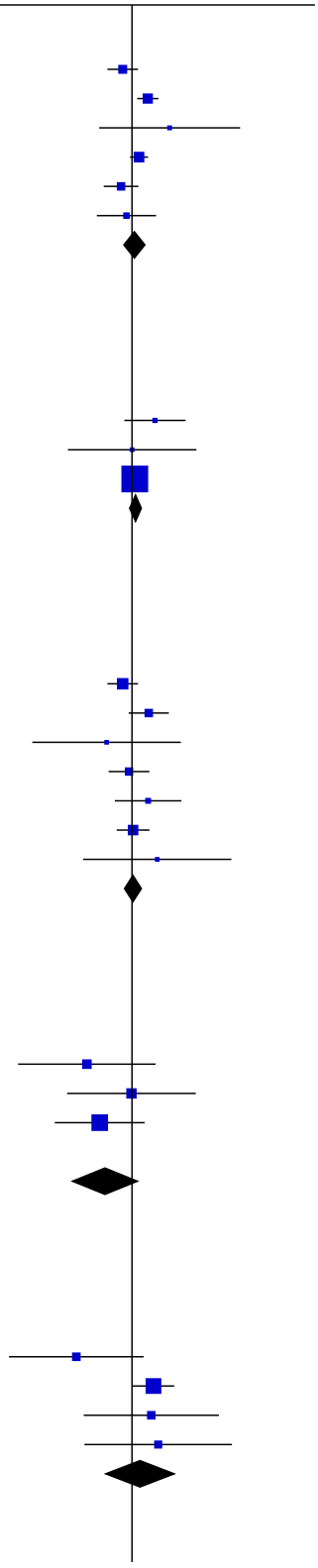
**Analysis 6.3. Comparison 6: Whole cell vaccines (all types) versus placebo - Safety outcomes (first dose), Outcome 3: Adverse events - Whole cell plus recombinant B subunit (WC-rBS) versus placebo**

| Study or Subgroup | Vaccine Events | Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **6.3.1 Abdominal pain or stomach cramps** | | | | | | |
| Begue 1995 (1) | 14 | 311 | 21 | 313 | 19.5% | 0.67 [0.35 , 1.30] |
| Concha 1995 (2) | 47 | 604 | 28 | 709 | 24.9% | 1.97 [1.25 , 3.11] |
| Hallander 2002 (3) | 2 | 124 | 0 | 125 | 2.1% | 5.04 [0.24 , 103.93] |
| Sanchez 1995 Peru (4) | 47 | 175 | 34 | 171 | 26.8% | 1.35 [0.92 , 1.99] |
| Taylor 1999a (5) | 20 | 164 | 8 | 41 | 17.5% | 0.63 [0.30 , 1.32] |
| Trach 2002 (6) | 4 | 71 | 5 | 70 | 9.1% | 0.79 [0.22 , 2.82] |
| **Subtotal (95% CI)** | | **1449** | | **1429** | **100.0%** | **1.11 [0.70 , 1.74]** |
| Total events: | 134 | | 96 | | | |
| Heterogeneity: Tau² = 0.16; Chi² = 12.09, df = 5 (P = 0.03); I² = 59% | | | | | | |
| Test for overall effect: Z = 0.44 (P = 0.66) | | | | | | |
| **6.3.2 Stomach gurgling** | | | | | | |
| Begue 1995 | 8 | 311 | 3 | 313 | 3.6% | 2.68 [0.72 , 10.02] |
| Hallander 2002 | 1 | 124 | 1 | 125 | 0.8% | 1.01 [0.06 , 15.94] |
| Sanchez 1995 Peru | 75 | 175 | 65 | 171 | 95.5% | 1.13 [0.87 , 1.46] |
| **Subtotal (95% CI)** | | **610** | | **609** | **100.0%** | **1.16 [0.90 , 1.49]** |
| Total events: | 84 | | 69 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 1.65, df = 2 (P = 0.44); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.18 (P = 0.24) | | | | | | |
| **6.3.3 Diarrhoea** | | | | | | |
| Begue 1995 | 14 | 311 | 21 | 313 | 30.1% | 0.67 [0.35 , 1.30] |
| Concha 1995 | 14 | 604 | 8 | 709 | 17.6% | 2.05 [0.87 , 4.86] |
| Hallander 2002 | 0 | 124 | 1 | 125 | 1.3% | 0.34 [0.01 , 8.17] |
| Sanchez 1995 Peru | 9 | 175 | 10 | 171 | 17.0% | 0.88 [0.37 , 2.11] |
| Taylor 1999a | 16 | 164 | 2 | 41 | 6.4% | 2.00 [0.48 , 8.35] |
| Taylor 2000 Peru (7) | 16 | 10592 | 15 | 10400 | 26.3% | 1.05 [0.52 , 2.12] |
| Trach 2002 | 1 | 71 | 0 | 70 | 1.3% | 2.96 [0.12 , 71.41] |
| **Subtotal (95% CI)** | | **12041** | | **11829** | **100.0%** | **1.04 [0.73 , 1.49]** |
| Total events: | 70 | | 57 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 5.95, df = 6 (P = 0.43); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.22 (P = 0.83) | | | | | | |
| **6.3.4 Fever** | | | | | | |
| Hallander 2002 | 0 | 124 | 3 | 125 | 22.3% | 0.14 [0.01 , 2.76] |
| Sanchez 1995 Peru | 1 | 175 | 1 | 171 | 25.5% | 0.98 [0.06 , 15.50] |
| Taylor 1999a | 2 | 164 | 2 | 41 | 52.2% | 0.25 [0.04 , 1.72] |
| Trach 2002 | 0 | 71 | 0 | 70 | | Not estimable |
| **Subtotal (95% CI)** | | **534** | | **407** | **100.0%** | **0.31 [0.08 , 1.26]** |
| Total events: | 3 | | 6 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.97, df = 2 (P = 0.61); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.63 (P = 0.10) | | | | | | |
| **6.3.5 Nausea** | | | | | | |
| Begue 1995 | 0 | 311 | 5 | 313 | 18.0% | 0.09 [0.01 , 1.65] |
| Concha 1995 | 15 | 604 | 7 | 709 | 48.4% | 2.52 [1.03 , 6.13] |
| Taylor 1999a | 4 | 164 | 0 | 41 | 17.9% | 2.29 [0.13 , 41.72] |
| Trach 2002 | 1 | 35 | 0 | 36 | 15.8% | 3.08 [0.13 , 73.23] |
| **Subtotal (95% CI)** | | **1114** | | **1099** | **100.0%** | **1.41 [0.32 , 6.13]** |
| Total events: | 20 | | 12 | | | |
| Heterogeneity: Tau² = 0.96; Chi² = 5.13, df = 3 (P = 0.16); I² = 42% | | | | | | |
| Test for overall effect: Z = 0.46 (P = 0.65) | | | | | | |





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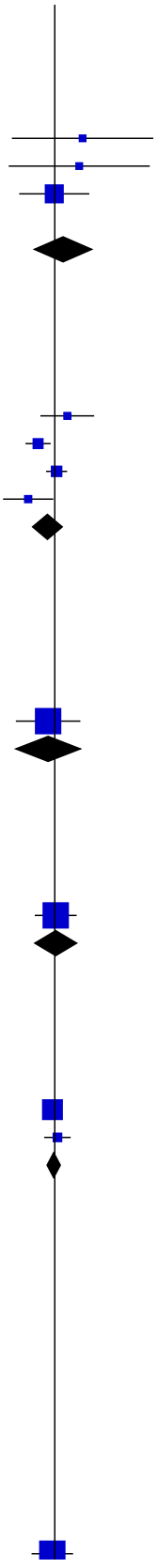
## Analysis 6.3. (Continued)

| | | | | | | |
|---|---|---|---|---|---|---|
| Heterogeneity: Tau² = 0.96; Chi² = 5.13, df = 3 (P = 0.16); I² = 42% | | | | | | |
| Test for overall effect: Z = 0.46 (P = 0.65) | | | | | | |
| **6.3.6 Vomiting** | | | | | | |
| Concha 1995 | 1 | 604 | 0 | 709 | 16.5% | 3.52 [0.14 , 86.26] |
| Hallander 2002 | 1 | 124 | 0 | 125 | 16.6% | 3.02 [0.12 , 73.52] |
| Sanchez 1995 Peru | 3 | 175 | 3 | 171 | 67.0% | 0.98 [0.20 , 4.77] |
| Trach 2002 | 0 | 71 | 0 | 70 | | Not estimable |
| **Subtotal (95% CI)** | | **974** | | **1075** | **100.0%** | **1.46 [0.40 , 5.33]** |
| Total events: | 5 | | 3 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 2 (P = 0.69); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.57 (P = 0.57) | | | | | | |
| **6.3.7 Headache** | | | | | | |
| Begue 1995 | 7 | 311 | 4 | 313 | 17.2% | 1.76 [0.52 , 5.96] |
| Concha 1995 | 16 | 604 | 40 | 709 | 31.0% | 0.47 [0.27 , 0.83] |
| Sanchez 1995 Peru | 30 | 175 | 27 | 171 | 33.2% | 1.09 [0.67 , 1.75] |
| Taylor 1999a | 6 | 164 | 5 | 41 | 18.6% | 0.30 [0.10 , 0.93] |
| **Subtotal (95% CI)** | | **1254** | | **1234** | **100.0%** | **0.72 [0.37 , 1.40]** |
| Total events: | 59 | | 76 | | | |
| Heterogeneity: Tau² = 0.29; Chi² = 9.32, df = 3 (P = 0.03); I² = 68% | | | | | | |
| Test for overall effect: Z = 0.97 (P = 0.33) | | | | | | |
| **6.3.8 Loss of appetite** | | | | | | |
| Hallander 2002 | 0 | 125 | 0 | 124 | | Not estimable |
| Trach 2002 | 3 | 71 | 4 | 70 | 100.0% | 0.74 [0.17 , 3.18] |
| **Subtotal (95% CI)** | | **196** | | **194** | **100.0%** | **0.74 [0.17 , 3.18]** |
| Total events: | 3 | | 4 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.41 (P = 0.69) | | | | | | |
| **6.3.9 Dizziness** | | | | | | |
| Concha 1995 | 8 | 604 | 9 | 709 | 100.0% | 1.04 [0.41 , 2.69] |
| **Subtotal (95% CI)** | | **604** | | **709** | **100.0%** | **1.04 [0.41 , 2.69]** |
| Total events: | 8 | | 9 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.09 (P = 0.93) | | | | | | |
| **6.3.10 Any adverse event** | | | | | | |
| Begue 1995 | 51 | 311 | 57 | 313 | 75.2% | 0.90 [0.64 , 1.27] |
| Taylor 2000 Peru | 23 | 10592 | 20 | 10400 | 24.8% | 1.13 [0.62 , 2.05] |
| **Subtotal (95% CI)** | | **10903** | | **10713** | **100.0%** | **0.95 [0.71 , 1.28]** |
| Total events: | 74 | | 77 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.42, df = 1 (P = 0.52); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.32 (P = 0.75) | | | | | | |
| **6.3.11 Any serious adverse event** | | | | | | |
| Taylor 2000 Peru | 0 | 10592 | 0 | 10400 | | Not estimable |
| Trach 2002 | 0 | 71 | 0 | 70 | | Not estimable |
| **Subtotal (95% CI)** | | **10663** | | **10470** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **6.3.12 Other** | | | | | | |
| Begue 1995 | 8 | 311 | 9 | 313 | 100.0% | 0.89 [0.35 , 2.29] |

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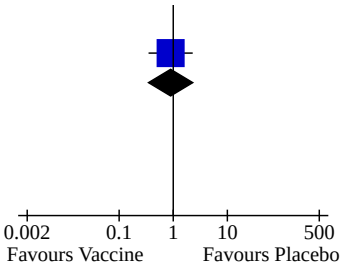
## Analysis 6.3. (Continued)

| | | | | | | |
|---|---|---|---|---|---|---|
| **6.3.12 Other** | | | | | | |
| Begue 1995 | 8 | 311 | 9 | 313 | 100.0% | 0.89 [0.35 , 2.29] |
| **Subtotal (95% CI)** | | **311** | | **313** | **100.0%** | **0.89 [0.35 , 2.29]** |
| Total events: | 8 | | 9 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.23 (P = 0.82) | | | | | | |




**Footnotes**

(1) Begue 1995: Ages 2 to 65 years, 2 days AE monitoring
(2) Concha 1995: Ages 1 to 65 years, 3 days AE monitoring
(3) Hallander 2002: Ages 1 to 12 years, 3 days AE monitoring
(4) Sanchez 1995: Ages 17 to 23, 24 hours AE monitoring
(5) Taylor 1999b: Age 2 to 65 years, 3 days AE monitoring after each dose.
(6) Trach 2002: Ages 1 to 12 years and 17 to 25 years, 3 days AE monitoring
(7) Taylor 2000 Peru: Ages 2 to 65 years, reporting symptoms during the period between dosesults and children 14 days (collected at time of second dose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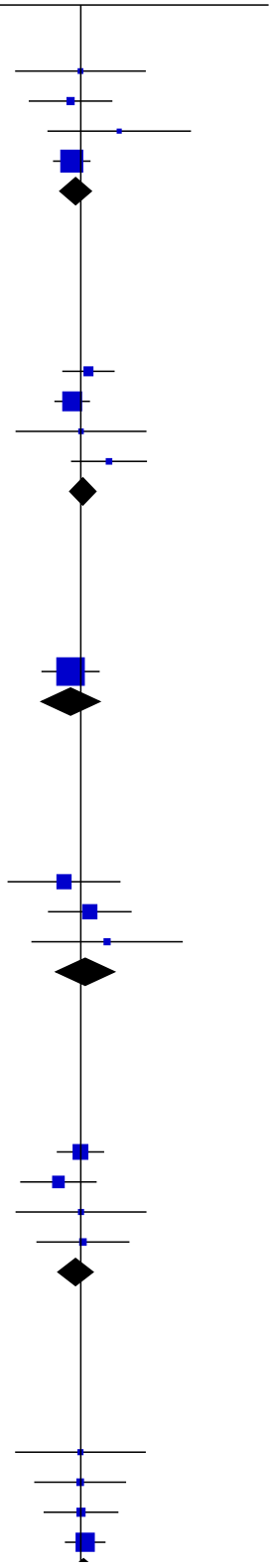
**Analysis 6.4. Comparison 6: Whole cell vaccines (all types) versus placebo - Safety outcomes (first dose), Outcome 4: Adverse events - Bivalent whole cell (BivWC) versus placebo**

| Study or Subgroup | Vaccine Events | Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **6.4.1 Diarrhoea** | | | | | | |
| Anh 2007 (1) | 1 | 77 | 1 | 76 | 5.1% | 0.99 [0.06 , 15.50] |
| Kanungo 2009 (2) | 2 | 81 | 3 | 79 | 15.3% | 0.65 [0.11 , 3.79] |
| Mahalanabis 2008 (3) | 2 | 100 | 0 | 101 | 2.5% | 5.05 [0.25 , 103.87] |
| Sur 2009 India (4) | 10 | 31932 | 16 | 34968 | 77.1% | 0.68 [0.31 , 1.51] |
| **Subtotal (95% CI)** | | **32190** | | **35224** | **100.0%** | **0.80 [0.42 , 1.55]** |
| Total events: | 15 | | 20 | | | |
| Heterogeneity: Chi² = 1.66, df = 3 (P = 0.65); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.65 (P = 0.52) | | | | | | |
| **6.4.2 Abdo pain** | | | | | | |
| Anh 2007 | 7 | 77 | 5 | 76 | 22.8% | 1.38 [0.46 , 4.16] |
| Kanungo 2009 | 10 | 81 | 14 | 79 | 64.1% | 0.70 [0.33 , 1.47] |
| Mahalanabis 2008 | 1 | 100 | 1 | 101 | 4.5% | 1.01 [0.06 , 15.93] |
| Sur 2009 India | 6 | 31932 | 2 | 34968 | 8.6% | 3.29 [0.66 , 16.28] |
| **Subtotal (95% CI)** | | **32190** | | **35224** | **100.0%** | **1.09 [0.63 , 1.88]** |
| Total events: | 24 | | 22 | | | |
| Heterogeneity: Chi² = 3.38, df = 3 (P = 0.34); I² = 11% | | | | | | |
| Test for overall effect: Z = 0.31 (P = 0.76) | | | | | | |
| **6.4.3 Gas** | | | | | | |
| Kanungo 2009 | 4 | 81 | 6 | 79 | 100.0% | 0.65 [0.19 , 2.22] |
| **Subtotal (95% CI)** | | **81** | | **79** | **100.0%** | **0.65 [0.19 , 2.22]** |
| Total events: | 4 | | 6 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.69 (P = 0.49) | | | | | | |
| **6.4.4 Loss of appetite** | | | | | | |
| Anh 2007 | 1 | 77 | 2 | 76 | 44.4% | 0.49 [0.05 , 5.33] |
| Kanungo 2009 | 3 | 81 | 2 | 79 | 44.6% | 1.46 [0.25 , 8.52] |
| Mahalanabis 2008 | 1 | 100 | 0 | 101 | 11.0% | 3.03 [0.12 , 73.50] |
| **Subtotal (95% CI)** | | **258** | | **256** | **100.0%** | **1.20 [0.35 , 4.13]** |
| Total events: | 5 | | 4 | | | |
| Heterogeneity: Chi² = 0.91, df = 2 (P = 0.63); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.30 (P = 0.77) | | | | | | |
| **6.4.5 Nausea** | | | | | | |
| Anh 2007 | 7 | 77 | 7 | 76 | 46.9% | 0.99 [0.36 , 2.68] |
| Kanungo 2009 | 2 | 81 | 5 | 79 | 33.7% | 0.39 [0.08 , 1.95] |
| Mahalanabis 2008 | 1 | 100 | 1 | 101 | 6.6% | 1.01 [0.06 , 15.93] |
| Sur 2009 India | 2 | 31932 | 2 | 34968 | 12.7% | 1.10 [0.15 , 7.77] |
| **Subtotal (95% CI)** | | **32190** | | **35224** | **100.0%** | **0.80 [0.38 , 1.67]** |
| Total events: | 12 | | 15 | | | |
| Heterogeneity: Chi² = 1.06, df = 3 (P = 0.79); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.59 (P = 0.55) | | | | | | |
| **6.4.6 Vomiting** | | | | | | |
| Anh 2007 | 1 | 77 | 1 | 76 | 6.5% | 0.99 [0.06 , 15.50] |
| Kanungo 2009 | 2 | 81 | 2 | 79 | 13.0% | 0.98 [0.14 , 6.76] |
| Mahalanabis 2008 | 3 | 100 | 3 | 101 | 19.2% | 1.01 [0.21 , 4.89] |
| Sur 2009 India | 11 | 31932 | 10 | 34968 | 61.3% | 1.20 [0.51 , 2.84] |

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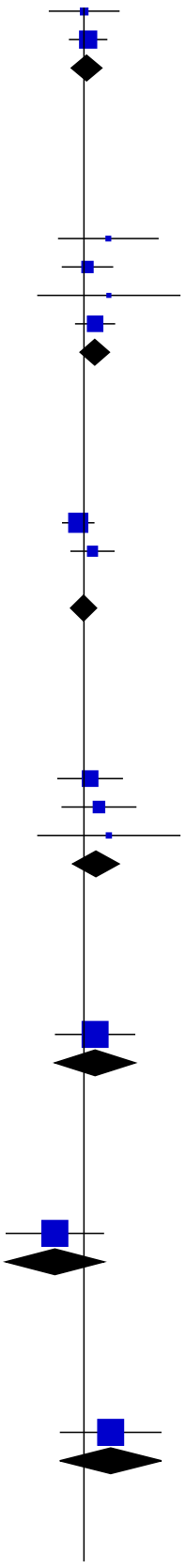
## Analysis 6.4. (Continued)

| | | | | | | |
|---|---|---|---|---|---|---|
| Sur 2009 India | 11 | 31932 | 10 | 34968 | 61.3% | 1.20 [0.51 , 2.84] |
| **Subtotal (95% CI)** | | **32190** | | **35224** | **100.0%** | **1.12 [0.57 , 2.21]** |
| Total events: | 17 | | 16 | | | |
| Heterogeneity: Chi² = 0.07, df = 3 (P = 0.99); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.34 (P = 0.74) | | | | | | |
| **6.4.7 Fever** | | | | | | |
| Anh 2007 | 3 | 77 | 1 | 76 | 7.1% | 2.96 [0.31 , 27.84] |
| Kanungo 2009 | 6 | 81 | 5 | 79 | 35.6% | 1.17 [0.37 , 3.68] |
| Mahalanabis 2008 | 1 | 100 | 0 | 101 | 3.5% | 3.03 [0.12 , 73.50] |
| Sur 2009 India | 12 | 31932 | 8 | 34968 | 53.8% | 1.64 [0.67 , 4.02] |
| **Subtotal (95% CI)** | | **32190** | | **35224** | **100.0%** | **1.62 [0.84 , 3.10]** |
| Total events: | 22 | | 14 | | | |
| Heterogeneity: Chi² = 0.74, df = 3 (P = 0.86); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.44 (P = 0.15) | | | | | | |
| **6.4.8 Headache** | | | | | | |
| Anh 2007 | 11 | 77 | 14 | 76 | 69.9% | 0.78 [0.38 , 1.60] |
| Kanungo 2009 | 9 | 81 | 6 | 79 | 30.1% | 1.46 [0.55 , 3.92] |
| Mahalanabis 2008 | 0 | 100 | 0 | 101 | | Not estimable |
| **Subtotal (95% CI)** | | **258** | | **256** | **100.0%** | **0.98 [0.55 , 1.75]** |
| Total events: | 20 | | 20 | | | |
| Heterogeneity: Chi² = 1.04, df = 1 (P = 0.31); I² = 4% | | | | | | |
| Test for overall effect: Z = 0.06 (P = 0.95) | | | | | | |
| **6.4.9 General ill feeling** | | | | | | |
| Anh 2007 | 4 | 77 | 3 | 76 | 54.5% | 1.32 [0.30 , 5.68] |
| Kanungo 2009 | 4 | 81 | 2 | 79 | 36.5% | 1.95 [0.37 , 10.35] |
| Mahalanabis 2008 | 1 | 100 | 0 | 101 | 9.0% | 3.03 [0.12 , 73.50] |
| **Subtotal (95% CI)** | | **258** | | **256** | **100.0%** | **1.70 [0.61 , 4.77]** |
| Total events: | 9 | | 5 | | | |
| Heterogeneity: Chi² = 0.27, df = 2 (P = 0.87); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.01 (P = 0.31) | | | | | | |
| **6.4.10 Rash** | | | | | | |
| Sur 2009 India | 3 | 31932 | 2 | 34968 | 100.0% | 1.64 [0.27 , 9.83] |
| **Subtotal (95% CI)** | | **31932** | | **34968** | **100.0%** | **1.64 [0.27 , 9.83]** |
| Total events: | 3 | | 2 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.54 (P = 0.59) | | | | | | |
| **6.4.11 Weakness** | | | | | | |
| Sur 2009 India | 1 | 31932 | 4 | 34968 | 100.0% | 0.27 [0.03 , 2.45] |
| **Subtotal (95% CI)** | | **31932** | | **34968** | **100.0%** | **0.27 [0.03 , 2.45]** |
| Total events: | 1 | | 4 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.16 (P = 0.25) | | | | | | |
| **6.4.12 Itch** | | | | | | |
| Sur 2009 India | 3 | 31932 | 1 | 34968 | 100.0% | 3.29 [0.34 , 31.58] |
| **Subtotal (95% CI)** | | **31932** | | **34968** | **100.0%** | **3.29 [0.34 , 31.58]** |
| Total events: | 3 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.03 (P = 0.30) | | | | | | |

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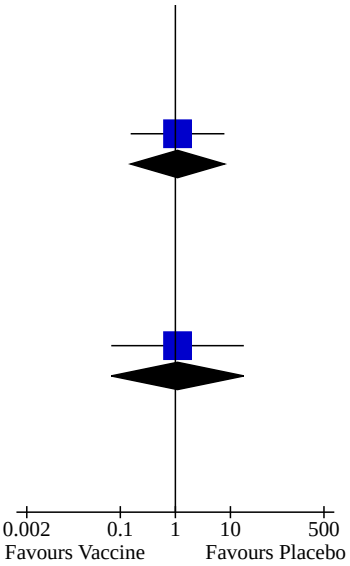
## Analysis 6.4. (Continued)

| | | | | | | |
|---|---|---|---|---|---|---|
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.03 (P = 0.30) | | | | | | |
| **6.4.13 Cough** | | | | | | |
| Sur 2009 India | 2 | 31932 | 2 | 34968 | 100.0% | 1.10 [0.15 , 7.77] |
| **Subtotal (95% CI)** | | **31932** | | **34968** | **100.0%** | **1.10 [0.15 , 7.77]** |
| Total events: | 2 | | 2 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.09 (P = 0.93) | | | | | | |
| **6.4.14 Dizziness** | | | | | | |
| Sur 2009 India | 1 | 31932 | 1 | 34968 | 100.0% | 1.10 [0.07 , 17.51] |
| **Subtotal (95% CI)** | | **31932** | | **34968** | **100.0%** | **1.10 [0.07 , 17.51]** |
| Total events: | 1 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.06 (P = 0.95) | | | | | | |




**Footnotes**

(1) Anh 2007: Ages 18 to 40, 3 days of AE monitoring after each dose
(2) Kanungo 2009: Ages 1 to 40 yrs, 3 days of AE monitoringafter each dose
(3) Mahalanabis 2008: Ages 1 to 40, 3 days of AE monitoring after each dose
(4) Sur 2009: Age >1 yr, passively reporting symptoms within 14 days of the 1st dose

## Comparison 7. Whole cell vaccines (all types) versus placebo - Safety outcomes (second dose)

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 7.1 Adverse events - Whole cell plus recombinant B subunit (WC-rBS) versus placebo | 5 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 7.1.1 Abdominal pain or stomach cramps | 5 | 2061 | Risk Ratio (M-H, Fixed, 95% CI) | 0.95 [0.69, 1.32] |
| 7.1.2 Stomach gurgling | 2 | 556 | Risk Ratio (M-H, Fixed, 95% CI) | 7.82 [4.36, 14.03] |
| 7.1.3 Diarrhoea | 5 | 2061 | Risk Ratio (M-H, Fixed, 95% CI) | 1.20 [0.70, 2.05] |
| 7.1.4 Fever | 4 | 896 | Risk Ratio (M-H, Fixed, 95% CI) | 1.19 [0.34, 4.20] |
| 7.1.5 Nausea | 3 | 1438 | Risk Ratio (M-H, Fixed, 95% CI) | 1.04 [0.26, 4.06] |
| 7.1.6 Vomiting | 4 | 1859 | Risk Ratio (M-H, Fixed, 95% CI) | 2.13 [0.54, 8.44] |
| 7.1.7 Headache | 3 | 1674 | Risk Ratio (M-H, Fixed, 95% CI) | 1.26 [0.79, 1.99] |
| 7.1.8 Loss of appetite | 2 | 387 | Risk Ratio (M-H, Fixed, 95% CI) | 6.80 [0.36, 129.27] |
| 7.1.9 Dizziness | 1 | 1165 | Risk Ratio (M-H, Fixed, 95% CI) | 4.79 [0.54, 42.75] |
| 7.1.10 Any adverse event | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |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| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 7.1.11 Any serious adverse event | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 7.1.12 Other | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 7.2 Adverse events - Bivalent whole cell (BivWC) versus placebo | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 7.2.1 Diarrhoea | 4 | 67397 | Risk Ratio (M-H, Fixed, 95% CI) | 1.17 [0.53, 2.57] |
| 7.2.2 Abdo pain | 4 | 67397 | Risk Ratio (M-H, Fixed, 95% CI) | 1.41 [0.64, 3.12] |
| 7.2.3 Gas | 1 | 155 | Risk Ratio (M-H, Fixed, 95% CI) | 0.68 [0.12, 3.93] |
| 7.2.4 Loss of appetite | 3 | 497 | Risk Ratio (M-H, Fixed, 95% CI) | 9.12 [0.50, 166.49] |
| 7.2.5 Nausea | 4 | 67397 | Risk Ratio (M-H, Fixed, 95% CI) | 5.08 [1.12, 22.92] |
| 7.2.6 Vomiting | 4 | 67397 | Risk Ratio (M-H, Fixed, 95% CI) | 0.91 [0.41, 2.01] |
| 7.2.7 Fever | 4 | 67397 | Risk Ratio (M-H, Fixed, 95% CI) | 0.97 [0.46, 2.04] |
| 7.2.8 Headache | 3 | 497 | Risk Ratio (M-H, Fixed, 95% CI) | 1.24 [0.59, 2.62] |
| 7.2.9 General ill feeling | 3 | 497 | Risk Ratio (M-H, Fixed, 95% CI) | 1.22 [0.36, 4.15] |
| 7.2.10 Rash | 1 | 66900 | Risk Ratio (M-H, Fixed, 95% CI) | 0.37 [0.01, 8.96] |
| 7.2.11 Weakness | 1 | 66900 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 7.2.12 Itch | 1 | 66900 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 7.2.13 Cough | 1 | 66900 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 7.2.14 Dizziness | 1 | 66900 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |


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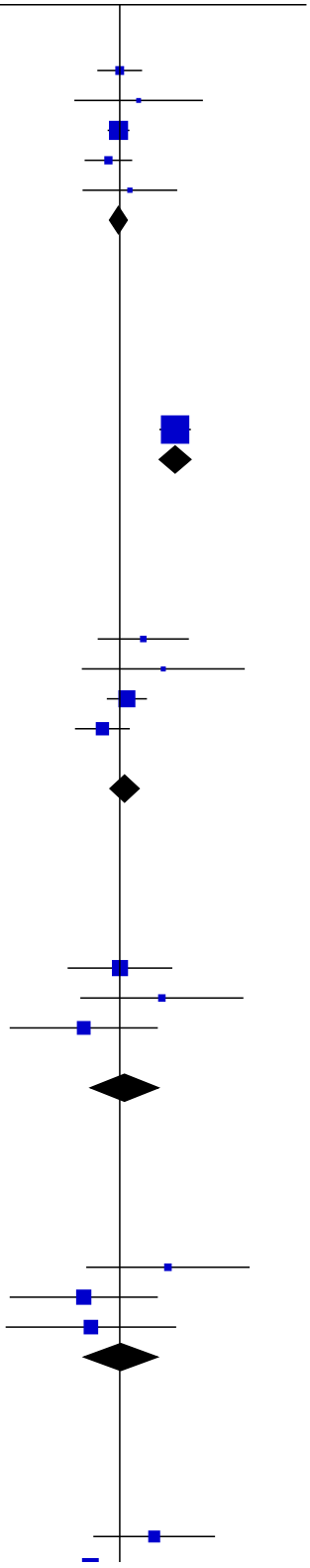
**Analysis 7.1. Comparison 7: Whole cell vaccines (all types) versus placebo - Safety outcomes (second dose), Outcome 1: Adverse events - Whole cell plus recombinant B subunit (WC-rBS) versus placebo**

| Study or Subgroup | Vaccine Events | Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **7.1.1 Abdominal pain or stomach cramps** | | | | | | |
| Concha 1995 | 10 | 530 | 12 | 635 | 18.1% | 1.00 [0.43 , 2.29] |
| Hallander 2002 | 2 | 124 | 1 | 125 | 1.7% | 2.02 [0.19 , 21.95] |
| Sanchez 1995 Peru | 36 | 157 | 36 | 150 | 61.1% | 0.96 [0.64 , 1.43] |
| Taylor 1999a | 15 | 160 | 6 | 42 | 15.8% | 0.66 [0.27 , 1.59] |
| Trach 2002 | 3 | 70 | 2 | 68 | 3.4% | 1.46 [0.25 , 8.45] |
| **Subtotal (95% CI)** | | **1041** | | **1020** | **100.0%** | **0.95 [0.69 , 1.32]** |
| Total events: | 66 | | 57 | | | |
| Heterogeneity: Chi² = 1.30, df = 4 (P = 0.86); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.30 (P = 0.76) | | | | | | |
| **7.1.2 Stomach gurgling** | | | | | | |
| Hallander 2002 | 0 | 124 | 0 | 125 | | Not estimable |
| Sanchez 1995 Peru | 90 | 157 | 11 | 150 | 100.0% | 7.82 [4.36 , 14.03] |
| **Subtotal (95% CI)** | | **281** | | **275** | **100.0%** | **7.82 [4.36 , 14.03]** |
| Total events: | 90 | | 11 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 6.89 (P < 0.00001) | | | | | | |
| **7.1.3 Diarrhoea** | | | | | | |
| Concha 1995 | 4 | 530 | 2 | 635 | 8.5% | 2.40 [0.44 , 13.03] |
| Hallander 2002 | 2 | 124 | 0 | 125 | 2.3% | 5.04 [0.24 , 103.93] |
| Sanchez 1995 Peru | 15 | 157 | 11 | 150 | 52.4% | 1.30 [0.62 , 2.74] |
| Taylor 1999a | 10 | 160 | 5 | 42 | 36.9% | 0.53 [0.19 , 1.45] |
| Trach 2002 | 0 | 70 | 0 | 68 | | Not estimable |
| **Subtotal (95% CI)** | | **1041** | | **1020** | **100.0%** | **1.20 [0.70 , 2.05]** |
| Total events: | 31 | | 18 | | | |
| Heterogeneity: Chi² = 4.08, df = 3 (P = 0.25); I² = 26% | | | | | | |
| Test for overall effect: Z = 0.65 (P = 0.52) | | | | | | |
| **7.1.4 Fever** | | | | | | |
| Hallander 2002 | 2 | 124 | 2 | 125 | 48.7% | 1.01 [0.14 , 7.04] |
| Sanchez 1995 Peru | 2 | 157 | 0 | 150 | 12.5% | 4.78 [0.23 , 98.72] |
| Taylor 1999a | 1 | 160 | 1 | 42 | 38.8% | 0.26 [0.02 , 4.11] |
| Trach 2002 | 0 | 70 | 0 | 68 | | Not estimable |
| **Subtotal (95% CI)** | | **511** | | **385** | **100.0%** | **1.19 [0.34 , 4.20]** |
| Total events: | 5 | | 3 | | | |
| Heterogeneity: Chi² = 2.00, df = 2 (P = 0.37); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.27 (P = 0.79) | | | | | | |
| **7.1.5 Nausea** | | | | | | |
| Concha 1995 | 2 | 530 | 0 | 635 | 12.9% | 5.99 [0.29 , 124.47] |
| Taylor 1999a | 1 | 160 | 1 | 42 | 45.0% | 0.26 [0.02 , 4.11] |
| Trach 2002 | 0 | 35 | 1 | 36 | 42.0% | 0.34 [0.01 , 8.14] |
| **Subtotal (95% CI)** | | **725** | | **713** | **100.0%** | **1.04 [0.26 , 4.06]** |
| Total events: | 3 | | 2 | | | |
| Heterogeneity: Chi² = 2.71, df = 2 (P = 0.26); I² = 26% | | | | | | |
| Test for overall effect: Z = 0.05 (P = 0.96) | | | | | | |
| **7.1.6 Vomiting** | | | | | | |
| Concha 1995 | 3 | 530 | 1 | 635 | 31.2% | 3.59 [0.37 , 34.45] |
| Hallander 2002 | 0 | 124 | 1 | 125 | 51.2% | 0.34 [0.01 , 8.17] |

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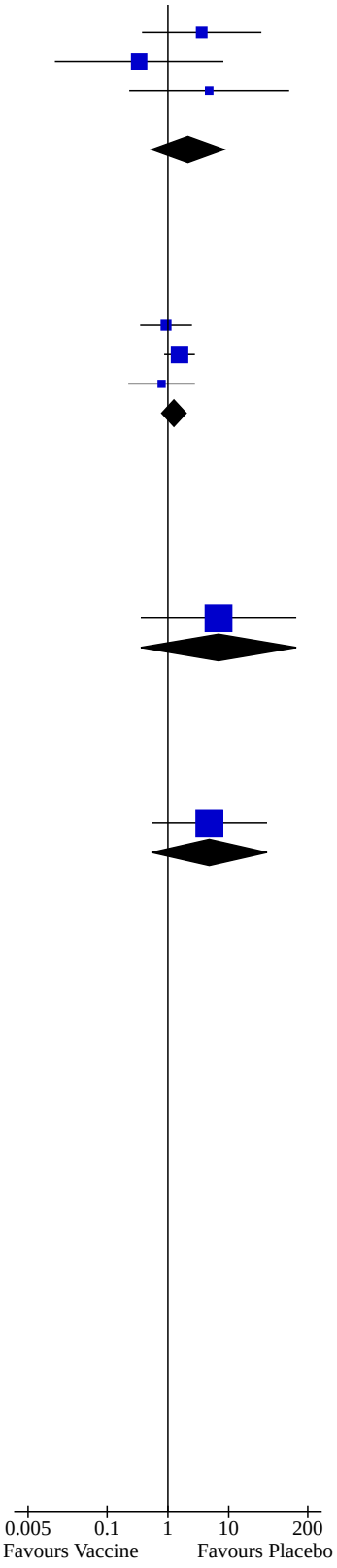
## Analysis 7.1. (Continued)

| | | | | | | |
|---|---|---|---|---|---|---|
| Concha 1995 | 3 | 530 | 1 | 635 | 31.2% | 3.59 [0.37 , 34.45] |
| Hallander 2002 | 0 | 124 | 1 | 125 | 51.2% | 0.34 [0.01 , 8.17] |
| Sanchez 1995 Peru | 2 | 157 | 0 | 150 | 17.5% | 4.78 [0.23 , 98.72] |
| Trach 2002 | 0 | 70 | 0 | 68 | | Not estimable |
| **Subtotal (95% CI)** | | **881** | | **978** | **100.0%** | **2.13 [0.54 , 8.44]** |
| Total events: | 5 | | 2 | | | |
| Heterogeneity: Chi² = 1.77, df = 2 (P = 0.41); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.08 (P = 0.28) | | | | | | |
| **7.1.7 Headache** | | | | | | |
| Concha 1995 | 7 | 530 | 9 | 635 | 27.9% | 0.93 [0.35 , 2.49] |
| Sanchez 1995 Peru | 26 | 157 | 16 | 150 | 55.8% | 1.55 [0.87 , 2.78] |
| Taylor 1999a | 9 | 160 | 3 | 42 | 16.2% | 0.79 [0.22 , 2.78] |
| **Subtotal (95% CI)** | | **847** | | **827** | **100.0%** | **1.26 [0.79 , 1.99]** |
| Total events: | 42 | | 28 | | | |
| Heterogeneity: Chi² = 1.39, df = 2 (P = 0.50); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.97 (P = 0.33) | | | | | | |
| **7.1.8 Loss of appetite** | | | | | | |
| Hallander 2002 | 0 | 124 | 0 | 125 | | Not estimable |
| Trach 2002 | 3 | 70 | 0 | 68 | 100.0% | 6.80 [0.36 , 129.27] |
| **Subtotal (95% CI)** | | **194** | | **193** | **100.0%** | **6.80 [0.36 , 129.27]** |
| Total events: | 3 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.28 (P = 0.20) | | | | | | |
| **7.1.9 Dizziness** | | | | | | |
| Concha 1995 | 4 | 530 | 1 | 635 | 100.0% | 4.79 [0.54 , 42.75] |
| **Subtotal (95% CI)** | | **530** | | **635** | **100.0%** | **4.79 [0.54 , 42.75]** |
| Total events: | 4 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.40 (P = 0.16) | | | | | | |
| **7.1.10 Any adverse event** | | | | | | |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **7.1.11 Any serious adverse event** | | | | | | |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **7.1.12 Other** | | | | | | |
| **Subtotal (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |





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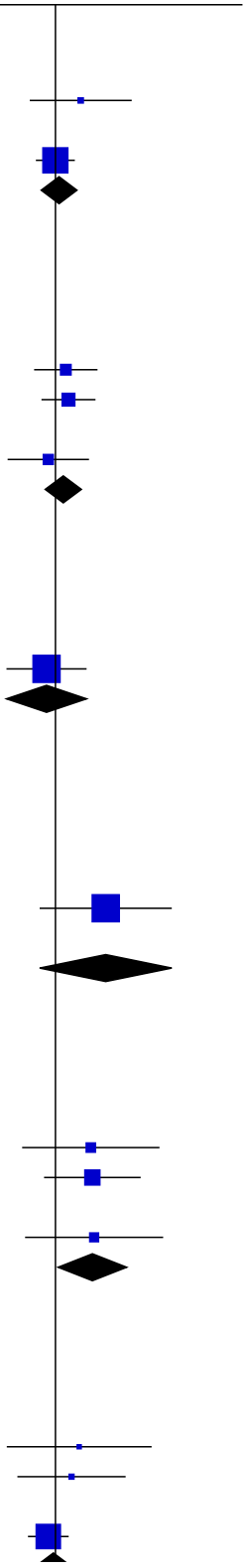
**Analysis 7.2. Comparison 7: Whole cell vaccines (all types) versus placebo - Safety outcomes (second dose), Outcome 2: Adverse events - Bivalent whole cell (BivWC) versus placebo**

| Study or Subgroup | Vaccine Events | Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **7.2.1 Diarrhoea** | | | | | | |
| Anh 2007 | 0 | 74 | 0 | 70 | | Not estimable |
| Kanungo 2009 | 3 | 77 | 1 | 78 | 8.6% | 3.04 [0.32 , 28.58] |
| Mahalanabis 2008 | 0 | 98 | 0 | 100 | | Not estimable |
| Sur 2009 India (1) | 10 | 31932 | 11 | 34968 | 91.4% | 1.00 [0.42 , 2.34] |
| **Subtotal (95% CI)** | | **32181** | | **35216** | **100.0%** | **1.17 [0.53 , 2.57]** |
| Total events: | 13 | | 12 | | | |
| Heterogeneity: Chi² = 0.83, df = 1 (P = 0.36); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.40 (P = 0.69) | | | | | | |
| **7.2.2 Abdo pain** | | | | | | |
| Anh 2007 | 5 | 74 | 3 | 70 | 31.1% | 1.58 [0.39 , 6.35] |
| Kanungo 2009 | 7 | 77 | 4 | 78 | 40.1% | 1.77 [0.54 , 5.81] |
| Mahalanabis 2008 | 0 | 98 | 0 | 100 | | Not estimable |
| Sur 2009 India | 2 | 31932 | 3 | 34968 | 28.9% | 0.73 [0.12 , 4.37] |
| **Subtotal (95% CI)** | | **32181** | | **35216** | **100.0%** | **1.41 [0.64 , 3.12]** |
| Total events: | 14 | | 10 | | | |
| Heterogeneity: Chi² = 0.69, df = 2 (P = 0.71); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.85 (P = 0.40) | | | | | | |
| **7.2.3 Gas** | | | | | | |
| Kanungo 2009 | 2 | 77 | 3 | 78 | 100.0% | 0.68 [0.12 , 3.93] |
| **Subtotal (95% CI)** | | **77** | | **78** | **100.0%** | **0.68 [0.12 , 3.93]** |
| Total events: | 2 | | 3 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.44 (P = 0.66) | | | | | | |
| **7.2.4 Loss of appetite** | | | | | | |
| Anh 2007 | 0 | 74 | 0 | 70 | | Not estimable |
| Kanungo 2009 | 4 | 77 | 0 | 78 | 100.0% | 9.12 [0.50 , 166.49] |
| Mahalanabis 2008 | 0 | 98 | 0 | 100 | | Not estimable |
| **Subtotal (95% CI)** | | **249** | | **248** | **100.0%** | **9.12 [0.50 , 166.49]** |
| Total events: | 4 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.49 (P = 0.14) | | | | | | |
| **7.2.5 Nausea** | | | | | | |
| Anh 2007 | 2 | 74 | 0 | 70 | 25.9% | 4.73 [0.23 , 96.89] |
| Kanungo 2009 | 5 | 77 | 1 | 78 | 50.1% | 5.06 [0.61 , 42.36] |
| Mahalanabis 2008 | 0 | 98 | 0 | 100 | | Not estimable |
| Sur 2009 India | 2 | 31932 | 0 | 34968 | 24.1% | 5.48 [0.26 , 114.04] |
| **Subtotal (95% CI)** | | **32181** | | **35216** | **100.0%** | **5.08 [1.12 , 22.92]** |
| Total events: | 9 | | 1 | | | |
| Heterogeneity: Chi² = 0.00, df = 2 (P = 1.00); I² = 0% | | | | | | |
| Test for overall effect: Z = 2.11 (P = 0.03) | | | | | | |
| **7.2.6 Vomiting** | | | | | | |
| Anh 2007 | 1 | 74 | 0 | 70 | 4.0% | 2.84 [0.12 , 68.57] |
| Kanungo 2009 | 2 | 77 | 1 | 78 | 7.7% | 2.03 [0.19 , 21.88] |
| Mahalanabis 2008 | 0 | 98 | 0 | 100 | | Not estimable |
| Sur 2009 India | 8 | 31932 | 12 | 34968 | 88.4% | 0.73 [0.30 , 1.79] |
| **Subtotal (95% CI)** | | **32181** | | **35216** | **100.0%** | **0.91 [0.41 , 2.01]** |

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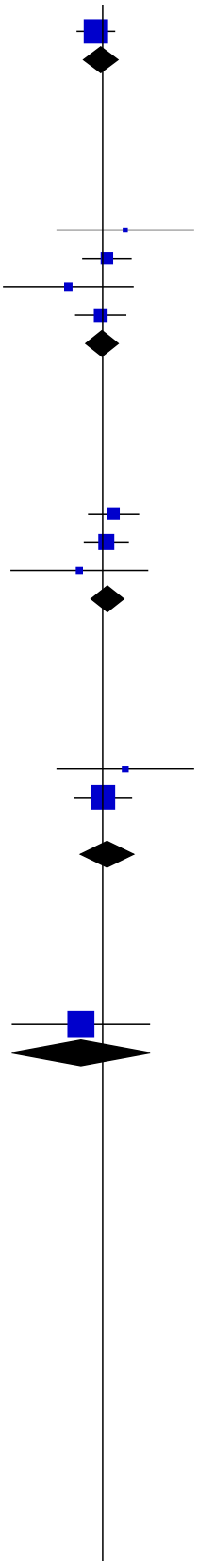
## Analysis 7.2. (Continued)

| | | | | | | |
|---|---|---|---|---|---|---|
| Sur 2009 India | 8 | 31932 | 12 | 34968 | 88.4% | 0.73 [0.30 , 1.79] |
| **Subtotal (95% CI)** | | **32181** | | **35216** | **100.0%** | **0.91 [0.41 , 2.01]** |
| Total events: | 11 | | 13 | | | |
| Heterogeneity: Chi² = 1.16, df = 2 (P = 0.56); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.23 (P = 0.82) | | | | | | |
| | | | | | | |
| **7.2.7 Fever** | | | | | | |
| Anh 2007 | 1 | 74 | 0 | 70 | 3.8% | 2.84 [0.12 , 68.57] |
| Kanungo 2009 | 6 | 77 | 5 | 78 | 36.3% | 1.22 [0.39 , 3.82] |
| Mahalanabis 2008 | 0 | 98 | 2 | 100 | 18.1% | 0.20 [0.01 , 4.20] |
| Sur 2009 India | 5 | 31932 | 6 | 34968 | 41.9% | 0.91 [0.28 , 2.99] |
| **Subtotal (95% CI)** | | **32181** | | **35216** | **100.0%** | **0.97 [0.46 , 2.04]** |
| Total events: | 12 | | 13 | | | |
| Heterogeneity: Chi² = 1.62, df = 3 (P = 0.65); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.09 (P = 0.93) | | | | | | |
| | | | | | | |
| **7.2.8 Headache** | | | | | | |
| Anh 2007 | 7 | 74 | 4 | 70 | 35.6% | 1.66 [0.51 , 5.41] |
| Kanungo 2009 | 7 | 77 | 6 | 78 | 51.6% | 1.18 [0.42 , 3.36] |
| Mahalanabis 2008 | 0 | 98 | 1 | 100 | 12.8% | 0.34 [0.01 , 8.25] |
| **Subtotal (95% CI)** | | **249** | | **248** | **100.0%** | **1.24 [0.59 , 2.62]** |
| Total events: | 14 | | 11 | | | |
| Heterogeneity: Chi² = 0.87, df = 2 (P = 0.65); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.57 (P = 0.57) | | | | | | |
| | | | | | | |
| **7.2.9 General ill feeling** | | | | | | |
| Anh 2007 | 1 | 74 | 0 | 70 | 11.4% | 2.84 [0.12 , 68.57] |
| Kanungo 2009 | 4 | 77 | 4 | 78 | 88.6% | 1.01 [0.26 , 3.91] |
| Mahalanabis 2008 | 0 | 98 | 0 | 100 | | Not estimable |
| **Subtotal (95% CI)** | | **249** | | **248** | **100.0%** | **1.22 [0.36 , 4.15]** |
| Total events: | 5 | | 4 | | | |
| Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.32 (P = 0.75) | | | | | | |
| | | | | | | |
| **7.2.10 Rash** | | | | | | |
| Sur 2009 India | 0 | 31932 | 1 | 34968 | 100.0% | 0.37 [0.01 , 8.96] |
| **Subtotal (95% CI)** | | **31932** | | **34968** | **100.0%** | **0.37 [0.01 , 8.96]** |
| Total events: | 0 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.62 (P = 0.54) | | | | | | |
| | | | | | | |
| **7.2.11 Weakness** | | | | | | |
| Sur 2009 India | 0 | 31932 | 0 | 34968 | | Not estimable |
| **Subtotal (95% CI)** | | **31932** | | **34968** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| | | | | | | |
| **7.2.12 Itch** | | | | | | |
| Sur 2009 India | 0 | 31932 | 0 | 34968 | | Not estimable |
| **Subtotal (95% CI)** | | **31932** | | **34968** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |

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## Analysis 7.2. (Continued)

Test for overall effect: Not applicable

**7.2.13 Cough**

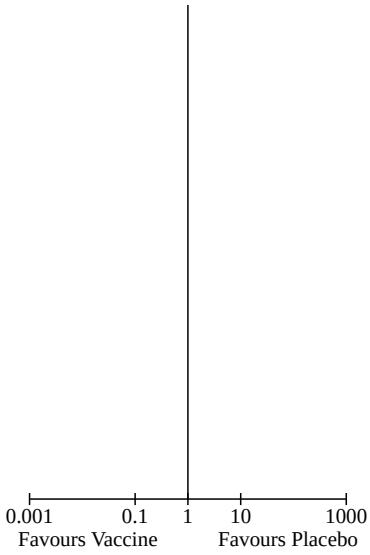
| | | | | | |
|---|---|---|---|---|---|
| Sur 2009 India | 0 | 31932 | 0 | 34968 | Not estimable |
| **Subtotal (95% CI)** | | **31932** | | **34968** | **Not estimable** |
| Total events: | 0 | | 0 | | |

Heterogeneity: Not applicable
Test for overall effect: Not applicable

**7.2.14 Dizziness**

| | | | | | |
|---|---|---|---|---|---|
| Sur 2009 India | 0 | 31932 | 0 | 34968 | Not estimable |
| **Subtotal (95% CI)** | | **31932** | | **34968** | **Not estimable** |
| Total events: | 0 | | 0 | | |

Heterogeneity: Not applicable
Test for overall effect: Not applicable




**Footnotes**

(1) Sur 2009 includes age >1 yr reporting symptoms within 14 days of the 1st dose

## Comparison 8. Live attenuated vaccines (all types) versus placebo - Efficacy outcomes

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 8.1 Cases of cholera following natural infection - CVD 103HgR versus placebo | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 8.1.1 First year after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 8.1.2 Second year after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 8.1.3 Third year after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 8.2 Severe cholera following natural infection - CVD 103HgR versus placebo | 1 | 67508 | Risk Ratio (M-H, Fixed, 95% CI) | 1.58 [0.61, 4.07] |
| 8.3 Death from any cause (except motor accidents) | 1 | 67508 | Risk Ratio (M-H, Fixed, 95% CI) | 1.03 [0.83, 1.28] |
| 8.4 Death from diarrhoea (any organism) | 1 | 67508 | Risk Ratio (M-H, Fixed, 95% CI) | 0.75 [0.26, 2.17] |
| 8.5 Cases of moderate to severe diarrhoea - following artificial challenge | 3 | 108 | Risk Ratio (M-H, Fixed, 95% CI) | 0.08 [0.02, 0.34] |
| 8.5.1 CVD 103HgR | 1 | 51 | Risk Ratio (M-H, Fixed, 95% CI) | 0.09 [0.01, 0.67] |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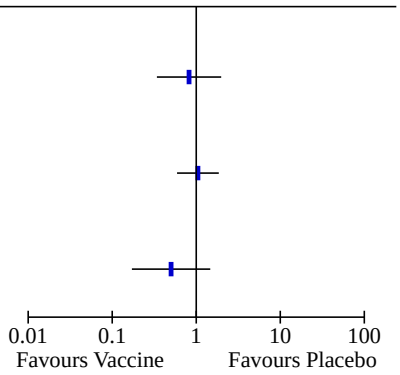
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 8.5.2 Peru 15 | 1 | 36 | Risk Ratio (M-H, Fixed, 95% CI) | 0.05 [0.00, 0.79] |
| 8.5.3 VC638 | 1 | 21 | Risk Ratio (M-H, Fixed, 95% CI) | 0.15 [0.01, 2.86] |
| 8.6 Cases of any diarrhoea -following artificial challenge | 3 | 108 | Risk Ratio (M-H, Fixed, 95% CI) | 0.14 [0.07, 0.28] |
| 8.6.1 CVD 103HgR | 1 | 51 | Risk Ratio (M-H, Fixed, 95% CI) | 0.20 [0.09, 0.44] |
| 8.6.2 Peru 15 | 1 | 36 | Risk Ratio (M-H, Fixed, 95% CI) | 0.07 [0.01, 0.52] |
| 8.6.3 VC638 | 1 | 21 | Risk Ratio (M-H, Fixed, 95% CI) | 0.05 [0.00, 0.80] |

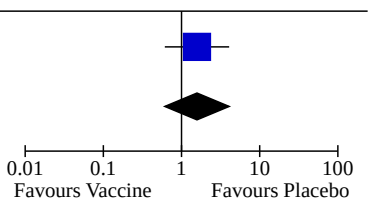
**Analysis 8.1. Comparison 8: Live attenuated vaccines (all types) versus placebo - Efficacy outcomes, Outcome 1: Cases of cholera following natural infection - CVD 103HgR versus placebo**

| Study or Subgroup | Vaccine Events | Vaccine Total | Placebo Events | Placebo Total | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **8.1.1 First year after vaccination** | | | | | |
| Richie 2000 Indonesia | 9 | 33696 | 11 | 33812 | 0.82 [0.34 , 1.98] |
| **8.1.2 Second year after vaccination** | | | | | |
| Richie 2000 Indonesia | 24 | 33696 | 23 | 33812 | 1.05 [0.59 , 1.85] |
| **8.1.3 Third year after vaccination** | | | | | |
| Richie 2000 Indonesia | 5 | 33696 | 10 | 33812 | 0.50 [0.17 , 1.47] |




**Analysis 8.2. Comparison 8: Live attenuated vaccines (all types) versus placebo - Efficacy outcomes, Outcome 2: Severe cholera following natural infection - CVD 103HgR versus placebo**

| Study or Subgroup | Vaccine Events | Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Richie 2000 Indonesia | 11 | 33696 | 7 | 33812 | 100.0% | 1.58 [0.61 , 4.07] |
| **Total (95% CI)** | | **33696** | | **33812** | **100.0%** | **1.58 [0.61 , 4.07]** |
| Total events: | 11 | | 7 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.94 (P = 0.35) | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | |





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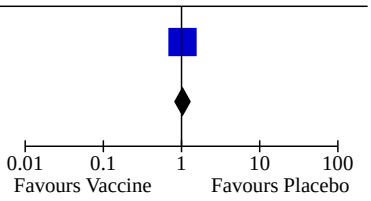
### Analysis 8.3. Comparison 8: Live attenuated vaccines (all types) versus placebo - Efficacy outcomes, Outcome 3: Death from any cause (except motor accidents)

| Study or Subgroup | Vaccine Events | Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Richie 2000 Indonesia | 159 | 33696 | 155 | 33812 | 100.0% | 1.03 [0.83 , 1.28] |
| **Total (95% CI)** | | **33696** | | **33812** | **100.0%** | **1.03 [0.83 , 1.28]** |
| Total events: | 159 | | 155 | | | |

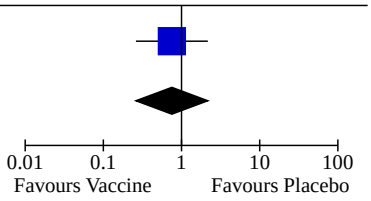
Heterogeneity: Not applicable
Test for overall effect: Z = 0.26 (P = 0.80)
Test for subgroup differences: Not applicable




### Analysis 8.4. Comparison 8: Live attenuated vaccines (all types) versus placebo - Efficacy outcomes, Outcome 4: Death from diarrhoea (any organism)

| Study or Subgroup | Vaccine Events | Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Richie 2000 Indonesia | 6 | 33696 | 8 | 33812 | 100.0% | 0.75 [0.26 , 2.17] |
| **Total (95% CI)** | | **33696** | | **33812** | **100.0%** | **0.75 [0.26 , 2.17]** |
| Total events: | 6 | | 8 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.60)
Test for subgroup differences: Not applicable





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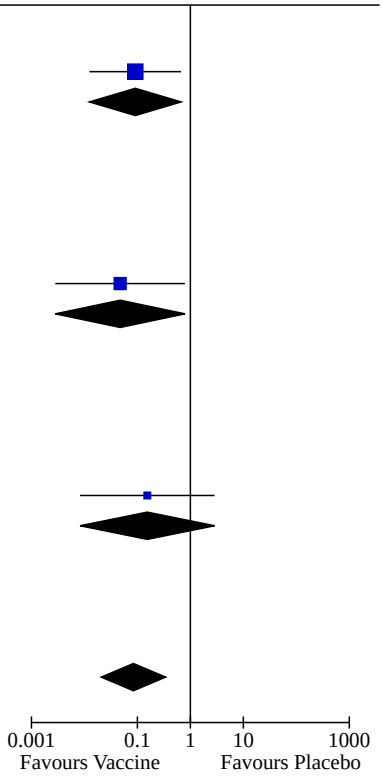
## Analysis 8.5. Comparison 8: Live attenuated vaccines (all types) versus placebo - Efficacy outcomes, Outcome 5: Cases of moderate to severe diarrhoea - following artificial challenge

| Study or Subgroup | Vaccine Events | Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **8.5.1 CVD 103HgR** | | | | | | |
| Tacket 1999 | 1 | 28 | 9 | 23 | 49.5% | 0.09 [0.01 , 0.67] |
| **Subtotal (95% CI)** | | **28** | | **23** | **49.5%** | **0.09 [0.01 , 0.67]** |
| Total events: | 1 | | 9 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.36 (P = 0.02) | | | | | | |
| **8.5.2 Peru 15** | | | | | | |
| Cohen 2002 | 0 | 24 | 5 | 12 | 36.3% | 0.05 [0.00 , 0.79] |
| **Subtotal (95% CI)** | | **24** | | **12** | **36.3%** | **0.05 [0.00 , 0.79]** |
| Total events: | 0 | | 5 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.12 (P = 0.03) | | | | | | |
| **8.5.3 VC638** | | | | | | |
| García 2005 | 0 | 12 | 2 | 9 | 14.2% | 0.15 [0.01 , 2.86] |
| **Subtotal (95% CI)** | | **12** | | **9** | **14.2%** | **0.15 [0.01 , 2.86]** |
| Total events: | 0 | | 2 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.26 (P = 0.21) | | | | | | |
| **Total (95% CI)** | | **64** | | **44** | **100.0%** | **0.08 [0.02 , 0.34]** |
| Total events: | 1 | | 16 | | | |
| Heterogeneity: Chi² = 0.33, df = 2 (P = 0.85); I² = 0% | | | | | | |
| Test for overall effect: Z = 3.47 (P = 0.0005) | | | | | | |
| Test for subgroup differences: Chi² = 0.33, df = 2 (P = 0.85), I² = 0% | | | | | | |





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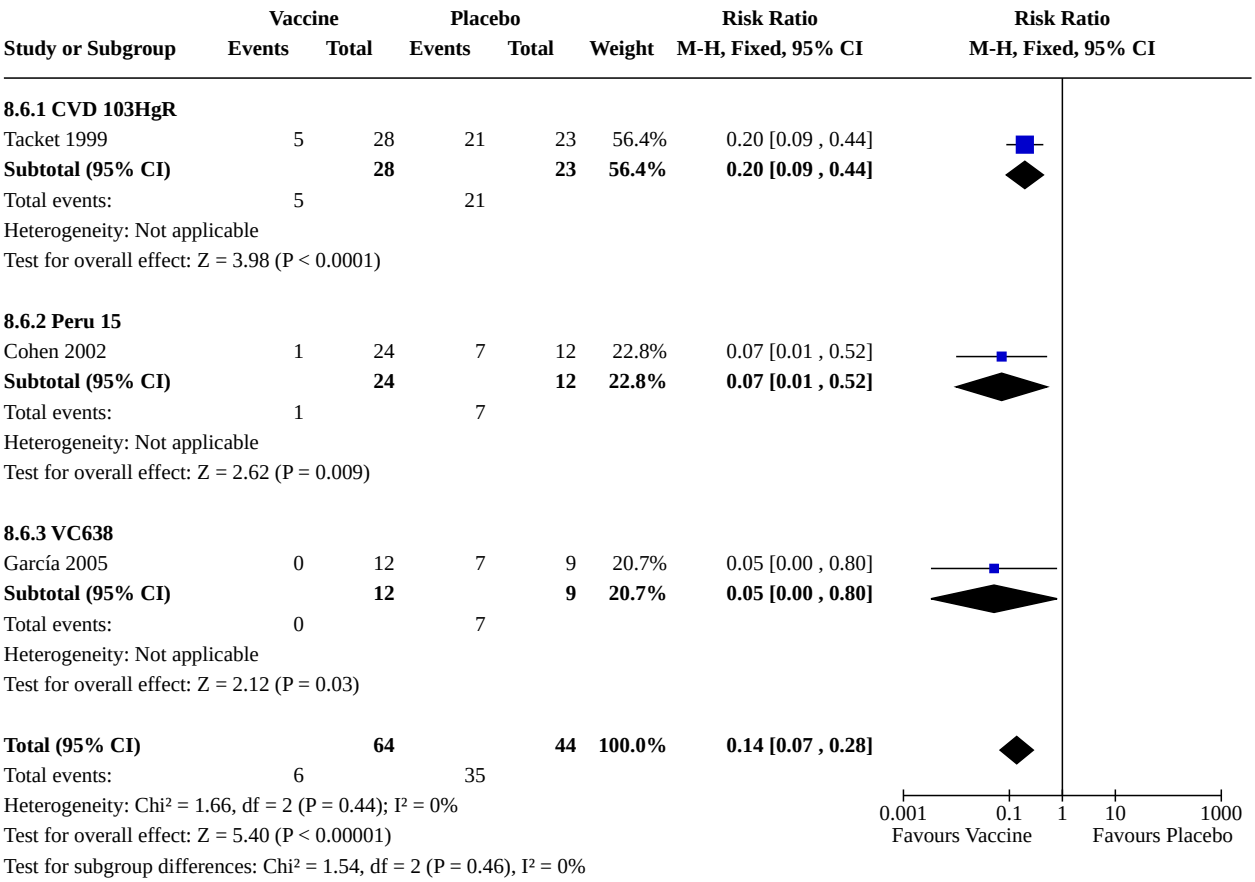
**Analysis 8.6. Comparison 8: Live attenuated vaccines (all types) versus placebo - Efficacy outcomes, Outcome 6: Cases of any diarrhoea -following artificial challenge**




## Comparison 9. Live attenuated vaccines (all types) versus placebo - Safety outcomes

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 9.1 Adverse events - CVD 103-HgR versus placebo | 12 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 9.1.1 Diarrhoea | 12 | 3320 | Risk Ratio (M-H, Random, 95% CI) | 1.09 [0.81, 1.47] |
| 9.1.2 Fever | 8 | 2516 | Risk Ratio (M-H, Random, 95% CI) | 0.84 [0.57, 1.23] |
| 9.1.3 Vomiting | 9 | 2866 | Risk Ratio (M-H, Random, 95% CI) | 1.22 [0.84, 1.79] |
| 9.1.4 Nausea | 3 | 1474 | Risk Ratio (M-H, Random, 95% CI) | 1.10 [0.67, 1.80] |
| 9.1.5 Seizure | 1 | 1077 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 9.1.6 Itching | 1 | 1077 | Risk Ratio (M-H, Random, 95% CI) | 2.00 [0.61, 6.61] |
| 9.1.7 Rash | 3 | 1489 | Risk Ratio (M-H, Random, 95% CI) | 0.94 [0.26, 3.49] |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| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 9.1.8 Abdominal pain | 7 | 2155 | Risk Ratio (M-H, Random, 95% CI) | 1.12 [0.86, 1.46] |
| 9.1.9 Headache | 3 | 1243 | Risk Ratio (M-H, Random, 95% CI) | 1.20 [0.91, 1.58] |
| 9.1.10 Anorexia | 3 | 478 | Risk Ratio (M-H, Random, 95% CI) | 1.06 [0.48, 2.36] |
| 9.1.11 Malaise | 2 | 434 | Risk Ratio (M-H, Random, 95% CI) | 0.88 [0.61, 1.26] |
| 9.1.12 Borborygmus | 1 | 81 | Risk Ratio (M-H, Random, 95% CI) | 0.89 [0.59, 1.35] |
| 9.1.13 Liquid stools | 1 | 81 | Risk Ratio (M-H, Random, 95% CI) | 1.37 [0.33, 5.72] |
| 9.2 Adverse events - Peru 15 versus placebo | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 9.2.1 Loss of appetite | 1 | 59 | Risk Ratio (M-H, Fixed, 95% CI) | 0.63 [0.16, 2.55] |
| 9.2.2 Loss of energy | 1 | 59 | Risk Ratio (M-H, Fixed, 95% CI) | 1.42 [0.32, 6.41] |
| 9.2.3 Abdominal cramps | 3 | 369 | Risk Ratio (M-H, Fixed, 95% CI) | 2.92 [0.62, 13.82] |
| 9.2.4 Headache | 3 | 349 | Risk Ratio (M-H, Fixed, 95% CI) | 4.14 [1.27, 13.48] |
| 9.2.5 Vomiting | 2 | 299 | Risk Ratio (M-H, Fixed, 95% CI) | 5.01 [0.26, 96.01] |
| 9.2.6 Nausea | 1 | 59 | Risk Ratio (M-H, Fixed, 95% CI) | 1.66 [0.38, 7.26] |
| 9.2.7 Diarrhoea | 3 | 369 | Risk Ratio (M-H, Fixed, 95% CI) | 2.44 [0.12, 48.45] |
| 9.2.8 Gas | 1 | 70 | Risk Ratio (M-H, Fixed, 95% CI) | 2.27 [0.10, 53.81] |
| 9.2.9 Fever | 2 | 310 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 9.2.10 Respiratory symptoms | 1 | 50 | Risk Ratio (M-H, Fixed, 95% CI) | 0.94 [0.25, 3.47] |
| 9.2.11 Gastrointestinal symptoms | 1 | 50 | Risk Ratio (M-H, Fixed, 95% CI) | 1.50 [0.72, 3.14] |
| 9.3 Adverse events - VC638 versus placebo | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 9.3.1 Abdominal pain | 3 | 137 | Risk Ratio (M-H, Fixed, 95% CI) | 1.94 [0.94, 4.02] |
| 9.3.2 Nausea | 1 | 36 | Risk Ratio (M-H, Fixed, 95% CI) | 4.00 [0.56, 28.40] |
| 9.3.3 Diarrhoea | 3 | 137 | Risk Ratio (M-H, Fixed, 95% CI) | 2.05 [0.65, 6.48] |
| 9.3.4 Headache | 3 | 137 | Risk Ratio (M-H, Fixed, 95% CI) | 2.30 [0.83, 6.36] |
| 9.3.5 General discomfort | 1 | 36 | Risk Ratio (M-H, Fixed, 95% CI) | 2.60 [0.13, 50.25] |
| 9.3.6 Borborygmus | 3 | 137 | Risk Ratio (M-H, Fixed, 95% CI) | 1.23 [0.77, 1.95] |


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| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 9.3.7 Vomiting | 2 | 101 | Risk Ratio (M-H, Fixed, 95% CI) | 1.05 [0.05, 24.33] |
| 9.3.8 Fever | 2 | 101 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 9.3.9 Heartburn | 1 | 56 | Risk Ratio (M-H, Fixed, 95% CI) | 1.00 [0.23, 4.40] |
| 9.3.10 Malaise | 1 | 56 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |


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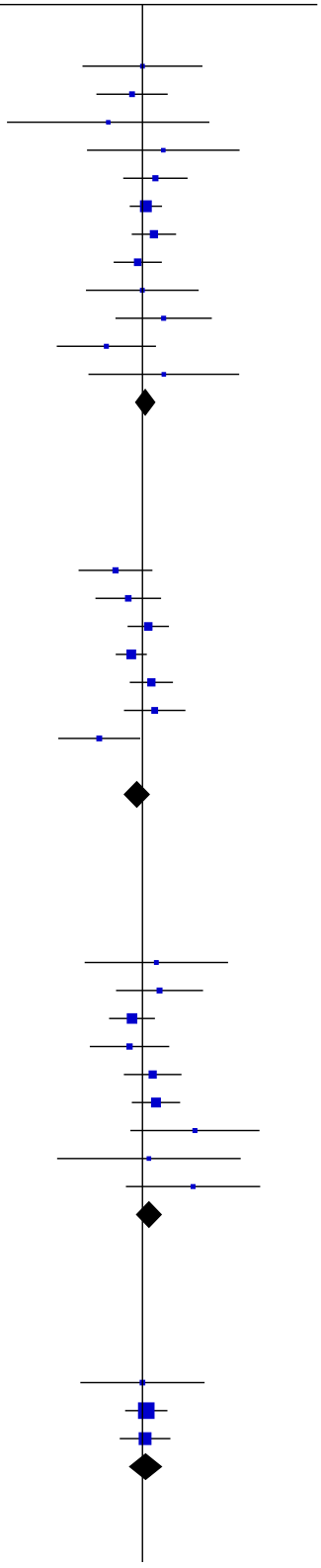
## Analysis 9.1. Comparison 9: Live attenuated vaccines (all types) versus placebo - Safety outcomes, Outcome 1: Adverse events - CVD 103-HgR versus placebo

| Study or Subgroup | Vaccine Events | Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **9.1.1 Diarrhoea** | | | | | | |
| Cryz 1990 (1) | 2 | 25 | 2 | 25 | 2.5% | 1.00 [0.15 , 6.55] |
| Gotuzzo 1993 (2) | 7 | 163 | 5 | 84 | 7.0% | 0.72 [0.24 , 2.20] |
| Lagos 1993 (3) | 0 | 40 | 1 | 41 | 0.9% | 0.34 [0.01 , 8.14] |
| Lagos 1995 (4) | 2 | 178 | 1 | 171 | 1.5% | 1.92 [0.18 , 21.00] |
| Lagos 1999 (5) | 9 | 156 | 6 | 156 | 8.6% | 1.50 [0.55 , 4.11] |
| Richie 2000 Indonesia (6) | 30 | 538 | 27 | 539 | 34.2% | 1.11 [0.67 , 1.85] |
| Simanjuntak 1993 (7) | 18 | 155 | 12 | 148 | 18.1% | 1.43 [0.71 , 2.87] |
| Su-Arehawaratana 1992a (8) | 11 | 102 | 13 | 104 | 15.4% | 0.86 [0.41 , 1.84] |
| Su-Arehawaratana 1992b (9) | 3 | 119 | 2 | 79 | 2.8% | 1.00 [0.17 , 5.83] |
| Suharyono 1992a (10) | 9 | 190 | 2 | 82 | 3.8% | 1.94 [0.43 , 8.79] |
| Suharyono 1992b (11) | 5 | 124 | 2 | 16 | 3.6% | 0.32 [0.07 , 1.53] |
| Tacket 1999 (12) | 2 | 43 | 1 | 42 | 1.6% | 1.95 [0.18 , 20.74] |
| **Subtotal (95% CI)** | | **1833** | | **1487** | **100.0%** | **1.09 [0.81 , 1.47]** |
| Total events: | 98 | | 74 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 5.80, df = 11 (P = 0.89); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.57 (P = 0.57) | | | | | | |
| **9.1.2 Fever** | | | | | | |
| Gotuzzo 1993 | 5 | 163 | 6 | 84 | 8.7% | 0.43 [0.13 , 1.37] |
| Lagos 1993 | 5 | 40 | 8 | 41 | 10.5% | 0.64 [0.23 , 1.79] |
| Lagos 1999 | 18 | 156 | 15 | 156 | 19.0% | 1.20 [0.63 , 2.29] |
| Richie 2000 Indonesia | 26 | 538 | 37 | 539 | 24.8% | 0.70 [0.43 , 1.15] |
| Simanjuntak 1993 | 18 | 155 | 13 | 148 | 18.1% | 1.32 [0.67 , 2.60] |
| Suharyono 1992a | 17 | 190 | 5 | 82 | 11.5% | 1.47 [0.56 , 3.84] |
| Suharyono 1992b | 6 | 124 | 3 | 16 | 7.4% | 0.26 [0.07 , 0.93] |
| Tacket 1999 | 0 | 42 | 0 | 42 | | Not estimable |
| **Subtotal (95% CI)** | | **1408** | | **1108** | **100.0%** | **0.84 [0.57 , 1.23]** |
| Total events: | 95 | | 87 | | | |
| Heterogeneity: Tau² = 0.09; Chi² = 9.49, df = 6 (P = 0.15); I² = 37% | | | | | | |
| Test for overall effect: Z = 0.90 (P = 0.37) | | | | | | |
| **9.1.3 Vomiting** | | | | | | |
| Gotuzzo 1993 | 3 | 163 | 1 | 84 | 2.9% | 1.55 [0.16 , 14.64] |
| Lagos 1993 | 5 | 40 | 3 | 41 | 7.8% | 1.71 [0.44 , 6.68] |
| Lagos 1995 | 12 | 178 | 16 | 171 | 28.2% | 0.72 [0.35 , 1.48] |
| Lagos 1999 | 4 | 156 | 6 | 156 | 9.4% | 0.67 [0.19 , 2.32] |
| Richie 2000 Indonesia | 11 | 538 | 8 | 539 | 17.8% | 1.38 [0.56 , 3.40] |
| Simanjuntak 1993 | 16 | 155 | 10 | 148 | 25.3% | 1.53 [0.72 , 3.26] |
| Suharyono 1992a | 12 | 190 | 1 | 82 | 3.6% | 5.18 [0.68 , 39.18] |
| Suharyono 1992b | 4 | 124 | 0 | 16 | 1.8% | 1.22 [0.07 , 21.75] |
| Tacket 1999 | 5 | 43 | 1 | 42 | 3.3% | 4.88 [0.60 , 40.06] |
| **Subtotal (95% CI)** | | **1587** | | **1279** | **100.0%** | **1.22 [0.84 , 1.79]** |
| Total events: | 72 | | 46 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 7.39, df = 8 (P = 0.50); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.04 (P = 0.30) | | | | | | |
| **9.1.4 Nausea** | | | | | | |
| Lagos 1999 | 2 | 156 | 2 | 156 | 6.4% | 1.00 [0.14 , 7.01] |
| Richie 2000 Indonesia | 18 | 538 | 16 | 539 | 55.2% | 1.13 [0.58 , 2.19] |
| Tacket 1999 | 10 | 43 | 9 | 42 | 38.4% | 1.09 [0.49 , 2.40] |
| **Subtotal (95% CI)** | | **737** | | **737** | **100.0%** | **1.10 [0.67 , 1.80]** |
| Total events: | 30 | | 27 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 2 (P = 0.99); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.39 (P = 0.70) | | | | | | |





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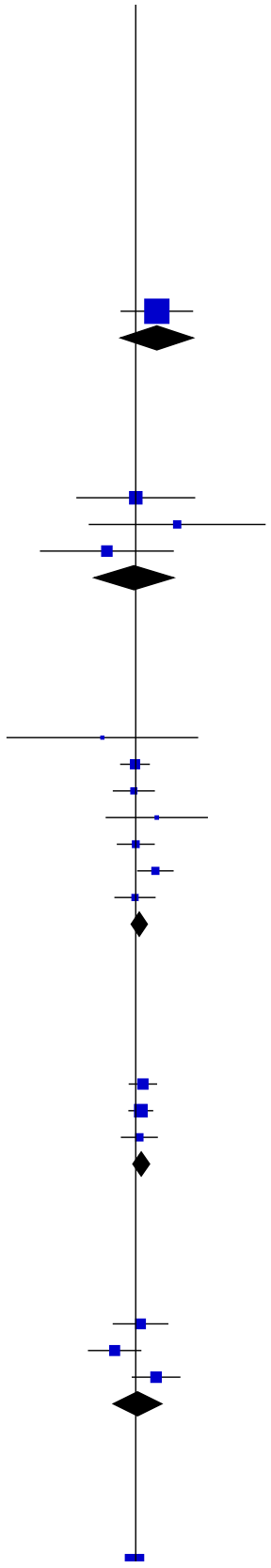
## Analysis 9.1. (Continued)

| | | | | | | |
|---|---|---|---|---|---|---|
| Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 2 (P = 0.99); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.39 (P = 0.70) | | | | | | |
| **9.1.5 Seizure** | | | | | | |
| Richie 2000 Indonesia | 0 | 538 | 0 | 539 | | Not estimable |
| **Subtotal (95% CI)** | | **538** | | **539** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **9.1.6 Itching** | | | | | | |
| Richie 2000 Indonesia | 8 | 538 | 4 | 539 | 100.0% | 2.00 [0.61 , 6.61] |
| **Subtotal (95% CI)** | | **538** | | **539** | **100.0%** | **2.00 [0.61 , 6.61]** |
| Total events: | 8 | | 4 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.14 (P = 0.25) | | | | | | |
| **9.1.7 Rash** | | | | | | |
| Richie 2000 Indonesia | 2 | 538 | 2 | 539 | 44.6% | 1.00 [0.14 , 7.09] |
| Suharyono 1992a | 4 | 190 | 0 | 82 | 20.2% | 3.91 [0.21 , 71.82] |
| Suharyono 1992b | 3 | 124 | 1 | 16 | 35.2% | 0.39 [0.04 , 3.50] |
| **Subtotal (95% CI)** | | **852** | | **637** | **100.0%** | **0.94 [0.26 , 3.49]** |
| Total events: | 9 | | 3 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 1.69, df = 2 (P = 0.43); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.09 (P = 0.93) | | | | | | |
| **9.1.8 Abdominal pain** | | | | | | |
| Cryz 1990 | 0 | 25 | 1 | 25 | 0.7% | 0.33 [0.01 , 7.81] |
| Gotuzzo 1993 | 36 | 163 | 19 | 84 | 29.3% | 0.98 [0.60 , 1.59] |
| Lagos 1993 | 11 | 40 | 12 | 41 | 14.7% | 0.94 [0.47 , 1.88] |
| Lagos 1999 | 4 | 156 | 2 | 156 | 2.5% | 2.00 [0.37 , 10.76] |
| Richie 2000 Indonesia | 19 | 538 | 19 | 539 | 18.0% | 1.00 [0.54 , 1.87] |
| Simanjuntak 1993 | 28 | 155 | 14 | 148 | 19.5% | 1.91 [1.05 , 3.48] |
| Tacket 1999 | 12 | 43 | 12 | 42 | 15.3% | 0.98 [0.50 , 1.92] |
| **Subtotal (95% CI)** | | **1120** | | **1035** | **100.0%** | **1.12 [0.86 , 1.46]** |
| Total events: | 110 | | 79 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 4.90, df = 6 (P = 0.56); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.86 (P = 0.39) | | | | | | |
| **9.1.9 Headache** | | | | | | |
| Lagos 1993 | 21 | 40 | 17 | 41 | 34.5% | 1.27 [0.79 , 2.02] |
| Richie 2000 Indonesia | 46 | 538 | 39 | 539 | 45.1% | 1.18 [0.78 , 1.78] |
| Tacket 1999 | 15 | 43 | 13 | 42 | 20.4% | 1.13 [0.61 , 2.07] |
| **Subtotal (95% CI)** | | **621** | | **622** | **100.0%** | **1.20 [0.91 , 1.58]** |
| Total events: | 82 | | 69 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 2 (P = 0.95); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.29 (P = 0.20) | | | | | | |
| **9.1.10 Anorexia** | | | | | | |
| Lagos 1993 | 8 | 40 | 7 | 41 | 31.8% | 1.17 [0.47 , 2.93] |
| Lagos 1999 | 7 | 156 | 14 | 156 | 32.9% | 0.50 [0.21 , 1.21] |
| Tacket 1999 | 14 | 43 | 7 | 42 | 35.3% | 1.95 [0.88 , 4.35] |
| **Subtotal (95% CI)** | | **239** | | **239** | **100.0%** | **1.06 [0.48 , 2.36]** |
| Total events: | 29 | | 28 | | | |
| Heterogeneity: Tau² = 0.30; Chi² = 5.11, df = 2 (P = 0.08); I² = 61% | | | | | | |
| Test for overall effect: Z = 0.14 (P = 0.89) | | | | | | |
| **9.1.11 Malaise** | | | | | | |
| Lagos 1995 | 34 | 178 | 34 | 171 | 72.4% | 0.96 [0.63 , 1.47] |

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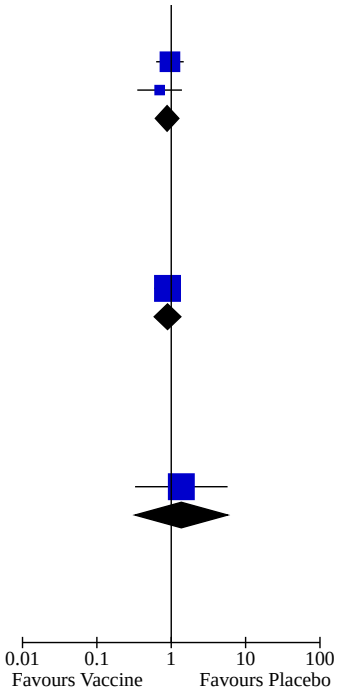
## Analysis 9.1. (Continued)

| | | | | | | |
|---|---|---|---|---|---|---|
| **9.1.11 Malaise** | | | | | | |
| Lagos 1995 | 34 | 178 | 34 | 171 | 72.4% | 0.96 [0.63 , 1.47] |
| Tacket 1999 | 10 | 43 | 14 | 42 | 27.6% | 0.70 [0.35 , 1.39] |
| **Subtotal (95% CI)** | | **221** | | **213** | **100.0%** | **0.88 [0.61 , 1.26]** |
| Total events: | 44 | | 48 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 1 (P = 0.44); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.69 (P = 0.49) | | | | | | |
| **9.1.12 Borborygmus** | | | | | | |
| Lagos 1993 | 20 | 40 | 23 | 41 | 100.0% | 0.89 [0.59 , 1.35] |
| **Subtotal (95% CI)** | | **40** | | **41** | **100.0%** | **0.89 [0.59 , 1.35]** |
| Total events: | 20 | | 23 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.55 (P = 0.58) | | | | | | |
| **9.1.13 Liquid stools** | | | | | | |
| Lagos 1993 | 4 | 40 | 3 | 41 | 100.0% | 1.37 [0.33 , 5.72] |
| **Subtotal (95% CI)** | | **40** | | **41** | **100.0%** | **1.37 [0.33 , 5.72]** |
| Total events: | 4 | | 3 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.43 (P = 0.67) | | | | | | |




**Footnotes**

(1) Cryz 1990: Age 21 to 45yrs, 7 days AE monitoring, vaccine dose: $5x10_8$
(2) Gotuzzo 1993: age 18 to 38 years, 7 days AE monitoring, vaccine doses: $5x10_8$, and $5x10_9$ were used
(3) Lagos 1993: Age 18 to 35 years, 7 days AE monitoring, vaccine dose: $5x10_9$
(4) Lagos 1995: Children age 5 to 9 years, 9 days AE monitoring, vaccine dose: $5x10_9$.
(5) Lagos 1999: Children age 3 to 17 months, 7 days AE monitoring, vaccine dose: $5x10_9$
(6) Richie 2000: Age 2 to 41 years, 3 days AE monitoring, vaccine dose: $5x10_9$
(7) Simanjuntak 1993: Children age 2 to 5 years, 9 days AE monitoring, vaccine dose: $5x10_9$
(8) Su-Arehawaratana 1992a: Age 18 to 26 years, 7 days AE monitoring, vaccine dose: $5x10_8$
(9) Su-Arehawaratana 1992b: Age 18 to 26 years, 7 days AE monitoring, vaccine doses: $5x10_8$, and $5x10_9$
(10) Suharyono 1992a: Children aged 5 to 9 years, 9 days AE monitoring, vaccine doses: $5x10_6$, $5x10_7$, and $5x10_8$
(11) Suharyono 1992b: Children aged 5 to 9 years, 9 days AE monitoring, vaccine doses: $5x10_9$, and $1x10_{10}$
(12) Tacket 1999: Ages 18 to 40 years, 3 days AE monitoring, vaccine dose: $2\text{-}8x10_8$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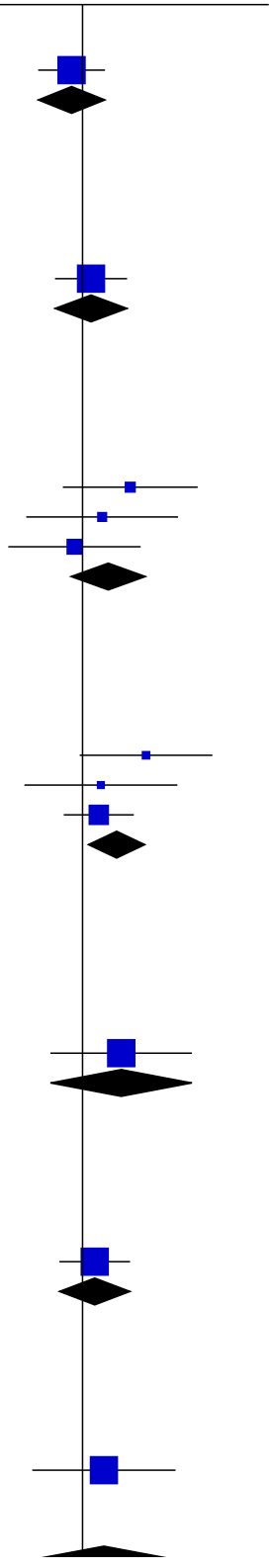
## Analysis 9.2. Comparison 9: Live attenuated vaccines (all types) versus placebo - Safety outcomes, Outcome 2: Adverse events - Peru 15 versus placebo

| Study or Subgroup | Vaccine Events | Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **9.2.1 Loss of appetite** | | | | | | |
| Cohen 2002 (1) | 4 | 40 | 3 | 19 | 100.0% | 0.63 [0.16 , 2.55] |
| **Subtotal (95% CI)** | | **40** | | **19** | **100.0%** | **0.63 [0.16 , 2.55]** |
| Total events: | 4 | | 3 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.64 (P = 0.52) | | | | | | |
| **9.2.2 Loss of energy** | | | | | | |
| Cohen 2002 | 6 | 40 | 2 | 19 | 100.0% | 1.43 [0.32 , 6.41] |
| **Subtotal (95% CI)** | | **40** | | **19** | **100.0%** | **1.43 [0.32 , 6.41]** |
| Total events: | 6 | | 2 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.46 (P = 0.64) | | | | | | |
| **9.2.3 Abdominal cramps** | | | | | | |
| Cohen 2002 | 7 | 40 | 0 | 19 | 27.9% | 7.32 [0.44 , 121.82] |
| Qadri 2005 (2) | 1 | 40 | 0 | 30 | 23.6% | 2.27 [0.10 , 53.81] |
| Qadri 2007 (3) | 1 | 140 | 1 | 100 | 48.4% | 0.71 [0.05 , 11.28] |
| **Subtotal (95% CI)** | | **220** | | **149** | **100.0%** | **2.92 [0.62 , 13.82]** |
| Total events: | 9 | | 1 | | | |
| Heterogeneity: $Chi^2$ = 1.44, df = 2 (P = 0.49); $I^2$ = 0% | | | | | | |
| Test for overall effect: Z = 1.35 (P = 0.18) | | | | | | |
| **9.2.4 Headache** | | | | | | |
| Cohen 2002 | 14 | 40 | 0 | 19 | 17.6% | 14.15 [0.89 , 225.32] |
| Qadri 2007 | 1 | 140 | 0 | 100 | 15.3% | 2.15 [0.09 , 52.21] |
| Sack 1997 (4) | 7 | 32 | 2 | 18 | 67.1% | 1.97 [0.46 , 8.49] |
| **Subtotal (95% CI)** | | **212** | | **137** | **100.0%** | **4.14 [1.27 , 13.48]** |
| Total events: | 22 | | 2 | | | |
| Heterogeneity: $Chi^2$ = 1.91, df = 2 (P = 0.38); $I^2$ = 0% | | | | | | |
| Test for overall effect: Z = 2.36 (P = 0.02) | | | | | | |
| **9.2.5 Vomiting** | | | | | | |
| Cohen 2002 | 0 | 40 | 0 | 19 | | Not estimable |
| Qadri 2007 | 3 | 140 | 0 | 100 | 100.0% | 5.01 [0.26 , 96.01] |
| **Subtotal (95% CI)** | | **180** | | **119** | **100.0%** | **5.01 [0.26 , 96.01]** |
| Total events: | 3 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.07 (P = 0.28) | | | | | | |
| **9.2.6 Nausea** | | | | | | |
| Cohen 2002 | 7 | 40 | 2 | 19 | 100.0% | 1.66 [0.38 , 7.26] |
| **Subtotal (95% CI)** | | **40** | | **19** | **100.0%** | **1.66 [0.38 , 7.26]** |
| Total events: | 7 | | 2 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.68 (P = 0.50) | | | | | | |
| **9.2.7 Diarrhoea** | | | | | | |
| Cohen 2002 | 2 | 40 | 0 | 19 | 100.0% | 2.44 [0.12 , 48.45] |
| Qadri 2005 | 0 | 40 | 0 | 30 | | Not estimable |
| Qadri 2007 | 0 | 140 | 0 | 100 | | Not estimable |
| **Subtotal (95% CI)** | | **220** | | **149** | **100.0%** | **2.44 [0.12 , 48.45]** |

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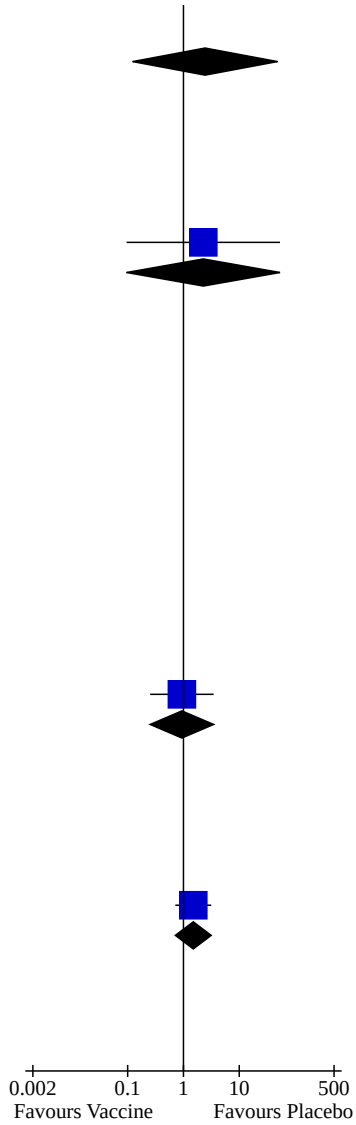
## Analysis 9.2. (Continued)

| | | | | | | |
|---|---|---|---|---|---|---|
| Qadri 2007 | 0 | 140 | 0 | 100 | | Not estimable |
| **Subtotal (95% CI)** | | **220** | | **149** | **100.0%** | **2.44 [0.12 , 48.45]** |
| Total events: | 2 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.58 (P = 0.56) | | | | | | |
| **9.2.8 Gas** | | | | | | |
| Qadri 2005 | 1 | 40 | 0 | 30 | 100.0% | 2.27 [0.10 , 53.81] |
| **Subtotal (95% CI)** | | **40** | | **30** | **100.0%** | **2.27 [0.10 , 53.81]** |
| Total events: | 1 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.51 (P = 0.61) | | | | | | |
| **9.2.9 Fever** | | | | | | |
| Qadri 2005 | 0 | 40 | 0 | 30 | | Not estimable |
| Qadri 2007 | 0 | 140 | 0 | 100 | | Not estimable |
| **Subtotal (95% CI)** | | **180** | | **130** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **9.2.10 Respiratory symptoms** | | | | | | |
| Sack 1997 | 5 | 32 | 3 | 18 | 100.0% | 0.94 [0.25 , 3.47] |
| **Subtotal (95% CI)** | | **32** | | **18** | **100.0%** | **0.94 [0.25 , 3.47]** |
| Total events: | 5 | | 3 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.10 (P = 0.92) | | | | | | |
| **9.2.11 Gastrointestinal symptoms** | | | | | | |
| Sack 1997 | 16 | 32 | 6 | 18 | 100.0% | 1.50 [0.72 , 3.14] |
| **Subtotal (95% CI)** | | **32** | | **18** | **100.0%** | **1.50 [0.72 , 3.14]** |
| Total events: | 16 | | 6 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.07 (P = 0.28) | | | | | | |




**Footnotes**

(1) Cohen 2002: Age 18 to 40 years, only records adverse events occurring on the day of vaccination although a diary was completed for 3 days

(2) Qadri 2005: Age 18 to 45 years, 4 days AE monitoring, all AEs are described as mild

(3) Qadri 2007: Age 9 months to 5 years, 4 days AE monitoring, all AE are described as mild.

(4) Sack 2007: Age 18 to 50 years, 3 days AE monitoring, all AE described as mild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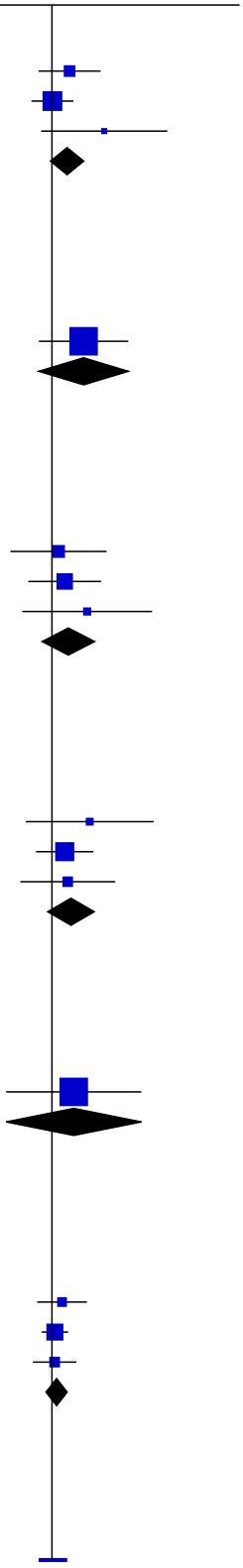
## Analysis 9.3. Comparison 9: Live attenuated vaccines (all types) versus placebo - Safety outcomes, Outcome 3: Adverse events - VC638 versus placebo

| Study or Subgroup | Vaccine Events | Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **9.3.1 Abdominal pain** | | | | | | |
| Benítez 1999 (1) | 13 | 42 | 2 | 14 | 29.8% | 2.17 [0.56 , 8.44] |
| García 2005 (2) | 7 | 24 | 6 | 21 | 63.6% | 1.02 [0.41 , 2.56] |
| Valera 2009 (3) | 9 | 24 | 0 | 12 | 6.5% | 9.88 [0.62 , 156.68] |
| **Subtotal (95% CI)** | | **90** | | **47** | **100.0%** | **1.94 [0.94 , 4.02]** |
| Total events: | 29 | | 8 | | | |
| Heterogeneity: Chi² = 3.23, df = 2 (P = 0.20); I² = 38% | | | | | | |
| Test for overall effect: Z = 1.79 (P = 0.07) | | | | | | |
| **9.3.2 Nausea** | | | | | | |
| Valera 2009 | 8 | 24 | 1 | 12 | 100.0% | 4.00 [0.56 , 28.40] |
| **Subtotal (95% CI)** | | **24** | | **12** | **100.0%** | **4.00 [0.56 , 28.40]** |
| Total events: | 8 | | 1 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.39 (P = 0.17) | | | | | | |
| **9.3.3 Diarrhoea** | | | | | | |
| Benítez 1999 | 4 | 42 | 1 | 14 | 35.0% | 1.33 [0.16 , 10.96] |
| García 2005 | 4 | 24 | 2 | 21 | 49.7% | 1.75 [0.36 , 8.61] |
| Valera 2009 | 4 | 24 | 0 | 12 | 15.3% | 4.68 [0.27 , 80.41] |
| **Subtotal (95% CI)** | | **90** | | **47** | **100.0%** | **2.05 [0.65 , 6.48]** |
| Total events: | 12 | | 3 | | | |
| Heterogeneity: Chi² = 0.52, df = 2 (P = 0.77); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.23 (P = 0.22) | | | | | | |
| **9.3.4 Headache** | | | | | | |
| Benítez 1999 | 7 | 42 | 0 | 14 | 14.1% | 5.23 [0.32 , 86.20] |
| García 2005 | 6 | 24 | 3 | 21 | 60.7% | 1.75 [0.50 , 6.15] |
| Valera 2009 | 4 | 24 | 1 | 12 | 25.3% | 2.00 [0.25 , 15.99] |
| **Subtotal (95% CI)** | | **90** | | **47** | **100.0%** | **2.30 [0.83 , 6.36]** |
| Total events: | 17 | | 4 | | | |
| Heterogeneity: Chi² = 0.53, df = 2 (P = 0.77); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.61 (P = 0.11) | | | | | | |
| **9.3.5 General discomfort** | | | | | | |
| Valera 2009 | 2 | 24 | 0 | 12 | 100.0% | 2.60 [0.13 , 50.25] |
| **Subtotal (95% CI)** | | **24** | | **12** | **100.0%** | **2.60 [0.13 , 50.25]** |
| Total events: | 2 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.63 (P = 0.53) | | | | | | |
| **9.3.6 Borborygmus** | | | | | | |
| Benítez 1999 | 14 | 42 | 3 | 14 | 22.0% | 1.56 [0.52 , 4.63] |
| García 2005 | 13 | 24 | 10 | 21 | 52.0% | 1.14 [0.64 , 2.03] |
| Valera 2009 | 9 | 24 | 4 | 12 | 26.0% | 1.13 [0.43 , 2.92] |
| **Subtotal (95% CI)** | | **90** | | **47** | **100.0%** | **1.23 [0.77 , 1.95]** |
| Total events: | 36 | | 17 | | | |
| Heterogeneity: Chi² = 0.28, df = 2 (P = 0.87); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.86 (P = 0.39) | | | | | | |
| **9.3.7 Vomiting** | | | | | | |

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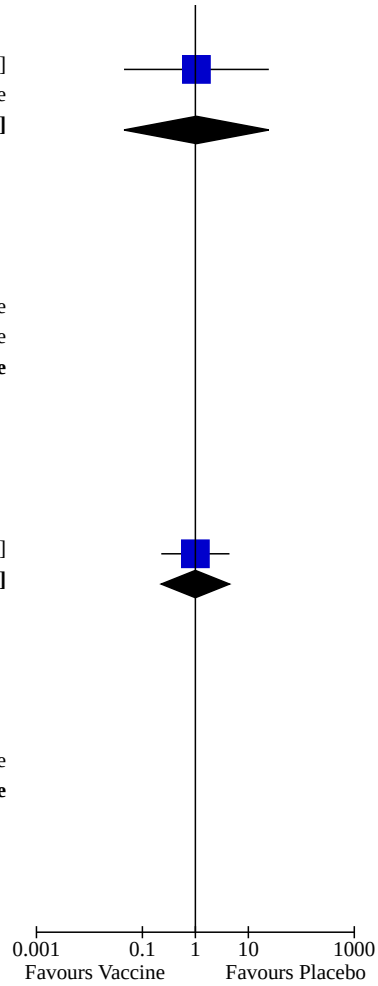
## Analysis 9.3. (Continued)

| | | | | | | |
|---|---|---|---|---|---|---|
| **9.3.7 Vomiting** | | | | | | |
| Benítez 1999 | 1 | 42 | 0 | 14 | 100.0% | 1.05 [0.05 , 24.33] |
| García 2005 | 0 | 24 | 0 | 21 | | Not estimable |
| **Subtotal (95% CI)** | | **66** | | **35** | **100.0%** | **1.05 [0.05 , 24.33]** |
| Total events: | 1 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.03 (P = 0.98) | | | | | | |
| **9.3.8 Fever** | | | | | | |
| Benítez 1999 | 0 | 42 | 0 | 14 | | Not estimable |
| García 2005 | 0 | 24 | 0 | 21 | | Not estimable |
| **Subtotal (95% CI)** | | **66** | | **35** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |
| **9.3.9 Heartburn** | | | | | | |
| Benítez 1999 | 6 | 42 | 2 | 14 | 100.0% | 1.00 [0.23 , 4.40] |
| **Subtotal (95% CI)** | | **42** | | **14** | **100.0%** | **1.00 [0.23 , 4.40]** |
| Total events: | 6 | | 2 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.00 (P = 1.00) | | | | | | |
| **9.3.10 Malaise** | | | | | | |
| Benítez 1999 | 0 | 42 | 0 | 14 | | Not estimable |
| **Subtotal (95% CI)** | | **42** | | **14** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Not applicable | | | | | | |




**Footnotes**

(1) Benitez 1999: Age 18 to 40 years, AE monitoring for 120 hours, all adverse events are described as mild

(2) Garcia 2005: Age 18 to 40 years, 5 days AE monitoring, all were mild except one headache described as moderate.

(3) Valera 2009: Age 18 to 40 years, 3 days AE monitoring, all adverse events are described as mild

## Comparison 10. Live attenuated CVD 103-HgR vaccine versus placebo - Subgroup analysis

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 10.1 Cases of cholera by age group (age 2-5 years) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 10.1.1 First year after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 10.1.2 Second year after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 10.1.3 Third year after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |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| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 10.2 Cases of confirmed cholera attending healthcare facilities (age over 5 years) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 10.2.1 First year after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 10.2.2 Second year after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 10.2.3 Third year after vaccination | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 10.3 Cases of cholera within four years and five months, by blood group | 1 | 67508 | Risk Ratio (M-H, Fixed, 95% CI) | 0.82 [0.54, 1.24] |
| 10.3.1 Blood group O | 1 | 24303 | Risk Ratio (M-H, Fixed, 95% CI) | 0.60 [0.34, 1.08] |
| 10.3.2 All other blood groups | 1 | 43205 | Risk Ratio (M-H, Fixed, 95% CI) | 1.15 [0.63, 2.10] |
| 10.4 Any diarrhoea following artifical challenge, by blood group | 1 | 51 | Risk Ratio (M-H, Fixed, 95% CI) | 0.17 [0.07, 0.43] |
| 10.4.1 Blood group O | 1 | 23 | Risk Ratio (M-H, Fixed, 95% CI) | 0.30 [0.13, 0.73] |
| 10.4.2 Blood group non-O | 1 | 28 | Risk Ratio (M-H, Fixed, 95% CI) | 0.08 [0.01, 0.54] |
| 10.5 Moderate or severe diarrhoea due to V. cholerae after artificial challenge, by blood group | 1 | 51 | Risk Ratio (M-H, Fixed, 95% CI) | 0.12 [0.02, 0.64] |
| 10.5.1 Blood group O | 1 | 23 | Risk Ratio (M-H, Fixed, 95% CI) | 0.13 [0.02, 1.00] |
| 10.5.2 Blood group non-O | 1 | 28 | Risk Ratio (M-H, Fixed, 95% CI) | 0.10 [0.01, 1.72] |
| 10.6 Additional adverse event data | 0 | | Other data | No numeric data |


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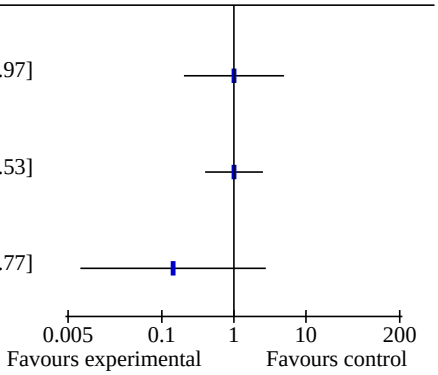
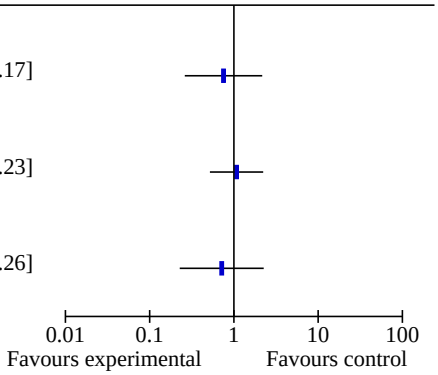
**Analysis 10.1. Comparison 10: Live attenuated CVD 103-HgR vaccine versus placebo - Subgroup analysis, Outcome 1: Cases of cholera by age group (age 2-5 years)**

| | Vaccine | | Placebo | | Risk Ratio | Risk Ratio |
|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| **10.1.1 First year after vaccination** | | | | | | |
| Richie 2000 Indonesia | 3 | 5728 | 3 | 5748 | 1.00 [0.20 , 4.97] | |
| **10.1.2 Second year after vaccination** | | | | | | |
| Richie 2000 Indonesia | 9 | 5728 | 9 | 5748 | 1.00 [0.40 , 2.53] | |
| **10.1.3 Third year after vaccination** | | | | | | |
| Richie 2000 Indonesia | 0 | 5728 | 3 | 5748 | 0.14 [0.01 , 2.77] | |




**Analysis 10.2. Comparison 10: Live attenuated CVD 103-HgR vaccine versus placebo - Subgroup analysis, Outcome 2: Cases of confirmed cholera attending healthcare facilities (age over 5 years)**

| | Vaccine | | Placebo | | Risk Ratio | Risk Ratio |
|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| **10.2.1 First year after vaccination** | | | | | | |
| Richie 2000 Indonesia | 6 | 27968 | 8 | 28064 | 0.75 [0.26 , 2.17] | |
| **10.2.2 Second year after vaccination** | | | | | | |
| Richie 2000 Indonesia | 15 | 27968 | 14 | 28064 | 1.08 [0.52 , 2.23] | |
| **10.2.3 Third year after vaccination** | | | | | | |
| Richie 2000 Indonesia | 5 | 27968 | 7 | 28064 | 0.72 [0.23 , 2.26] | |





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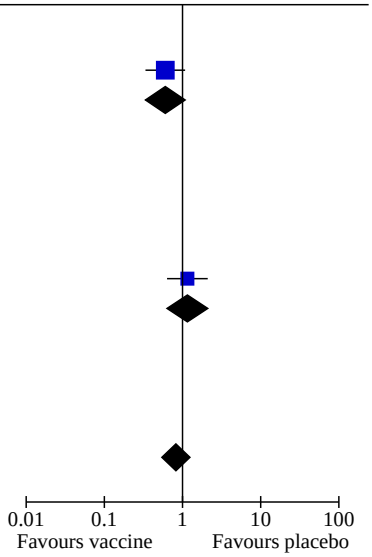
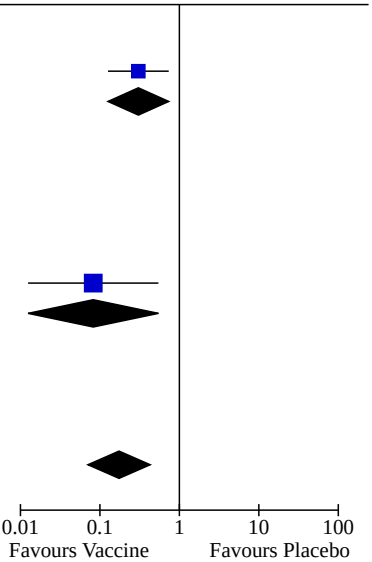
## Analysis 10.3. Comparison 10: Live attenuated CVD 103-HgR vaccine versus placebo - Subgroup analysis, Outcome 3: Cases of cholera within four years and five months, by blood group

| Study or Subgroup | Vaccine Events | Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **10.3.1 Blood group O** | | | | | | |
| Richie 2000 Indonesia | 18 | 12131 | 30 | 12172 | 60.0% | 0.60 [0.34 , 1.08] |
| **Subtotal (95% CI)** | | **12131** | | **12172** | **60.0%** | **0.60 [0.34 , 1.08]** |
| Total events: | 18 | | 30 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.70 (P = 0.09) | | | | | | |
| **10.3.2 All other blood groups** | | | | | | |
| Richie 2000 Indonesia | 23 | 21565 | 20 | 21640 | 40.0% | 1.15 [0.63 , 2.10] |
| **Subtotal (95% CI)** | | **21565** | | **21640** | **40.0%** | **1.15 [0.63 , 2.10]** |
| Total events: | 23 | | 20 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.47 (P = 0.64) | | | | | | |
| **Total (95% CI)** | | **33696** | | **33812** | **100.0%** | **0.82 [0.54 , 1.24]** |
| Total events: | 41 | | 50 | | | |
| Heterogeneity: Chi² = 2.33, df = 1 (P = 0.13); I² = 57% | | | | | | |
| Test for overall effect: Z = 0.93 (P = 0.35) | | | | | | |
| Test for subgroup differences: Chi² = 2.32, df = 1 (P = 0.13), I² = 57.0% | | | | | | |




## Analysis 10.4. Comparison 10: Live attenuated CVD 103-HgR vaccine versus placebo - Subgroup analysis, Outcome 4: Any diarrhoea following artifical challenge, by blood group

| Study or Subgroup | Vaccine Events | Vaccine Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **10.4.1 Blood group O** | | | | | | |
| Tacket 1999 | 4 | 15 | 7 | 8 | 41.3% | 0.30 [0.13 , 0.73] |
| **Subtotal (95% CI)** | | **15** | | **8** | **41.3%** | **0.30 [0.13 , 0.73]** |
| Total events: | 4 | | 7 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.65 (P = 0.008) | | | | | | |
| **10.4.2 Blood group non-O** | | | | | | |
| Tacket 1999 | 1 | 13 | 14 | 15 | 58.7% | 0.08 [0.01 , 0.54] |
| **Subtotal (95% CI)** | | **13** | | **15** | **58.7%** | **0.08 [0.01 , 0.54]** |
| Total events: | 1 | | 14 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.59 (P = 0.010) | | | | | | |
| **Total (95% CI)** | | **28** | | **23** | **100.0%** | **0.17 [0.07 , 0.43]** |
| Total events: | 5 | | 21 | | | |
| Heterogeneity: Chi² = 2.16, df = 1 (P = 0.14); I² = 54% | | | | | | |
| Test for overall effect: Z = 3.80 (P = 0.0001) | | | | | | |
| Test for subgroup differences: Chi² = 1.51, df = 1 (P = 0.22), I² = 34.0% | | | | | | |





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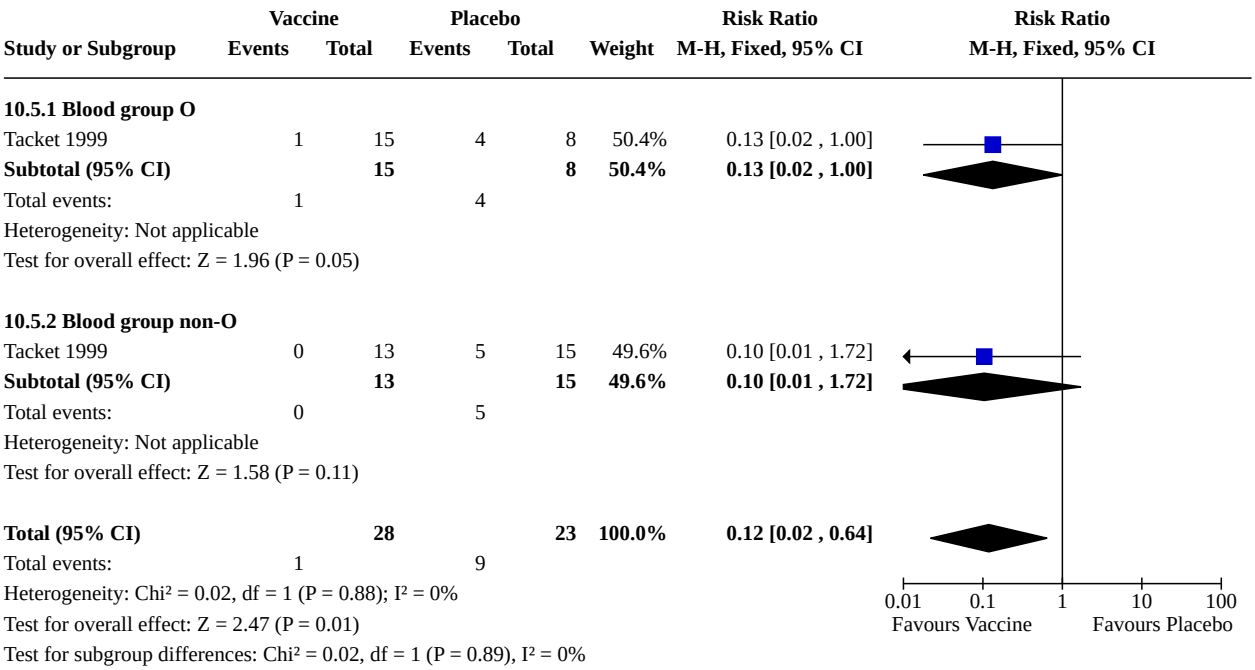
## Analysis 10.5. Comparison 10: Live attenuated CVD 103-HgR vaccine versus placebo - Subgroup analysis, Outcome 5: Moderate or severe diarrhoea due to V. cholerae after artificial challenge, by blood group




## Analysis 10.6. Comparison 10: Live attenuated CVD 103-HgR vaccine versus placebo - Subgroup analysis, Outcome 6: Additional adverse event data

Additional adverse event data

| Study | Adverse event monitoring | Adverse events reporting | Results |
|---|---|---|---|
| **Kotloff 1992** | Monitored daily for 7 days | Data presented in an unusable form | 'Among volunteers who experienced symptoms, the complaints were mild'. 'All episodes of fever were low grade. No subject exceeded the minimum definition of diarrhea (four stools within 24 h) or vomiting (one episode of emesis) or met these criteria for more than 1 day'. |
| **Migasena 1989a** | Seen daily for 5 days | Text summary only | 'No significant adverse reactions, including fever, diarrhea, vomiting, anorexia, or abdominal cramps were observed in any participant during the 7-day period of observation'. |
| **Perry 1998** | Seen daily for 6 days after each inoculation of vaccine or placebo | Data presented is from a crossover trial where all participants took vaccine and placebo 12 days apart | 'No significant difference was seen in reported diarrhoea, fever or vomiting following vaccine or placebo'. |
| **Su-Arehawaratana 1992a** | Monitored daily for 7 days | Numerical data is only provided for diarrhoea | 'No increased rate of diarrhoeal episodes or other gastrointestinal adverse reactions was observed among vaccine than among placebo recipients'. |
| **Su-Arehawaratana 1992b** | Monitored daily for seven days after each dose | Numerical data is only provided for diarrhoea | 'No increased rate of diarrhoeal episodes or other gastrointestinal adverse reactions was observed among vaccine than among placebo recipients'. |

## ADDITIONAL TABLES


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**Table 1. Detailed Search Strategy**

| Search set | CIDG SR^ | CENTRAL | MEDLINE^^ | EMBASE^^ | LILACS^^ |
|---|---|---|---|---|---|
| **1** | cholera | cholera | cholera | cholera | cholera |
| **2** | Vaccin* | Vaccin* | Vaccin* | Vaccin$ | Vaccin$ |
| **3** | 1 or 2 | 1 or 2 | 1 or 2 | 1 or 2 | 1 or 2 |
| **4** | | CHOLERA VACCINES | CHOLERA VACCINES | CHOLERA-VACCINE | |
| **5** | | 3 or 4 | 3 or 4 | 3 or 4 | |
| **6** | | | Limit 5 to human | Limit 5 to humans | |

**Table 2. The vaccine composition, dosing and participants in field trials of killed whole cell vaccines**

| Vaccine code (Trade name) | Item | Vaccine composition, dosing and population used in the field trials |
|---|---|---|
| **WC** (not currently available) | **Composition** | Three strains of *V. cholerae* O1:<br>• 2.5 x $10^{10}$ heat-killed *V. cholerae* classical Inaba whole cells (strain Cairo 48)<br>• 2.5 x $10^{10}$ heat-killed *V. cholerae* classical Ogawa whole cells (strain Cairo 50)<br>• 2.5 x $10^{10}$ formalin-killed*V. cholerae* El Tor Inaba whole cells (strain Phil 6973)<br>• 2.5 x $10^{10}$ formalin-killed*V. cholerae* classical Ogawa whole cells (strain Cairo 50) |
| | **Dosing schedule** | Three doses, at 6 week intervals |
| | **Field trial** | Clemens 1988 Bangladesh: 41580 participants in primary analysis |
| | **Population** | Children aged 2-15 years and women over the age of 15 |
| **WC-BS** (not currently available) | **Composition** | As for WC with additional:<br>• 1 mg purified cholera B subunit |
| | **Dosing schedule** | Three doses, at 6 week intervals |
| | **Field trial** | Clemens 1988 Bangladesh: 41,542 participants in primary analysis |
| | **Population** | Children aged 2-15 years and women over the age of 15 |
| **WC/rBS** (Dukoral®) | **Composition** | As for WC-BS except 1 mg purified cholera B subunit is replaced with:<br>• 1 mg recombinant cholera B subunit |
| | **Dosing schedule** | Two doses, 2 weeks apart<br>Taylor 2000 Peru also gave a booster dose at 10 months |
| | **Field trials** | Sanchez 1994 Peru: (1426 participants in primary analysis), Sanchez 1995 Peru: (307 participants), Taylor 2000 Peru: (17,799 participants) |


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**Table 2. The vaccine composition, dosing and participants in field trials of killed whole cell vaccines** *(Continued)*

| | | |
|---|---|---|
| | **Population** | Sanchez 1994 Peru and Sanchez 1995 Peru: Military recruits<br>Taylor 2000 Peru: Adults and children aged 2 to 65 years |
| **vWC**<br>**(ORCVAX®)** | **Composition** | Four strains of *V. cholerae* O1.<br>As for WC except the2.5 x $10^{10}$ formalin-killed*V. cholerae* classical Ogawa whole cells (strain Cairo 50) are replaced with:<br>• 2.5 x $10^{10}$ formalin-killed*V. cholerae* O1 Inaba, classical biotype cells (strain 569B) |
| | **Dosing schedule** | Two doses, 2 weeks apart |
| | **Field trial** | Trach 1997 Viet Nam: 114879 participants in primary analysis |
| | **Population** | Adults and children aged > 1 year |
| **BivWC**<br>**(Shanchol®)** | **Composition** | Three strains of *V. cholerae* O1 plus one strain of *V. cholerae* O139:<br>• 600 ELISA units of LPS of formalin-killed *V. cholerae* O1 El Tor Inaba (strain Phil 6973),<br>• 300 ELISA units of LPS of heat-killed *V. cholerae* O1 Classical Ogawa (strain Cairo 50),<br>• 300 ELISA units of LPS of formalin-killed *V. cholerae* O1 Classical Ogawa (strain Cairo 50),<br>• 300 ELISA units of LPS of heat-killed *V. cholerae* O1 Classical Ogawa (strain Cairo 48), and<br>• 600 ELISA units of LPS of formalin-killed *V. cholerae* O139 (strain 4260B). |
| | **Dosing schedule** | Two doses, 2 weeks apart |
| | **Field trial** | Sur 2009 India: 66,900 participants in primary analysis |
| | **Population** | Adults and children aged > 1 year, living in Kolkata, India |

WC = killed whole cell, BS = cholera toxin B subunit, rBS = recombinant cholera toxin B subunit, LPS = Lipopolysaccharide, ELISA = Enzyme-linked immunosorbent assay

**Table 3. The vaccine composition, dosing and participants in efficacy trials of live attenuated vaccines**

| **Vaccine code**<br>**(Trade name)** | **Item** | **Vaccine composition, dosing and population used in the field trials** |
|---|---|---|
| **CVD103-HGR**<br>**(not currently available)** | **Composition** | Richie 2000 Indonesia: 5 x $10^{9}$ lyophilized organisms of a genetically modified *V. cholerae* O1 Classical Inaba (569B)<br>Tacket 1999: 2 to 8 x $10^{8}$ CFU of lyophilized organisms of a genetically modified strain of *V. cholerae* O1 plus buffer |
| | **Dosing schedule** | A single dose |
| | **Field trial**<br>**Artificial challenge study** | Richie 2000 Indonesia: 67,508 participants<br>Tacket 1999: 51 participants |
| | **Population** | Richie 2000 Indonesia: Age 2 to 41 years in Jakarta, Indonesia |


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**Table 3. The vaccine composition, dosing and participants in efficacy trials of live attenuated vaccines** *(Continued)*

| | | |
|---|---|---|
| | | Tacket 1999: Adults aged 18 to 40 in USA |
| **Peru15**<br><br>**(not currently available)** | **Composition** | 5 x $10^8$ CFU of a live attenuated strain of *V. cholerae* O1 El Tor Inaba plus 200ml CeraVacx buffer (Cera Products, Columbia) |
| | **Dosing schedule** | A single dose |
| | **Artificial challenge study** | Cohen 2002: 36 participants |
| | **Population** | Volunteers aged 18 to 40 in USA |
| **VC638**<br><br>**(not currently available)** | **Composition** | 1 x $10^9$ CFU of a live attenuated strain of *V. cholerae* O1 El Tor Ogawa plus buffer |
| | **Dosing schedule** | A single dose |
| | **Artificial challenge study** | García 2005: 21 participants |
| | **Population** | Volunteer males aged 8 to 40 in Cuba |

CFU = Colony forming units

## WHAT'S NEW

| Date | Event | Description |
|---|---|---|
| 12 January 2024 | Amended | Editorial note added to direct readers to review that supersedes this one. |

## HISTORY

Protocol first published: Issue 7, 2010
Review first published: Issue 3, 2011

| Date | Event | Description |
|---|---|---|
| 3 August 2011 | Amended | Plain language summary amended. |

## CONTRIBUTIONS OF AUTHORS

This review is an update of a previous review (Graves 2001). The protocol was revised with input from KA, KZ, FQ, PG and DS. The search results were screened by KA, PG and DS. KA, KZ and DS extracted data. KA wrote the first draft which was revised by DS with additional input from all authors.

## DECLARATIONS OF INTEREST

We certify that we have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of the review (e.g. employment, consultancy, stock ownership, honoraria, expert testimony).


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## SOURCES OF SUPPORT

### Internal sources

- No sources of support provided

### External sources

- Department for International Development, UK

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Since the publication of the original review, several changes have occurred in standard Cochrane methodology which were not in the original review. Notably; the method of assessing risk of bias has changed, and summary of findings tables incorporating the GRADE methodology for assessing the quality of evidence have been added. The current methodology for these additions is described in the methods section.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Administration, Oral; Cholera [*prevention & control]; Cholera Vaccines [*administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic; Vaccines, Attenuated [administration & dosage] [adverse effects]

### MeSH check words

Adult; Child; Humans


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