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Oral vaccines for preventing cholera (Review)

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Cochrane Database of Systematic Reviews 2011, Issue 3. Art. No.: CD008603.
DOI: 10.1002/14651858.CD008603.pub2.

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[Intervention Review]

Oral vaccines for preventing cholera

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Editorial group: Cochrane Infectious Diseases Group.
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2024.

Citation: Sinclair D, Abba K, Zaman K, Qadri F, Graves PM. Oral vaccines for preventing cholera. *Cochrane Database of Systematic Reviews* 2011, Issue 3. Art. No.: CD008603. DOI: 10.1002/14651858.CD008603.pub2.

Editorial note: This review is superseded by the published Cochrane Review, Saif-Ur-Rahman 2024 [https://doi.org/10.1002/14651858.CD014573], which considers only the oral killed vaccines because the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

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.

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

					(14 studies)

*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.

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),

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

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.

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

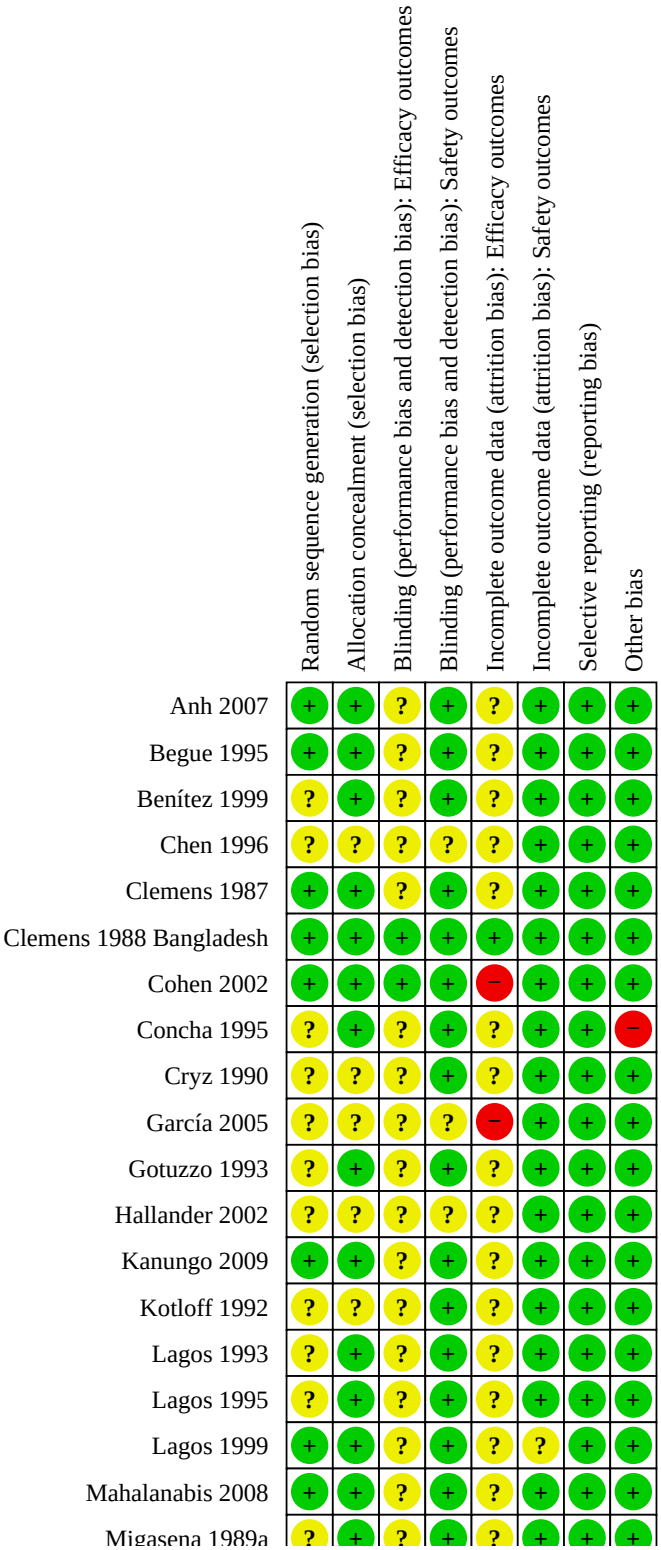
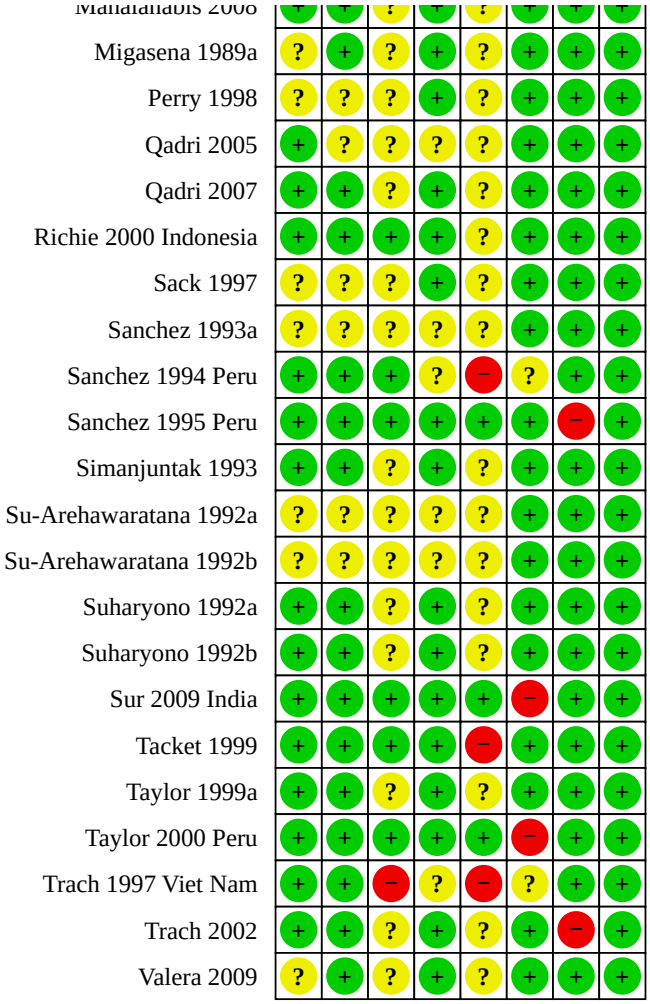


Figure 1. (Continued)



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.

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.

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).

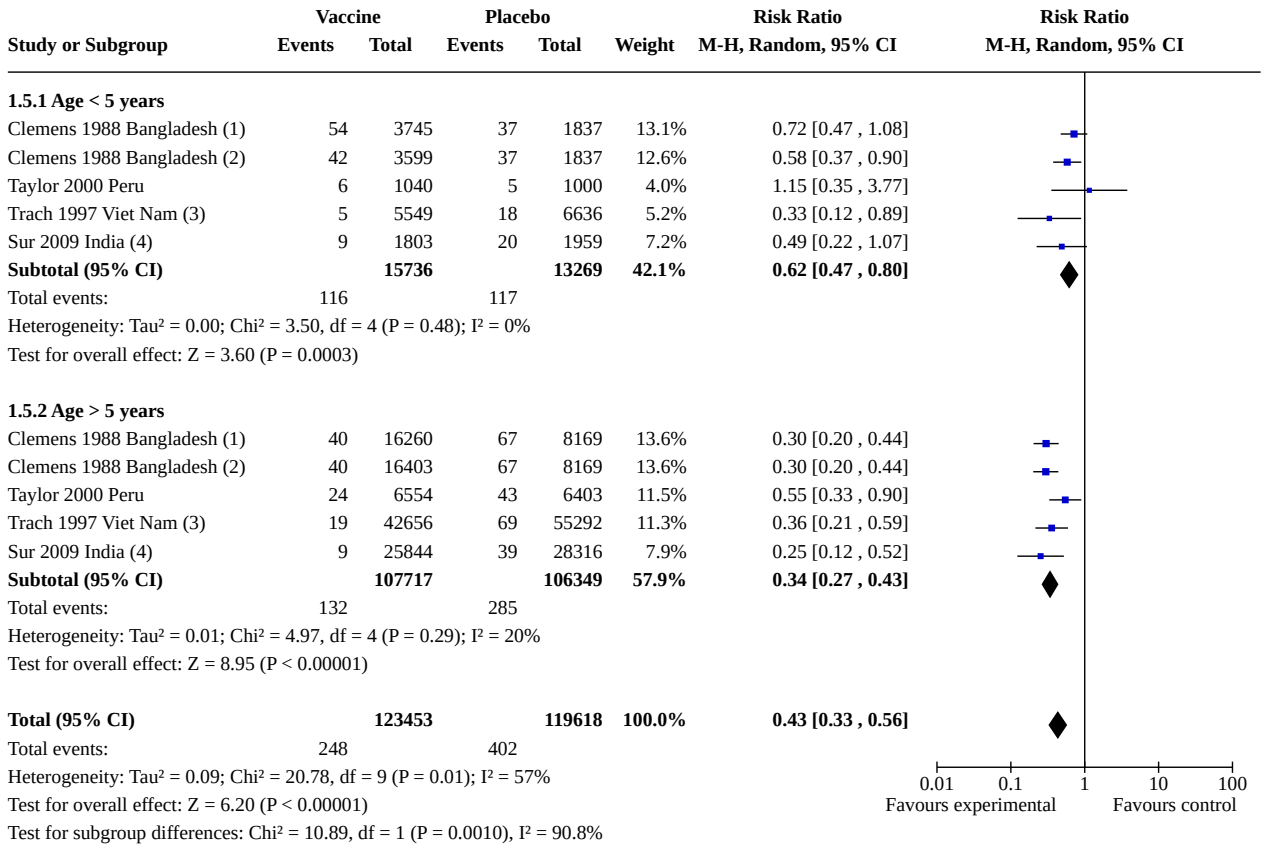
These vaccines are similar but not identical in composition (see Table 2). Despite the variation in dosing schedules, the protective efficacy against confirmed cholera of all five vaccines is similar in both the first and second years following vaccination. It should however be noted that protective 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).

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 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

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).

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

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%).

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

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.

ACKNOWLEDGEMENTS

The editorial base for the Cochrane Infectious Disease Group is funded by the Department for International Development (DFID), UK, for the benefit of developing countries.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Anh 2007

Study characteristics	
Methods	Design: A randomized controlled trial (individually randomized) Trial dates and duration: Enrollment from May to June 2005; follow-up for 28 days
Participants	Sample size: 153 participants enrolled Inclusion criteria: Age 18 to 40 years, healthy male and non-pregnant females, written informed consent 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) Placebo: Heat-killed *E. coli* K12 strain All participants were randomized to receive 2 doses, at an interval of 14 days.
Outcomes	*Included in review:* • Serious adverse events during 28 days follow-up • Adverse events within 3 days of each dose *Not included in the review:* • 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 Setting: 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

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) Duration and dates (field work): March 1993
Participants	Sample size: 624 received the first dose of vaccine, 541 received 2 doses Inclusion criteria: Persons aged 2 to 65 years Exclusion criteria: pregnancy
Interventions	Vaccine: Killed whole-cell vaccine plus recombinant cholera toxin subunit (WC-rBS; Dukoral®, SBL, Sweden) Placebo: Inactived *E. coli* K12 suspension Vaccine and placebo were administered along with freshly prepared antacid solution. Two doses were given two weeks apart.
Outcomes	*Included in the review:* • Adverse events after the first dose: participants were observed for one hour and then asked about symptoms at time of the second dose *Not included in the review:* • 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 Setting: Small community of 300 families. Source of funding: US Naval Medical Research and Development Command

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

Begue 1995 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "..administer the vaccine or placebo according to a pre-randomized list" 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) 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) Inclusion criteria: Age 18 to 40 years, male students or workers, good health, informed consent. 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 • 2×10^9 CFU • 1×10^9 CFU • 2×10^8 CFU • 4×10^{7} CFU Placebo: Buffer alone
Outcomes	*Included in review:* • Adverse events (detected through inpatient observation)

Benítez 1999 *(Continued)*

	Not included in the review: • 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 Setting: Institute of Tropical Medicine 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) Duration and dates (field work): Jun 1993 to Jan 1994
Participants	Sample size: 369 Inclusion criteria: Students from the primary and secondary school, and factory workers of Jiu-Fu area, Guang-Zhou.

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) • $1x10^{10}$ vibrio cholera whole cells + 5mg rBS Vaccine 1: Killed whole-cell vaccine plus recombinant cholera toxin B subunit (locally formulated) • $1x10^{10}$ vibrio cholera whole cells + 1mg rBS Placebo: Buffer alone
Outcomes	*Included in review:* • Adverse events (detected through observation) *Not included in the review:* • Immunological outcomes
Notes	Location: Jiu-Fu Area in Guang-Zhou city Setting: 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

Clemens 1987

Study characteristics	
Methods	Design: Randomized controlled trial (individual randomization) 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 Inclusion criteria: Children aged 2 to 15 years and women aged over 15 years. 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) Vaccine 2: Killed whole cell vaccine (WC) Placebo 1: Heat-inactivated *E. coli* K12 strain Placebo 2: Distilled water
Outcomes	*Included in the review:* • Adverse events for three consecutive days after each dose *Not included in the review:* • Immunogenicity
Notes	*Location:* Matlab, Bangladesh Setting: Community, within a health and demographic surveillance site 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" 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" 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

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) Trial dates and duration: Vaccination January to March 1985; follow-up 5 years 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 Inclusion criteria: children aged 2-15 years and women over the age of 15 Exclusion criteria: Pregnancy, illness requiring bed rest
Interventions	Vaccine 1: Killed whole cell plus purified cholera B subunit vaccine (WC-BS) Vaccine 2: Killed whole cell vaccine (WC) Placebo: *Escherichia coli* K12 strain placebo (K12) All subjects were randomized to receive three doses, at 6 week intervals. All doses were ingested with antacid.
Outcomes	*Included in review:* • Cholera infection (faecal excretion of *V. Cholerae* 01) • Symptomatic cholera infection (faecal excretion of *V. Cholerae* 01 from 48 hours before to 48 hours after a diarrhoea episode) • Cases of cholera (non-bloody diarrhoea, dehydration and excretion of *V. cholerae* 01). • Cases of cholera, excluding cases that are clinically atypical or associated with mixed infections. • 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. • Cases of diarrhoea, classified according to watery and non-watery, and severe and non-severe. • Deaths from cholera. • All deaths. • Adverse events within 3 days of first dose and within 3 days of second dose. 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. *Not included in the review:* • Immunological response in participants with cholera, comparing those receiving placebo and placebo.

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 Setting: Surveillance study area, served by three diarrhoea treatment centres. 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" 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) Trial dates and duration: 2000-2001
Participants	Number of participants: 59 (36 included in the challenge study)

Cohen 2002 *(Continued)*

	Inclusion criteria: Age 18 to 40 years, informed consent, and judged likely to comply with the study requirements. 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) Placebo: 200ml CeraVacx buffer (Cera Products, Columbia) 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:* • Adverse events during the first 3 days after the dose (assessed by a self completed diary) 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. • 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 • Moderate or severe cholera: diarrhoea with passage of >3,000 g during the study period plus a positive stool culture for *V. cholerae* 01 *Not included in the review:* • 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 Setting: Volunteer study. Outpatient phase for adverse events, inpatients phase for response to artificial challenge 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'.

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) Duration: Two months, January and February 1992
Participants	Sample size: 1313 received an initial dose of vaccine or placebo, 1165 received two doses. Inclusion criteria: People between the ages of 12 months and 64 years who have resided in the study area for at least two months. 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) Placebo: killed whole cells of *E. coli* K12. Both vaccine and placebo were administered with a buffer solution. Two doses were given, two weeks apart.
Outcomes	*Included in the review:* • Reported symptoms in the three days following ingestion of the vaccine (daily visits using pre-coded forms) *Not included in the review:* • Immunological outcomes: Geometric mean vibriocidal antibody, IgG antitoxin and IgA antitoxin titres pre and post vaccination.
Notes	Location: Los Olivios, Barraquilla, Colombia Setting: Households in a poor neighbourhood 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

Concha 1995 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Households were randomly selected to receive either vaccine or placebo" 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) Trial dates and duration: Study dates not given; follow-up 21 days
Participants	Sample size: 50 enrolled Inclusion criteria: Age 21 to 45 years, healthy, informed consent Exclusion criteria: None stated
Interventions	Vaccine: CVD 103-HgR live attenuated vaccine containing: • 5 x 10^8 CFU of lyophilized genetically modified *V. cholerae* O1 Classical Inaba (569B) Placebo: 5 x 10^8 CFU of heat-killed *E. coli* K12 strain
Outcomes	*Included in review:* • Adverse events during first 7 days after vaccination (interview on day 7) only diarrhoea and abdominal pain are reported. *Not included in the review:*

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 Setting: Not stated 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) Trial dates and duration: Dates not stated; artifical challenge took place 1 month after vaccination
Participants	Sample size: 45 (21 in challenge study) Inclusion criteria: Age 18 to 40 years, volunteer male workers among the western scientific community, good health, informed consent. 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

García 2005 *(Continued)*

Interventions	Vaccine: VC638 - A live attenuated strain of *V. Cholerae* O1 El Tor Ogawa • 1 x 10^9 CFU plus buffer Placebo: Buffer alone Artificial challenge: 7 x 10^5 CFU of fully virulent El Tor Ogawa strain 3008 (orally).
Outcomes	*Included in review:* • *V. cholerae* diarrhoea following oral challenge • Adverse events (inpatient monitoring for 5 days) *Not included in the review:* • Faecal virus shedding • 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 Setting: Inpatient trials unit, Institute of Tropical Medicine 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

Gotuzzo 1993

Study characteristics	
Methods	Design: A randomized controlled trial (individually randomized) Duration: Vaccination from Sept to Dec 1991; follow-up 28 days
Participants	Sample size: 241 enrolled Inclusion criteria: Adults aged 18 to 38 years Exclusion criteria: Pregnancy, antibiotics or diarrhoea within the previous 72 h, previous cholera vaccine.
Interventions	Vaccine 1: CVD 103-HgR live attenuated vaccine containing: • 5 x 10^9 lyophilized organisms of a genetically modified *V. cholerae* O1 Vaccine 2: CVD 103-HgR live attenuated vaccine containing: • 5 x 10^8 lyophilized organisms of a genetically modified *V. cholerae* O1 Placebo: 5 x 10^8 cells of heat-killed *E. coli* K-12 strain
Outcomes	*Included in review:* • Adverse events during the first 7 days *Not included in the review:* • 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 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. 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

Gotuzzo 1993 *(Continued)*

Efficacy outcomes		
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

Hallander 2002

Study characteristics	
Methods	Design: Randomized controlled trial (individually randomized) Duration: Enrolled; follow-up 28 days
Participants	Sample size: 249 Inclusion criteria: Age 1 to 12 years, permanent resident in study area, informed consent, good health Exclusion criteria: None stated
Interventions	Vaccine Killed whole-cell vaccine plus recombinant cholera toxin subunit (WC-rBS; Dukoral®, SBL, Sweden) Placebo: heat-killed *E. coli* K-12 strain (C 600) All participants were randomized to receive 2 doses, 14 days apart
Outcomes	*Included in review:* • Serious adverse events • Adverse events during the first 3 days after each dose (parental interview and diary cards for 3 days) *Not included in the review:* • 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 Setting: Source of funding: None declared *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.

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) 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 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 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) Placebo: Heat killed *E. coli* K12 strain 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:* • Serious adverse events during 28 days follow-up • Adverse events within 3 days of each dose *Not included in the review:*

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 Setting: The clinical trial unit of the National Institute of Cholera and Enteric Diseases (NICED) 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) Duration: Study dates not given; follow-up 28 days
Participants	Sample size: 94 enrolled Inclusion criteria: Age 18 to 40 years, college students, informed consent

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: • 5 x 10^8 CFU of lyophilized genetically modified *V. cholerae* O1 Classical Inaba (569B) Placebo: 5 x 10^8 CFU of heat-killed *E. coli* K12 strain All participants were randomized to receive one dose with crossover to receive the alternative arm after 8 days.
Outcomes	*Included in review:* • Adverse events during first 7 days after vaccination *Not included in the review:* • 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 Setting: College students 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

Lagos 1993

Study characteristics	
Methods	Design: A randomized controlled trial (individually randomized) Duration: Vaccination took place Nov to Dec 1991; follow-up 7 days.
Participants	Sample size: 81 enrolled 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 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: • 5 x 10^9 lyophilized organisms of a genetically modified *V. cholerae* O1 Placebo: 5 x 10^9 heat-killed *E. coli* K12 strain (C600) All participants were randomized to receive one dose
Outcomes	*Included in review:* • Adverse events during the first 7 days after the vaccine *Not included in the review:* • Immunological outcomes: 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: Chile Setting: 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

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) Duration: Study dates not given; follow-up 8 days
Participants	Sample size: 349 enrolled Inclusion criteria: Age 5 to 9 years, from public schools in a low-socioeconomic-level community Exclusion criteria: Fever, antibiotic therapy, or chronic disease
Interventions	Vaccine: CVD 103-HgR live attenuated vaccine containing: • 5 x 10^9 lyophilized organisms of a genetically modified *V. cholerae* O1 Classical Inaba (569B) Placebo: Heat-killed *E. coli* K12 strain All participants were randomized to receive one dose
Outcomes	*Included in review:* • Adverse events during first 8 days after vaccination *Not included in the review:* • 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 Setting: 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'.

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) Trial dates and duration: June 1995 to Nov 1997; follow-up 28 days
Participants	Sample size: 312 enrolled Inclusion criteria: Age 3 to 17 months, normal medical history, parental consent 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: • 5 x 10^9 CFU of lyophilized organisms of a genetically modified V. cholerae O1 Placebo: 5 x 10^8 CFU of heat-killed *E. coli* K12 strain 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:* • Adverse events during first 7 days after first vaccination (daily home visit and symptom enquiry), *Not included in the review:* • 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 Setting: Well-baby clinics at a semi-rural ambulatory health centre.

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) 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 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 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) Placebo: Heat-killed *E. coli* K12 strain

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 Setting: Clinical trial ward of the Infectious Diseases Hospital 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) Duration: Datesnot given; follow-up 5 days

Migasena 1989a *(Continued)*

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

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) Trial dates and duration: Dates not stated, cross-over after 12 days.
Participants	Number of participants: 76 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. 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: • 5 x 10^9 CFU of a genetically modified *V. cholerae* O1 Placebo: Lactate and aspartame only (these are also constituents of the vaccine) On day 12 those who initially received the placebo now received the vaccine, and vice versa.
Outcomes	*Included in the review:* • 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) *Not included in the review:* • Rectal swabs for vaccine virus on days of inoculation, daily for 4 days and on days 6 and 12 • Immunological outcomes: Goemetric mean vibriocidal antibodies pre and post vaccination. Seroconversion rates (criteria not stated)
Notes	Location: Mali Setting: Not clear 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

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) Trial dates and duration: Dates not stated, follow-up 21 days
Participants	Number of participants: 70 Inclusion criteria: Age 18 to 45 years, healthy, willing to participate, informed consent 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: • 2 x 10^8 CFU plus buffer Placebo: Buffer only All participants were given doxycycline for four days on day 6 to clear the vaccine strain.
Outcomes	*Included in the review:* • Adverse events: reported up to 4 days after vaccination (patients were seen twice daily by a clinician or visited daily at home) *Not included in the review:* • 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 Setting: Participants recruited from an urban slum, close to inpatient and outpatient facilities of ICC-DR,B

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) Trial dates and duration: Dates not stated, follow-up 21 days
Participants	Number of participants: 240 Inclusion criteria: age 9 months to 5 years, healthy, parental consent 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) • 2 x 10^8 CFU plus buffer Vaccine 2: Reduced dose Peru 15 - a live attenuated strain of *V. cholerae* 01 El Tor Inaba (AVANT Immunotherapeutics Inc, US)

Qadri 2007 *(Continued)*

	• 2 x 10^7 CFU plus buffer Placebo: Buffer only All participants were given erythromycin for four days on day 6 to clear the vaccine strain.
Outcomes	*Included in the review:* • 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) *Not included in the review:* • 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 Setting: Participants recruited from an urban slum, close to inpatient and outpatient facilities of ICC-DR,B 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

Richie 2000 Indonesia *(Continued)*

Methods	Design: Randomized controlled trial (individually randomized) Trial dates and duration: July 1993 to Dec 1997, 4 years Surveillance: Passive surveillance conducted through four North Jakarta hospitals distributed across the study area.
Participants	Sample size: 67,508 Inclusion criteria: Persons aged 2 to 41 years living in the study area. Exclusion criteria: Pregnancy, plans to move out of the study area, diagnosis of cancer
Interventions	Vaccine: CVD 103-HgR live attenuated vaccine containing: • 5 x 10^9 lyophilized organisms of a genetically modified *V. cholerae* O1 Classical Inaba (569B) Placebo: 5 x 10^8 heat-killed *E. coli* K12 strain (C600)
Outcomes	*Included in the review:* • Cases of cholera • Deaths other than those caused by vehicular accident • Adverse events reported during the three days after ingestion of the vaccine or placebo *Not included in the review:* • 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 Setting: Poor communities with poor sanitation and relative high cholera incidences 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" 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.

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) 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) Inclusion criteria: Age 18 to 50 years, healthy, willing to participate, informed consent 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 • 2 x 10^9 CFU plus buffer Vaccine 2: Reduced dose Peru 15 - a live attenuated strain of *V. cholerae* 01 El Tor Inaba (AVANT Immunotherapeutics Inc, US) • 2 x 10^8 CFU plus buffer Placebo: Buffer only
Outcomes	*Included in the review:* • Adverse events: reported up to 7 days after vaccination (using a self reported symptom diary) *Not included in the review:* • 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 Setting: Students or employee volunteers at John Hopkins University and Hospital Source of funding: National Institute Health, Virus Research Institute

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

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) Duration: Enrolled during October 1991; follow-up 28 days
Participants	Sample size: 186 enrolled and randomized to four groups* Inclusion criteria: Age 18 to 44 years 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) Placebo: Buffer alone All participants were randomized to receive 2 doses, at 11 to 16 days apart
Outcomes	*Included in review:* • Adverse events: text summary only *Not included in the review:*

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 Setting: Military personnel Source of funding: None stated * 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) Duration: Enrolled January to March 1994, follow-up to June 1994 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 Inclusion criteria: 17-65 years volunteers, available for three months

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) Placebo: Heat -inactivated *E. coli* K12 strain Vaccine and placebo were given with freshly prepared antacid solution. Two doses were given, 7 to 14 days apart.
Outcomes	*Included in the review:* • Cases of confirmed cholera *Not included in the review:* • Cases of severe cholera (cholera with signs of dehydration) as the treatment group is not stated • Cases subgrouped by blood group as the treatment group is not stated
Notes	Location: Lima, Peru Setting: Military training centres 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" 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. 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

Sanchez 1995 Peru

Study characteristics	
Methods	Design: Randomized controlled trial (individually randomized) Trial dates and duration: February 1992, 4 weeks 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 Inclusion criteria: Male Hispanics aged 17-23 years, informed consent 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) Placebo: suspension of heat-inactivated *E. coli* K12 strain Vaccines were given with a buffer solution. Two doses were given two weeks apart.
Outcomes	*Included in the review:* • Cholera cases • Adverse events within 24 hours of each dose (active surveillance was conducted for 3 days) *Not included in the review:* • 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 Setting: Military training centre 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' 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

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. Trial dates and duration and dates: 1991 to 1992
Participants	Number of participants: 303 Inclusion criteria: Children aged 24 to 59 months 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: • 5 x 10^9 CFU of a lyophilised genetically modified strain of *V. cholerae* O1 Placebo: • 5 x 10^8 CFU inactivated *E. coli* K12 (placebo) Both were given with aspartame sweetener and a buffer.
Outcomes	*Included in the review:* • Adverse events (active surveillance; daily visits by physicians to record complaints and conduct physical examination, up to day nine after vaccination *Not included in the review:* • Stools samples for vaccine virus on day 5 • 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 Setting: Villages 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	

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

Su-Arehawaratana 1992a *(Continued)*

Notes	Location: Thailand Setting: Field study using volunteers 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. Trial dates and duration: June 1991
Participants	Number of participants: 120 Inclusion criteria: Volunteers and Thai soldiers aged 18 to 26 Exclusion criteria: None stated
Interventions	Vaccine: CVD 103-HgR live attenuated vaccine containing: • 5 x 10^8 CFU of a lyophilised genetically modified strain of *V. cholerae* O1 • 5 x 10^9 CFU of a lyophilised genetically modified strain of *V. cholerae* O1

Su-Arehawaratana 1992b *(Continued)*

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

Suharyono 1992a *(Continued)*

	Trial dates and duration: February to March 1990
Participants	Number of participants: 274 Inclusion criteria: Children aged 5 to 9 years. Witten parental consent. Only one child per family was eligible to take part. 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: • 5 x 10^6 CFU CVD 103HgR centrifuged • 5 x 10^7 CFU CVD 103HgR centrifuged • 5 x 10^8 CFU CVD 103HgR filtered Placebo: 5 x 10^8 CFU inactivated *E. coli* K12 strain
Outcomes	*Included in the review:* • Adverse events (Active surveillance; daily visits by study staff for 9 days) *Not included in the review:* • Stools samples for vaccine virus on day 5 • 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 Setting: Small rural village, vaccinated at village health office 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.

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

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) Dates and duration: Vaccination July to September 2006; An interim analysis after 2 years of follow-up 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. 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. Inclusion criteria: Age > 1 year, written informed consent Exclusion criteria: Pregnancy
Interventions	Vaccine: Bivalent killed whole-cell vaccine (BivWC: Shanchol®, Shantha Biotechnics) Placebo: Heat killed *E. coli* K12 strain 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:* • 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. • All-cause death • Serious adverse events within 14 days of vaccination • Adverse events within 14 days of each dose. *Not included in the review:*
Notes	Location: Kolkata, India

Sur 2009 India *(Continued)*

	Setting: Surveillance study area, served by 9 study clinics, private practitioners and 2 hospitals. 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 Trial dates and duration: Dates not stated; challenge study was undertaken 3 months after vaccination
Participants	Sample size: 85 (51 included in challenge study) Inclusion criteria: Age 18 to 40, healthy, informed consent. 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

Tacket 1999 *(Continued)*

Interventions	Vaccine: CVD 103-HgR live attenuated vaccine containing: • 2 to 8 x 10^8 CFU of lyophilized organisms of a genetically modified strain of *V. cholerae* O1 plus buffer Placebo: heat-inactivated *E. coli* K12 plus buffer Challenge: 10^5 organisms of *V. cholerae* O1 El Tor Inaba (N16961)
Outcomes	*Included in review:* • Adverse events following vaccine (symptom diary for 3 days) • Any diarrhoea following artificial challenge • Moderate or severe cholera diarrhoea following artificial challenge *Not included in the review:* • 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 Setting: Hospital 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.

Taylor 1999a

Study characteristics	
Methods	Design: Randomized controlled trial (individually randomized) Duration: Enrollment from Jan to Feb 1995; follow-up for 28 days
Participants	Sample size: 216 enrolled Inclusion criteria: Age 2 to 64 years and residing in the study area, informed consent Exclusion criteria: None stated.
Interventions	Vaccine: Killed whole-cell vaccine plus recombinant cholera toxin subunit (WC-rBS; Dukoral®, SBL, Sweden) Placebo: Heat killed *E. coli* K12 strain 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:* • Adverse events within 3 days of each dose *Not included in the review:* • 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 Setting: 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

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) Duration: 1993 to 1995 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. Inclusion criteria: Aged 2 to 65 years old and residing in the vaccine trial area. Exclusion criteria: None stated.
Interventions	Vaccine: Killed whole-cell vaccine plus recombinant cholera toxin subunit (WC-rBS; Dukoral®, SBL, Sweden) Placebo: Heat-inactivated *E. coli* K12 strain Vaccine or placebo were given as two doses two weeks apart, followed by a third dose 10 months later.
Outcomes	*Included in the review:* • Cases of cholera identified through active household surveillance. Rectal swabs were collected from participants with diarrhoea and cultured to test for *V. cholerae.* • Cases of cholera identified through passive surveillance at the health post and hospital serving the area. • Level of dehydration in participants with cholera; using WHO definitions of mild, moderate or severe. • Adverse events after the first dose: Symptom enquiry at time of second dose *Not included in the review:* • 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. Setting: 36 poor marginal neighbourhoods, with a nearby hospital, 4 health posts and 40 neighbourhood rehydration units. Source of funding: US Army Medical Materiel and Development Command, Fort Detrick, Maryland

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

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

Trach 1997 Viet Nam *(Continued)*

Outcomes	*Included in the review:* • Cases of cholera requiring inpatient care in hospital or polyclinic (faecal sample yields *V. cholerae* 01) • Deaths from cholera • Visits to community health centres, polyclinics and hospitals for treatment of diarrhoea
Notes	Location: Hue, central Vietnam Setting: city community served by 19 health centres, four polyclinics and one regional hospital. 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'. 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) 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)

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 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) 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 Placebo: heat-killed *E. coli* K12 strain
Outcomes	*Included in review:* • Adverse events (visited for three consecutive days to ask about AE plus an interview at day 14) • Serious adverse events *Not included in the review:* • Immunological outcomes: Geometric mean vibriocidal antibody titres pre and post vaccination, and proportion who develop a ≥ 4 fold increase.
Notes	Location: Hanoi, Vietnam Setting: 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' 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

Trach 2002 *(Continued)*

Efficacy outcomes		
Incomplete outcome data (attrition bias) 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) Duration and dates (field work):
Participants	Sample size: 36 Inclusion criteria: Age 18 to 40 years, volunteers working in the scientific community, healthy, informed consent. 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) • 1 x 10^9 CFU plus buffer Placebo: Buffer alone All participants received 300mg of doxycycline on day 5.
Outcomes	*Included in review:* • Adverse events (active surveillance for 5 days, then passive up to day 30) *Not included in the review:* • 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 Setting: Unit for Isolation of Biological Risks at Tropical Medicine Institute 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.

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)

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

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

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

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)

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)

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

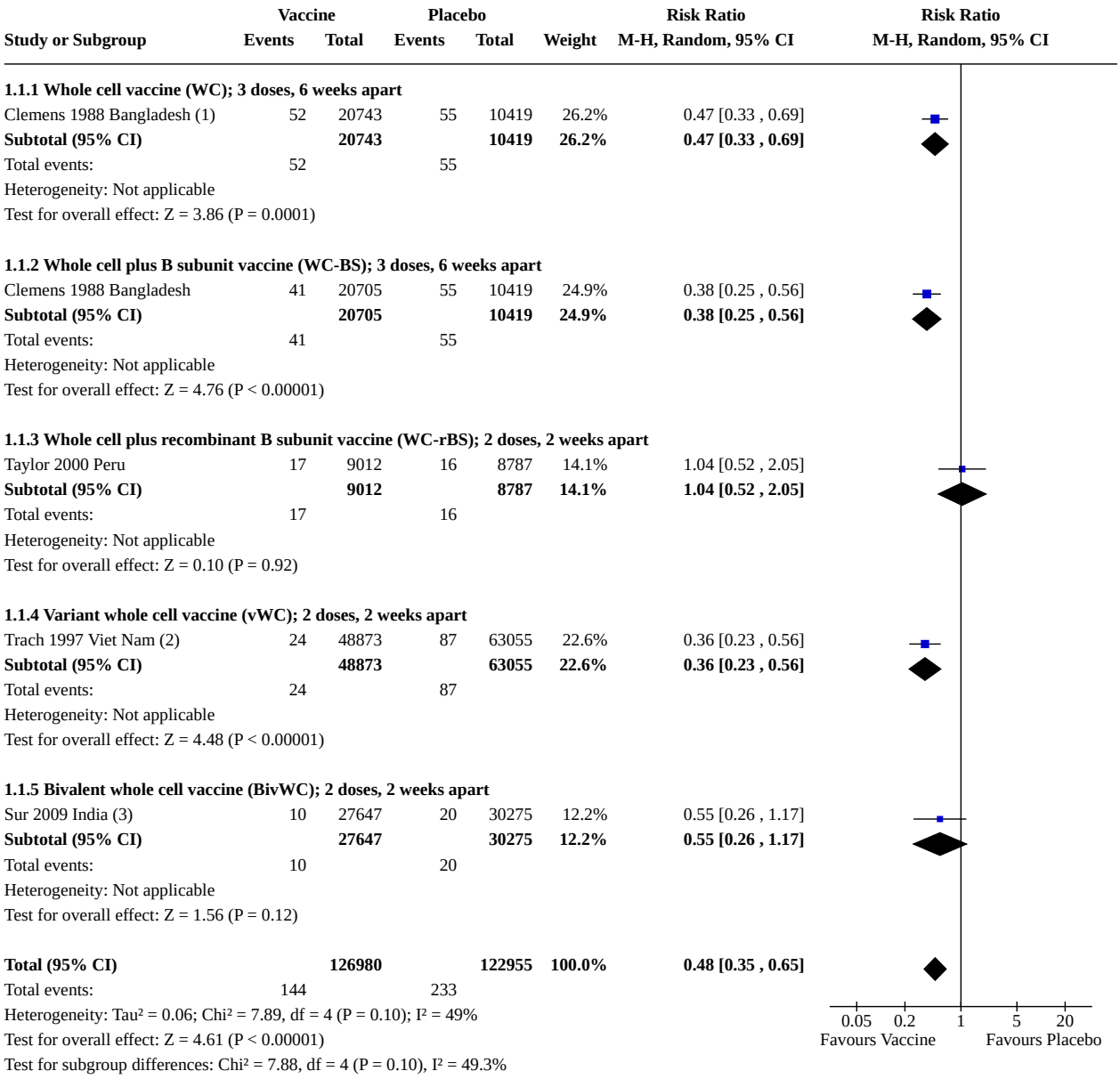
Comparison 1. Whole cell vaccines (all types) versus placebo - Primary efficacy outcomes

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]

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]

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]

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)



Footnotes

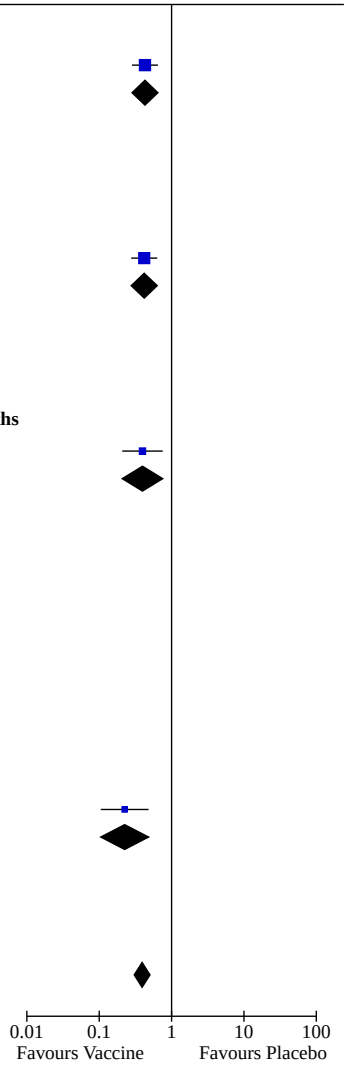
(1) For the purpose of this meta analysis the events and participants in the Placebo arm of Clemens 1985 Bangladesh have been divided equally between the two

(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

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

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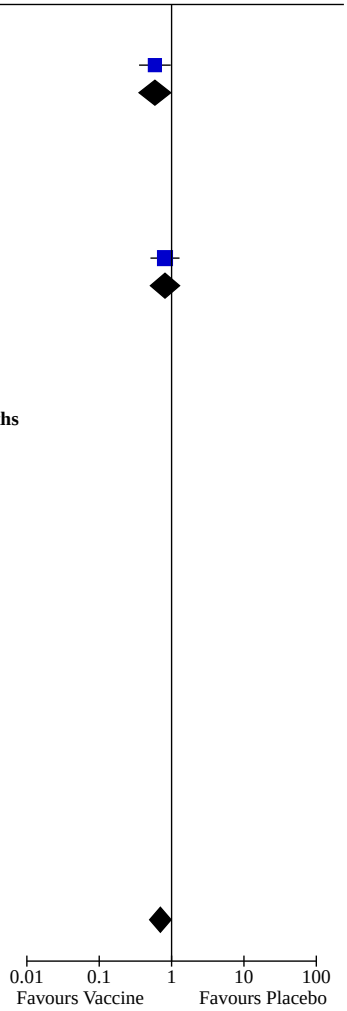
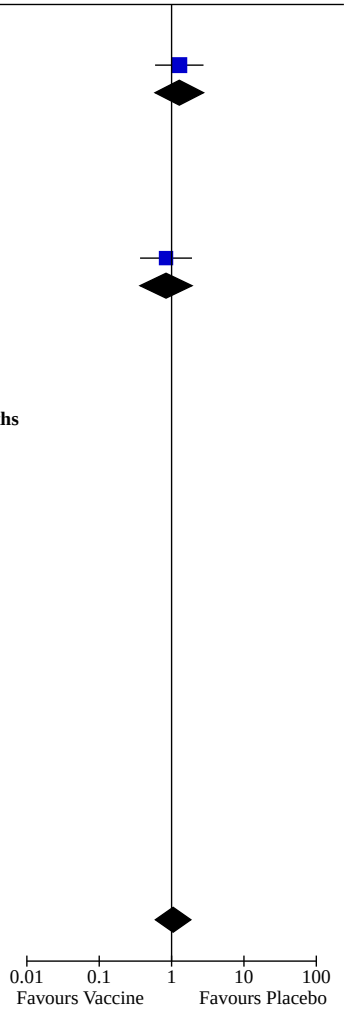
Analysis 1.3. Comparison 1: Whole cell vaccines (all types) versus placebo - Primary efficacy outcomes, Outcome 3: Cases of cholera - 3rd year of follow up (with meta analysis)

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%						



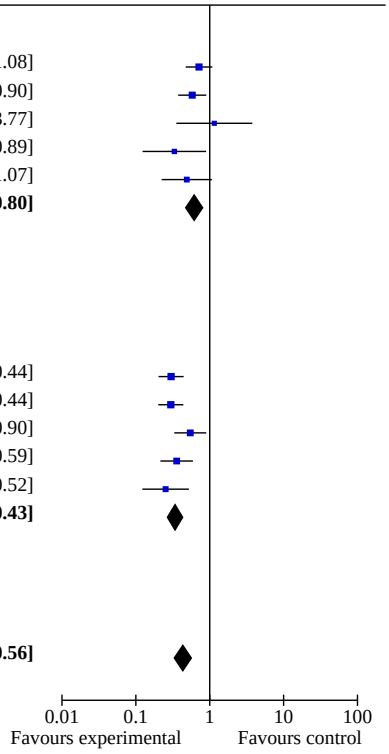
Analysis 1.4. Comparison 1: Whole cell vaccines (all types) versus placebo - Primary efficacy outcomes, Outcome 4: Cases of cholera - 4th year of follow up (with meta analysis)

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%						



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

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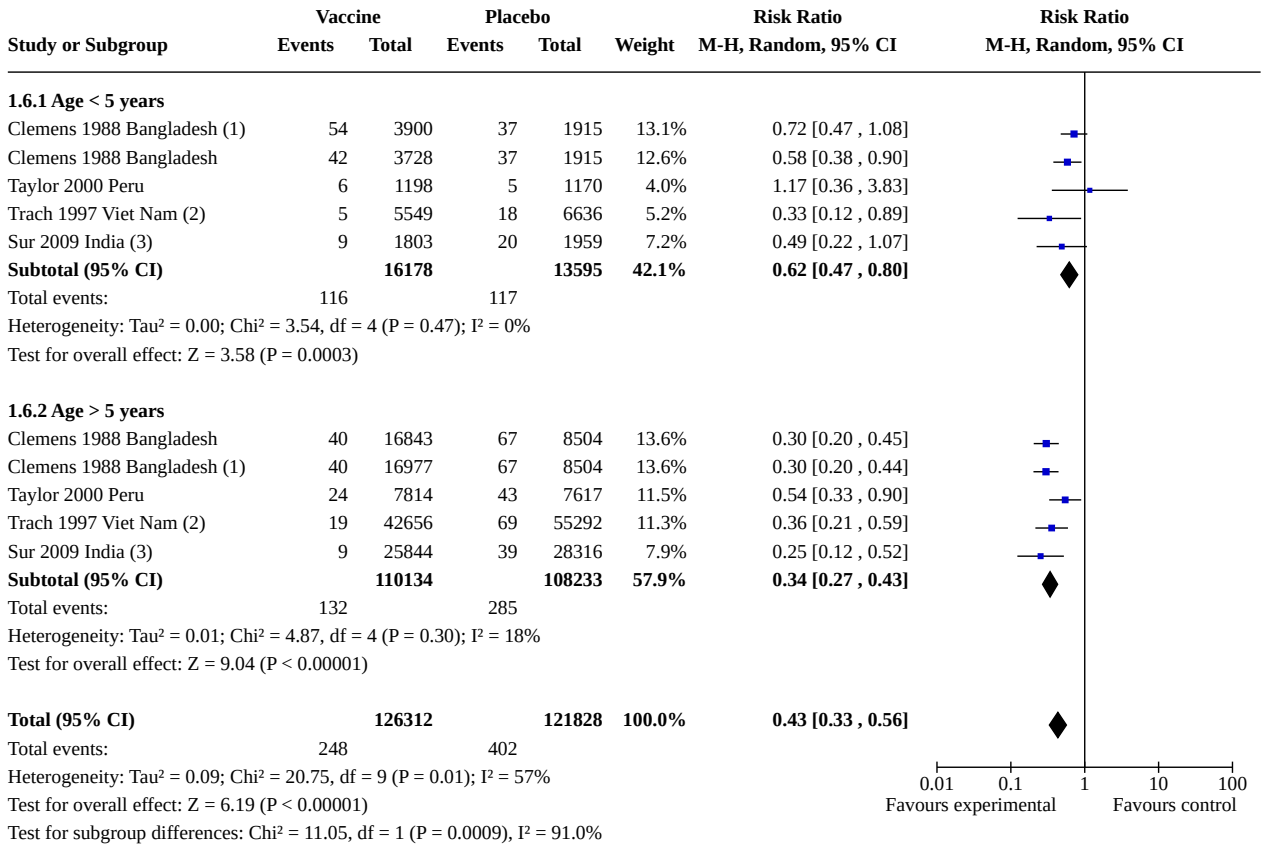
Analysis 1.6. Comparison 1: Whole cell vaccines (all types) versus placebo - Primary efficacy outcomes, Outcome 6: Cases of cholera by age group - First two years of follow-up (sensitivity analysis)



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

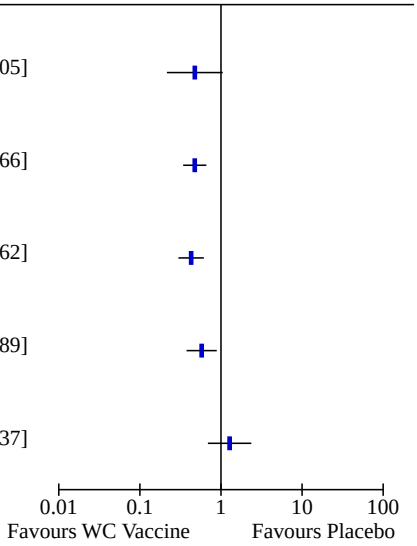
Comparison 2. Whole cell vaccine (WC) versus placebo - Subgroup analysis

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

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

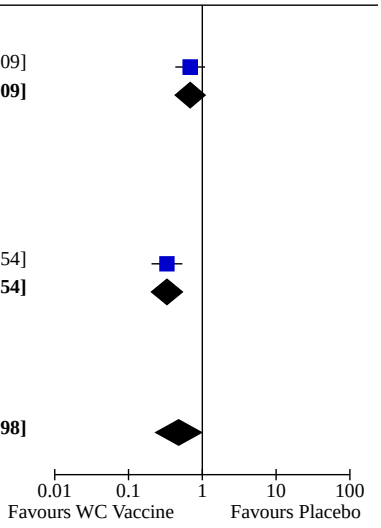
Analysis 2.1. Comparison 2: Whole cell vaccine (WC) versus placebo - Subgroup analysis, Outcome 1: Cases of cholera by time of follow-up (3-dose recipients)

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]



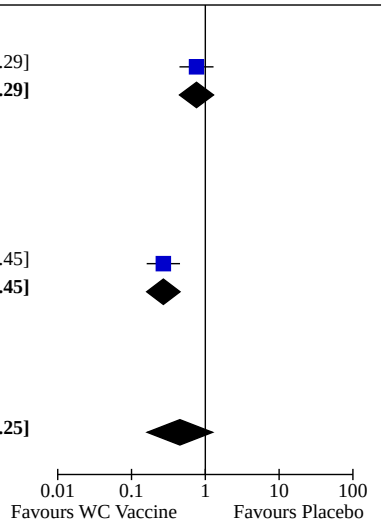
Analysis 2.2. Comparison 2: Whole cell vaccine (WC) versus placebo - Subgroup analysis, Outcome 2: Cases of cholera by age-group - 1st year of follow-up (3-dose recipients)

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%						



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%						

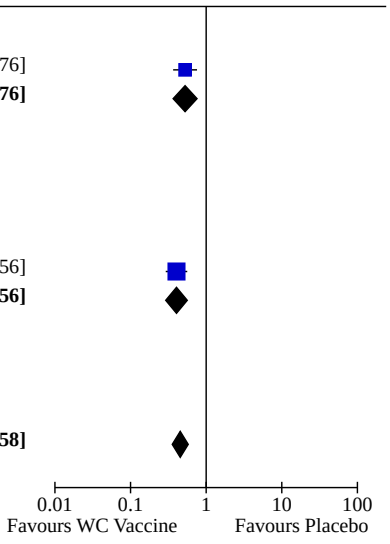


Footnotes

(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

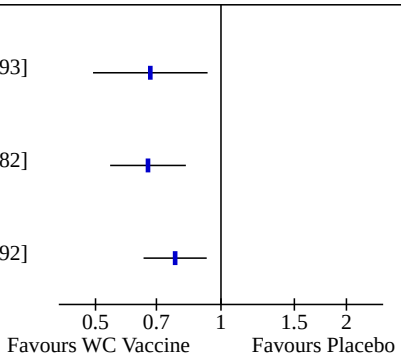
Analysis 2.4. Comparison 2: Whole cell vaccine (WC) versus placebo - Subgroup analysis, Outcome 4: Cases of cholera by blood group - First 2 years of follow-up (3-dose recipients)

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%						



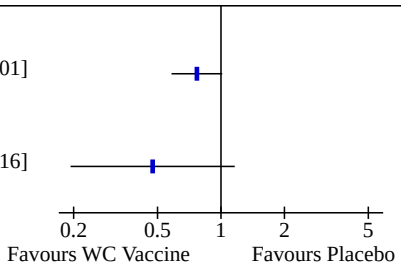
Analysis 2.5. Comparison 2: Whole cell vaccine (WC) versus placebo - Subgroup analysis, Outcome 5: Cases of all cause diarrhoea - 1st year of follow-up (3-dose recipients)

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]



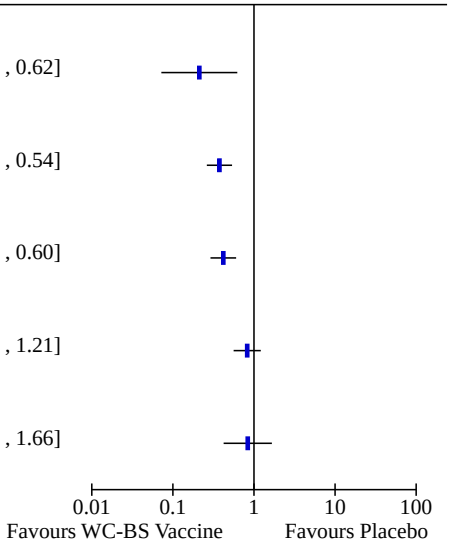
Comparison 3. Whole cell vaccine plus B subunit (WC-BS) versus placebo - Subgroup analysis

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

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

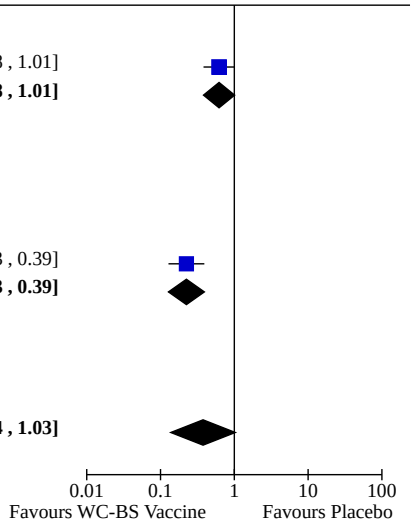
Analysis 3.1. Comparison 3: Whole cell vaccine plus B subunit (WC-BS) versus placebo - Subgroup analysis, Outcome 1: Cases of cholera by time of follow-up (3-dose recipients)

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]



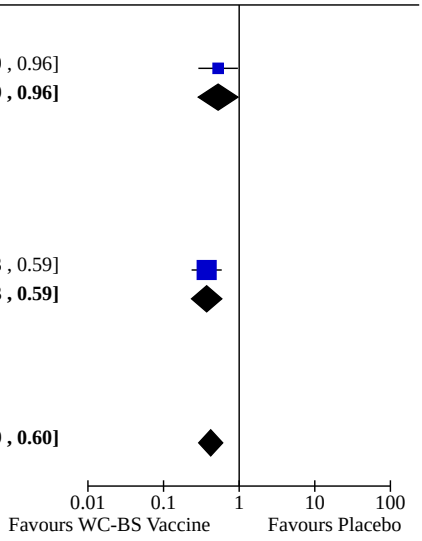
Analysis 3.2. Comparison 3: Whole cell vaccine plus B subunit (WC-BS) versus placebo - Subgroup analysis, Outcome 2: Cases of cholera by age-group - 1st year of follow-up (3-dose recipients)

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%						



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%						

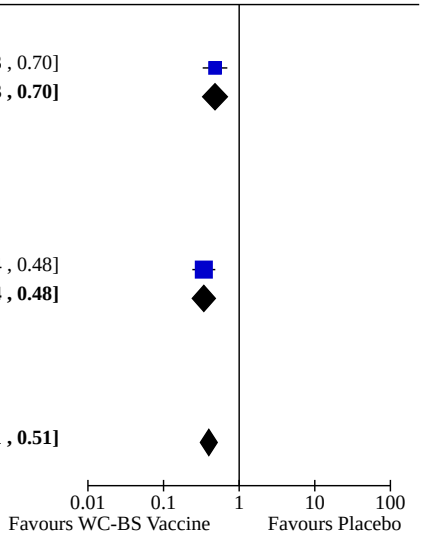


Footnotes

(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

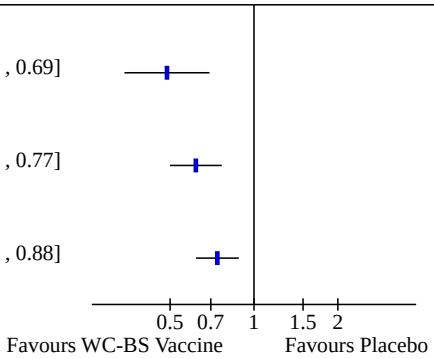
Analysis 3.4. Comparison 3: Whole cell vaccine plus B subunit (WC-BS) versus placebo - Subgroup analysis, Outcome 4: Cases of cholera by blood group - First 2 years of follow-up (3-dose recipients)

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%						



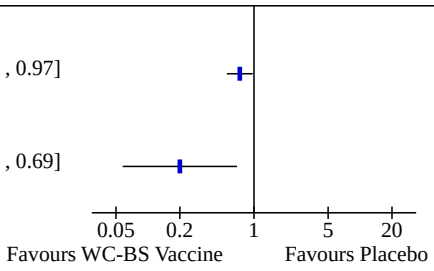
Analysis 3.5. Comparison 3: Whole cell vaccine plus B subunit (WC-BS) versus placebo - Subgroup analysis, Outcome 5: Cases of all cause diarrhoea - 1st year of follow-up (3-dose recipients)

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

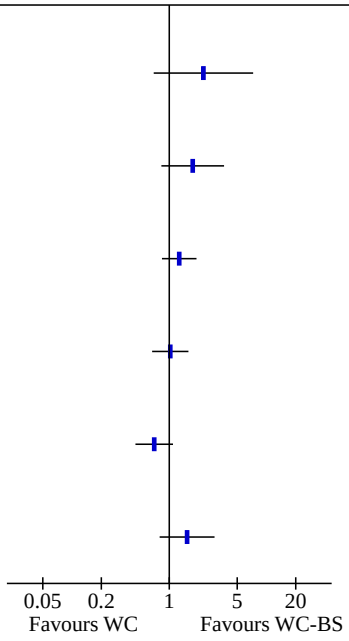
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Cases of confirmed cholera by time of follow-up (3-dose recipients)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1.1 First four months after vaccination	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals 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

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

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

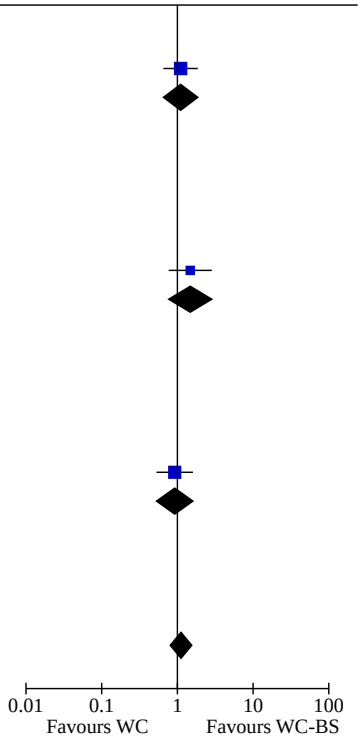
Analysis 4.1. Comparison 4: Whole cell vaccine (WC) versus Whole cell vaccine plus B subunit (WC-BS) - Subgroup analysis, Outcome 1: Cases of confirmed cholera by time of follow-up (3-dose recipients)

	WC Vaccine		WC-BS Vaccine		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	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]	



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%						

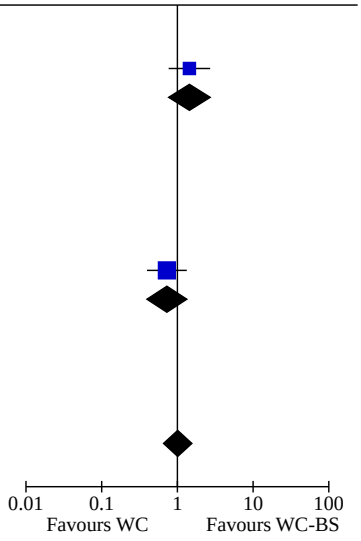


Footnotes

(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

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%						

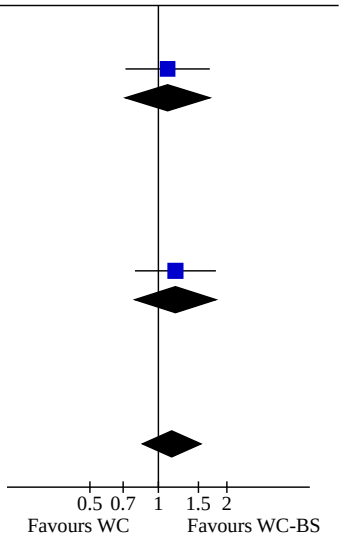


Footnotes

(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

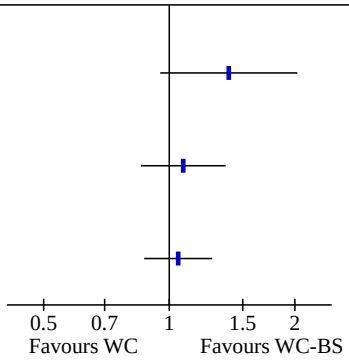
Analysis 4.4. Comparison 4: Whole cell vaccine (WC) versus Whole cell vaccine plus B subunit (WC-BS) - Subgroup analysis, Outcome 4: Cases of cholera by blood group, First 2 years of follow-up (3-dose recipients)

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%						



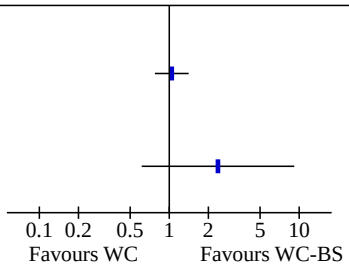
Analysis 4.5. Comparison 4: Whole cell vaccine (WC) versus Whole cell vaccine plus B subunit (WC-BS) - Subgroup analysis, Outcome 5: Cases of all cause diarrhoea - 1st year of follow-up (3-dose recipients)

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]



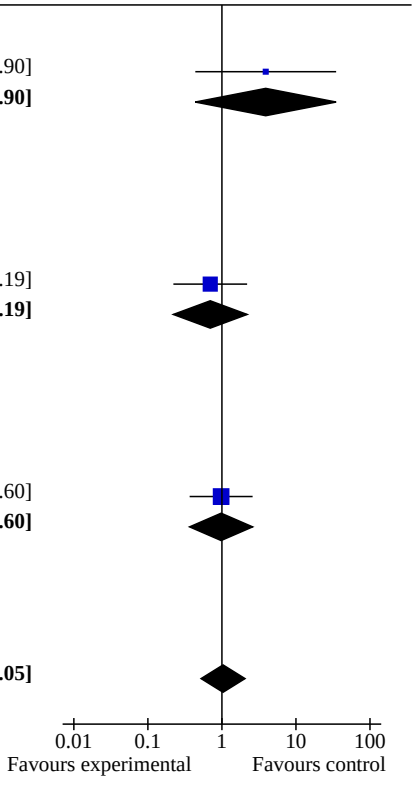
Comparison 5. Whole cell plus recombinant B subunit vaccine (WC-rBS) versus placebo - Subgroup analysis

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]

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

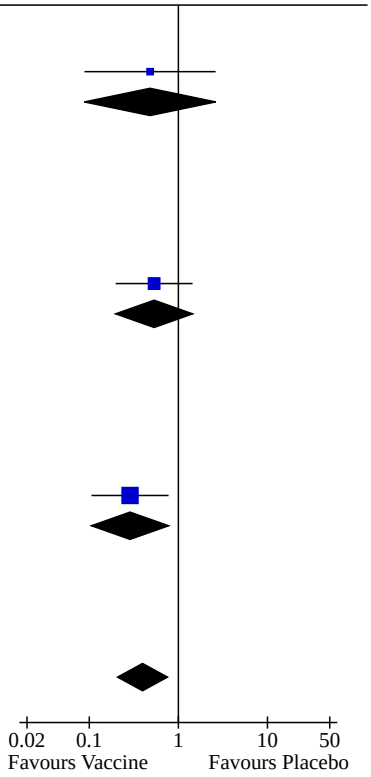
Analysis 5.1. Comparison 5: Whole cell plus recombinant B subunit vaccine (WC-rBS) versus placebo - Subgroup analysis, Outcome 1: Cases of cholera by age group - 1st year of follow-up (2 doses)

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: Chi^2 = 1.89, df = 2 (P = 0.39); I^2 = 0%						
Test for overall effect: Z = 0.10 (P = 0.92)						
Test for subgroup differences: Chi^2 = 1.87, df = 2 (P = 0.39), I^2 = 0%						



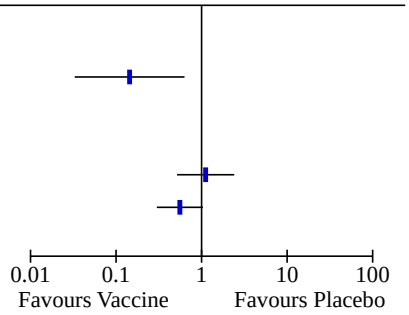
Analysis 5.2. Comparison 5: Whole cell plus recombinant B subunit vaccine (WC-rBS) versus placebo - Subgroup analysis, Outcome 2: Cases of cholera by age group - 2nd year of follow-up (2 doses plus booster)

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

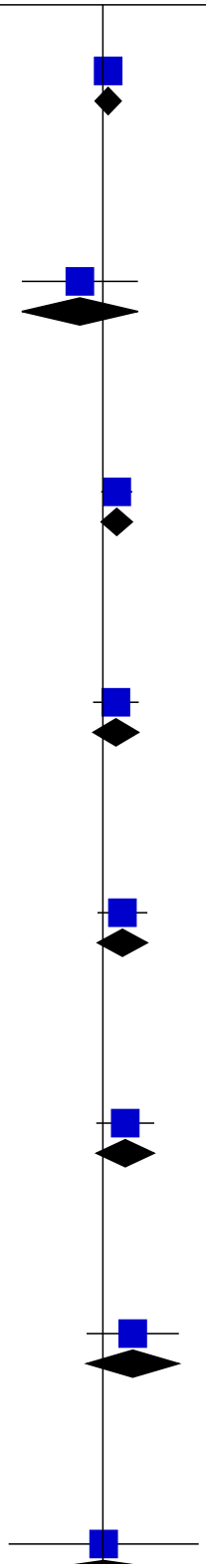
Comparison 6. Whole cell vaccines (all types) versus placebo - Safety outcomes (first dose)

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]

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]

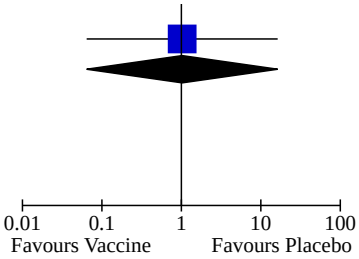
Analysis 6.1. Comparison 6: Whole cell vaccines (all types) versus placebo - Safety outcomes (first dose), Outcome 1: Adverse events - Whole cell (WC) versus placebo

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]



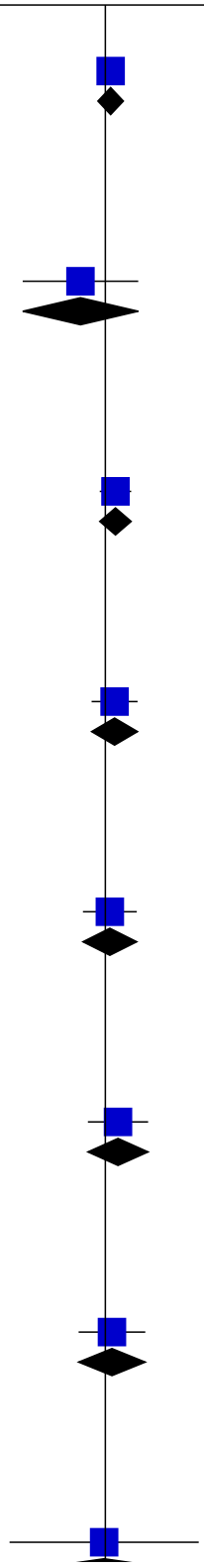
Analysis 6.1. (Continued)

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)						



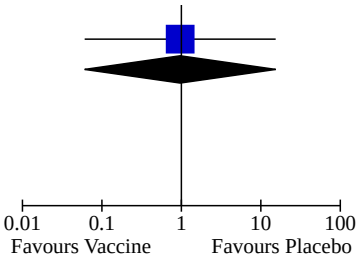
Analysis 6.2. Comparison 6: Whole cell vaccines (all types) versus placebo - Safety outcomes (first dose), Outcome 2: Adverse events - Whole cell plus B subunit (WC-BS) versus placebo

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]



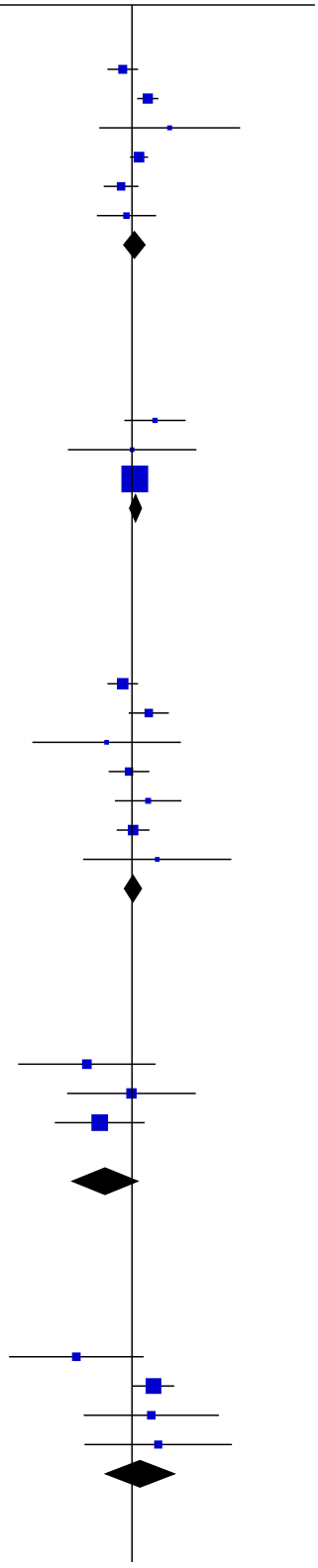
Analysis 6.2. (Continued)

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)						



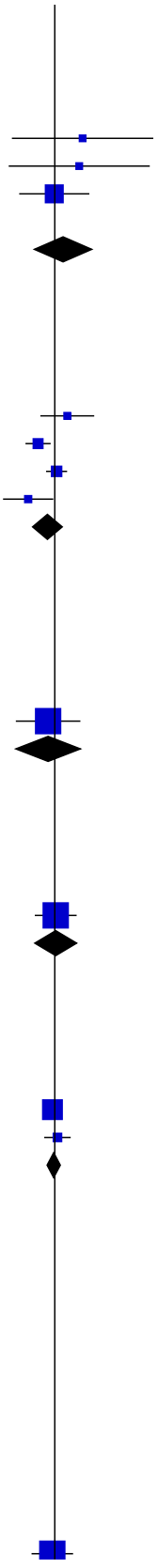
Analysis 6.3. Comparison 6: Whole cell vaccines (all types) versus placebo - Safety outcomes (first dose), Outcome 3: Adverse events - Whole cell plus recombinant B subunit (WC-rBS) versus placebo

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)						



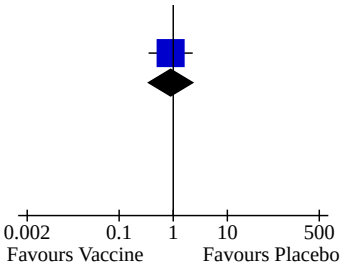
Analysis 6.3. (Continued)

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]



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)						

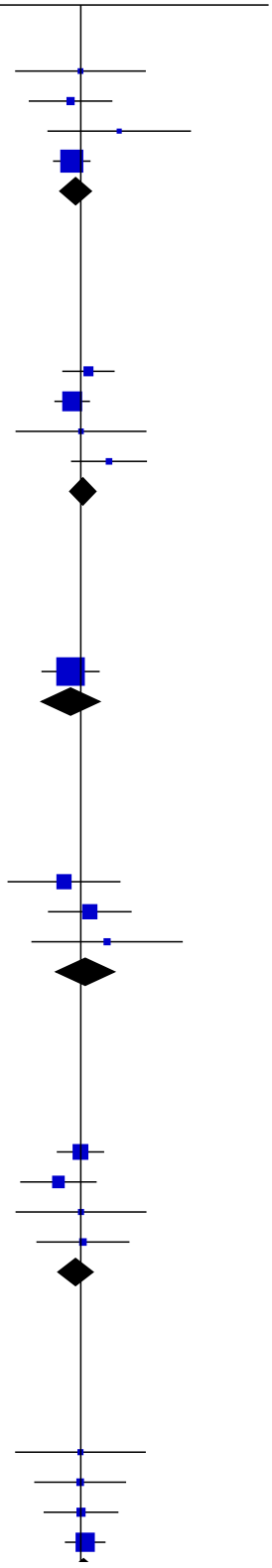


Footnotes

(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

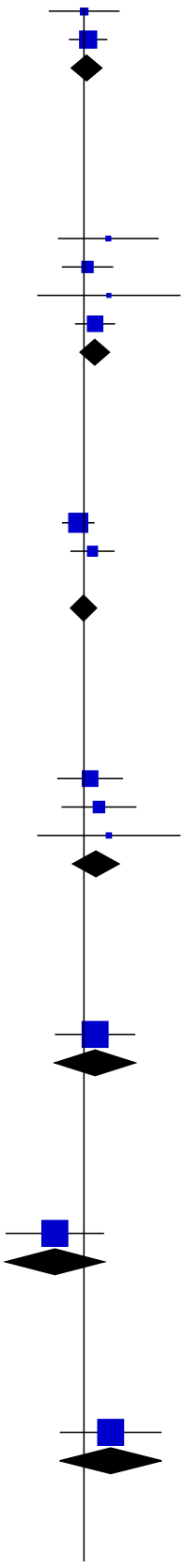
Analysis 6.4. Comparison 6: Whole cell vaccines (all types) versus placebo - Safety outcomes (first dose), Outcome 4: Adverse events - Bivalent whole cell (BivWC) versus placebo

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]



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)						



Analysis 6.4. (Continued)

Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)

6.4.13 Cough

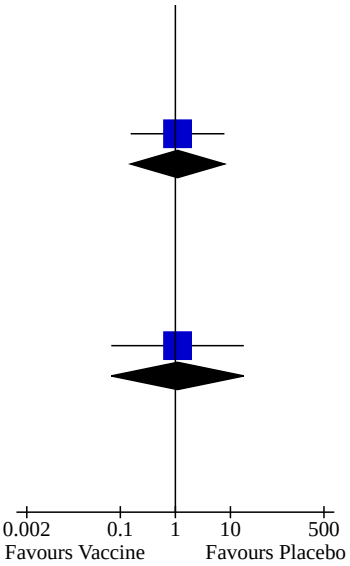
Sur 2009 India	2	31932	2	34968	100.0%	1.10 [0.15 , 7.77]
Subtotal (95% CI)		**31932**		**34968**	**100.0%**	**1.10 [0.15 , 7.77]**
Total events:	2		2			

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

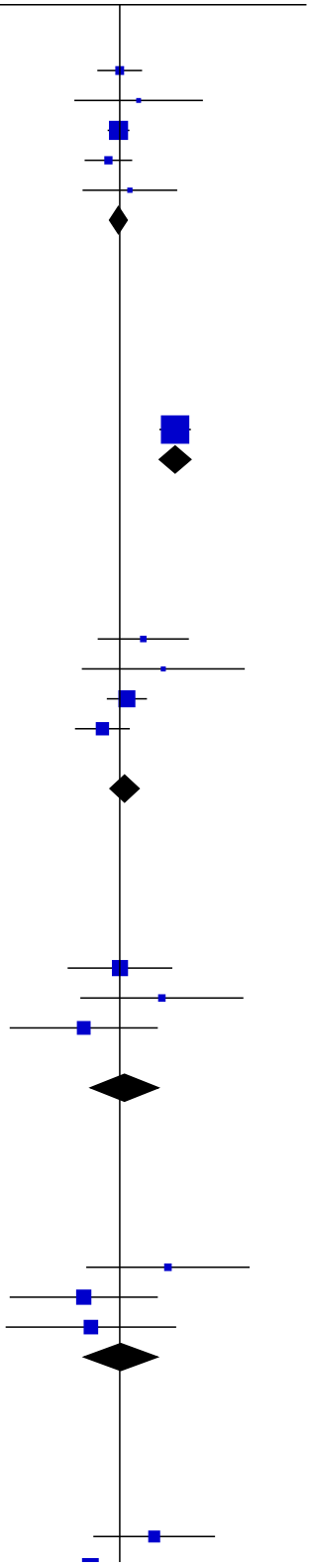
Comparison 7. Whole cell vaccines (all types) versus placebo - Safety outcomes (second dose)

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

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

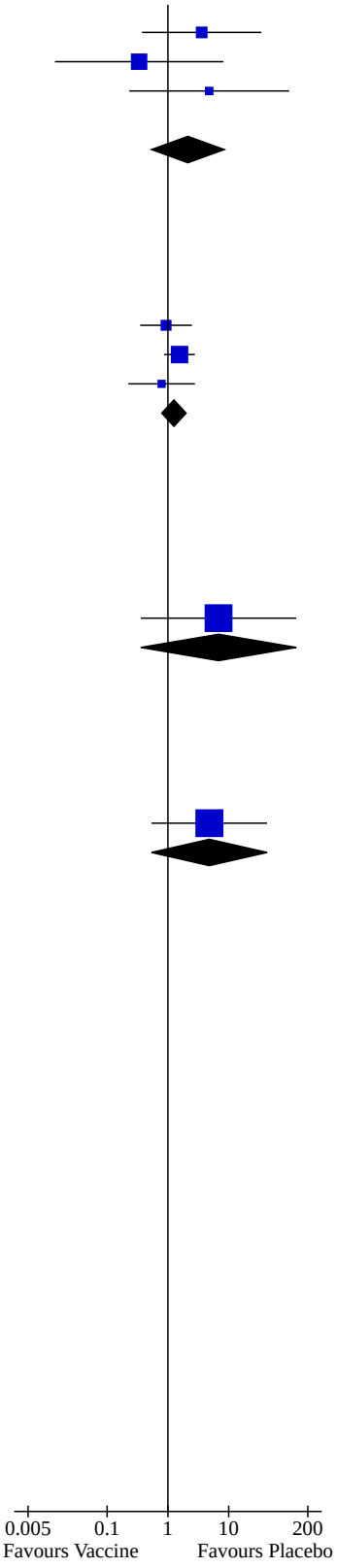
Analysis 7.1. Comparison 7: Whole cell vaccines (all types) versus placebo - Safety outcomes (second dose), Outcome 1: Adverse events - Whole cell plus recombinant B subunit (WC-rBS) versus placebo

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]



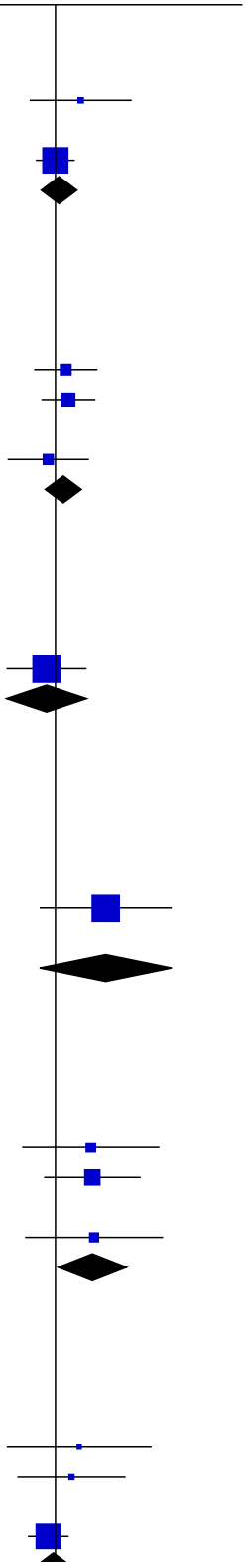
Analysis 7.1. (Continued)

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						



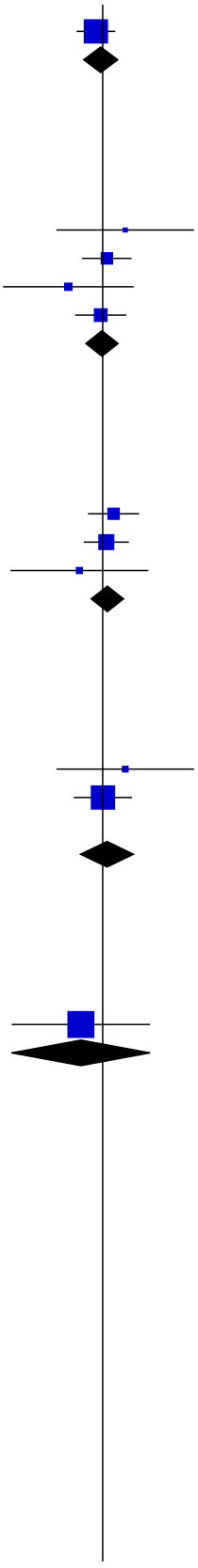
Analysis 7.2. Comparison 7: Whole cell vaccines (all types) versus placebo - Safety outcomes (second dose), Outcome 2: Adverse events - Bivalent whole cell (BivWC) versus placebo

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]**



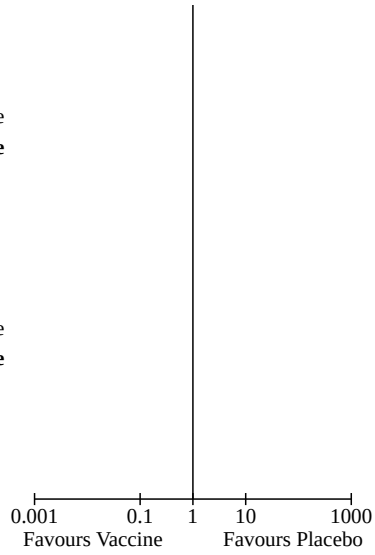
Analysis 7.2. (Continued)

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						



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

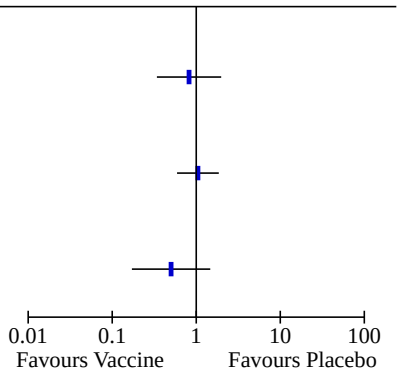
Comparison 8. Live attenuated vaccines (all types) versus placebo - Efficacy outcomes

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]

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]

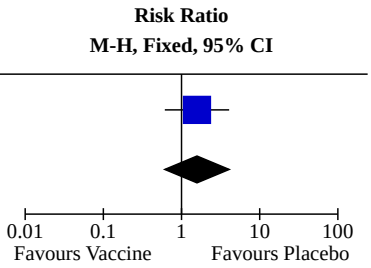
Analysis 8.1. Comparison 8: Live attenuated vaccines (all types) versus placebo - Efficacy outcomes, Outcome 1: Cases of cholera following natural infection - CVD 103HgR versus placebo

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

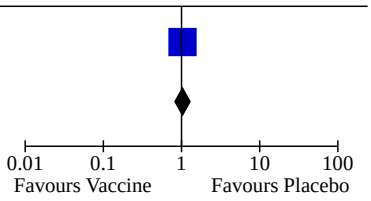
Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Richie 2000 Indonesia	11	33696	7	33812	100.0%	1.58 [0.61 , 4.07]
Total (95% CI)		**33696**		**33812**	**100.0%**	**1.58 [0.61 , 4.07]**
Total events:	11		7			
Heterogeneity: Not applicable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



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			

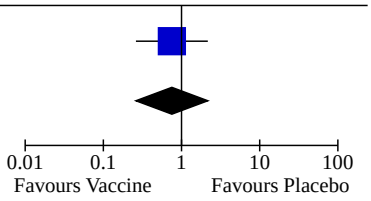
Heterogeneity: Not applicable
Test for overall effect: Z = 0.26 (P = 0.80)
Test for subgroup differences: Not applicable



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

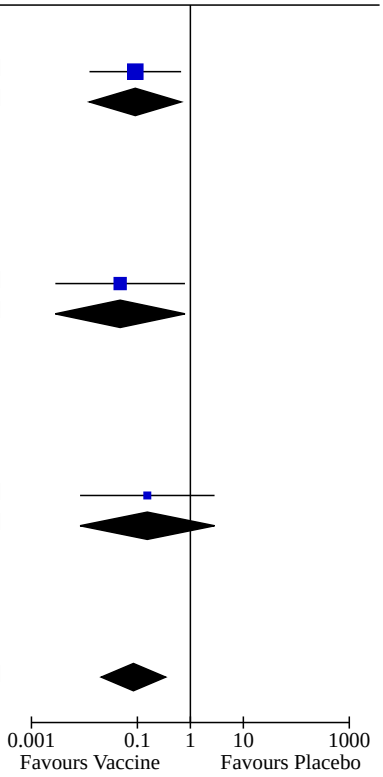
Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Richie 2000 Indonesia	6	33696	8	33812	100.0%	0.75 [0.26 , 2.17]
Total (95% CI)		**33696**		**33812**	**100.0%**	**0.75 [0.26 , 2.17]**
Total events:	6		8			

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

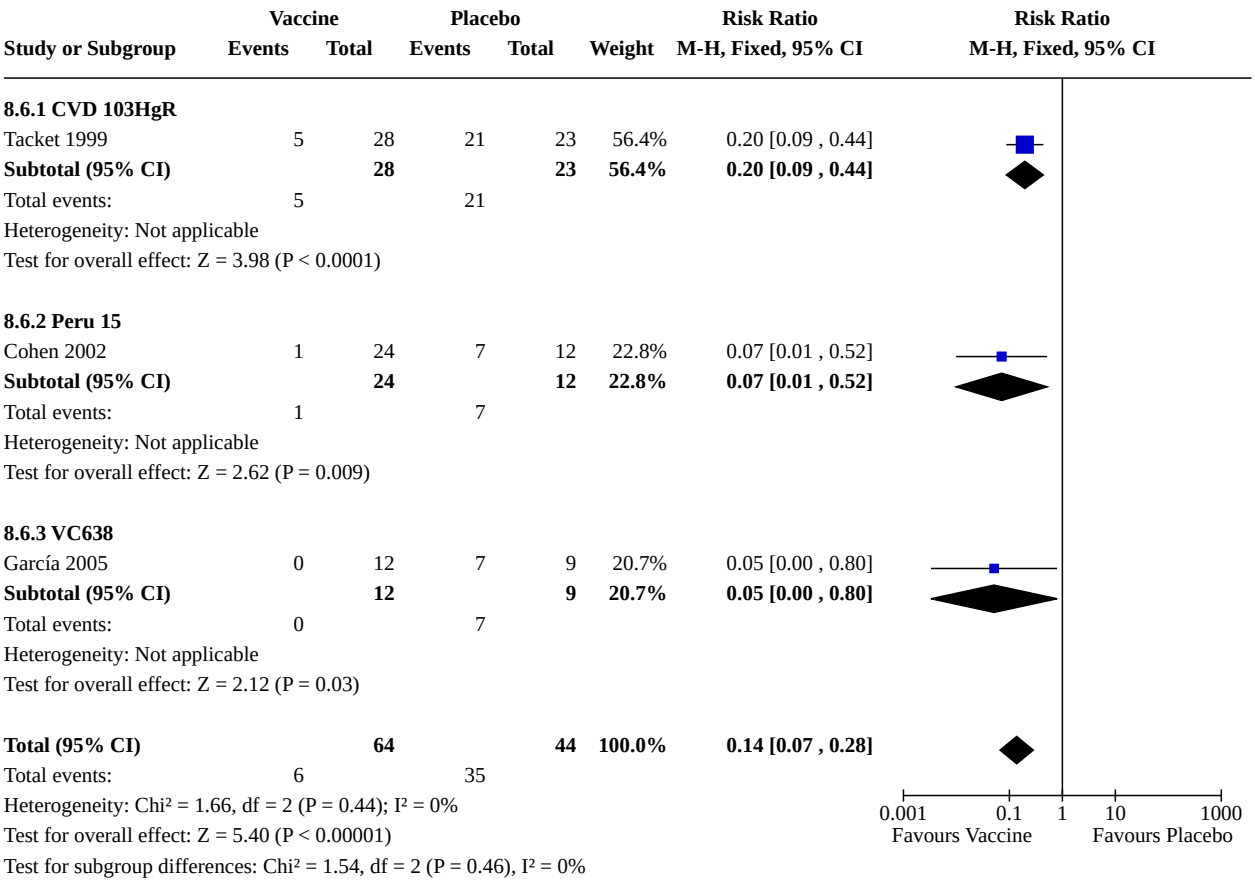


Analysis 8.5. Comparison 8: Live attenuated vaccines (all types) versus placebo - Efficacy outcomes, Outcome 5: Cases of moderate to severe diarrhoea - following artificial challenge

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%						



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

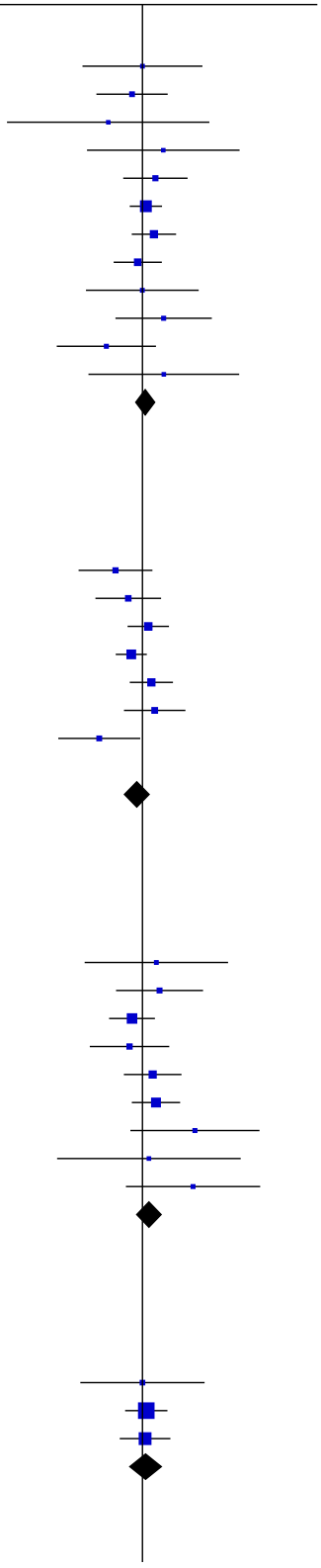
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Adverse events - CVD 103-HgR versus placebo	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1.1 Diarrhoea	12	3320	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.81, 1.47]
9.1.2 Fever	8	2516	Risk Ratio (M-H, 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]

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]

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

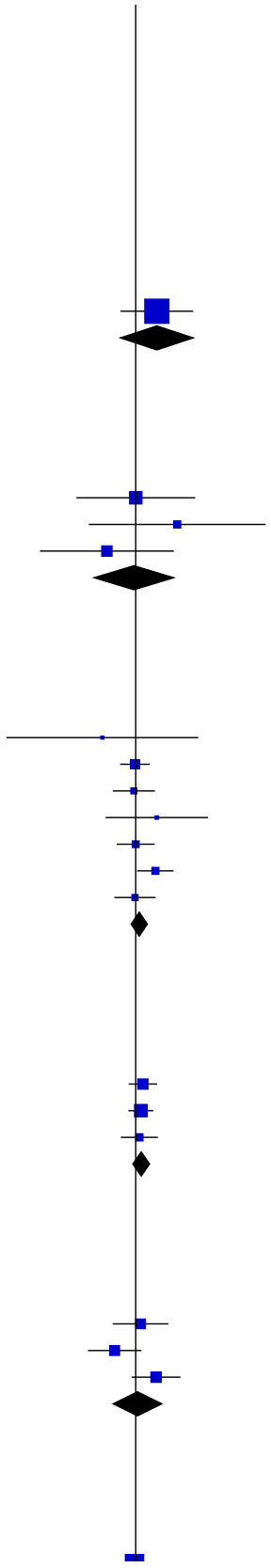
Analysis 9.1. Comparison 9: Live attenuated vaccines (all types) versus placebo - Safety outcomes, Outcome 1: Adverse events - CVD 103-HgR versus placebo

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)						



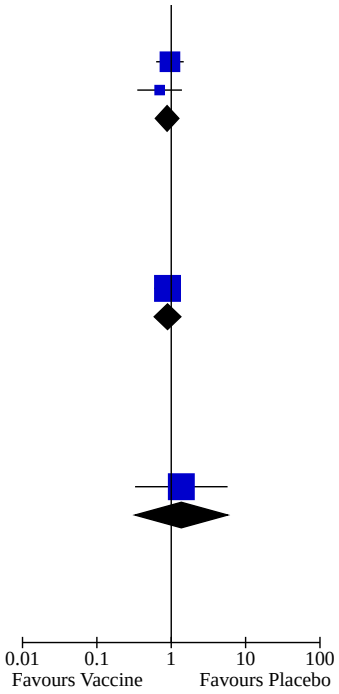
Analysis 9.1. (Continued)

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]



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: $Tau^2 = 0.00$; $Chi^2 = 0.60$, df = 1 (P = 0.44); $I^2 = 0\%$						
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)						

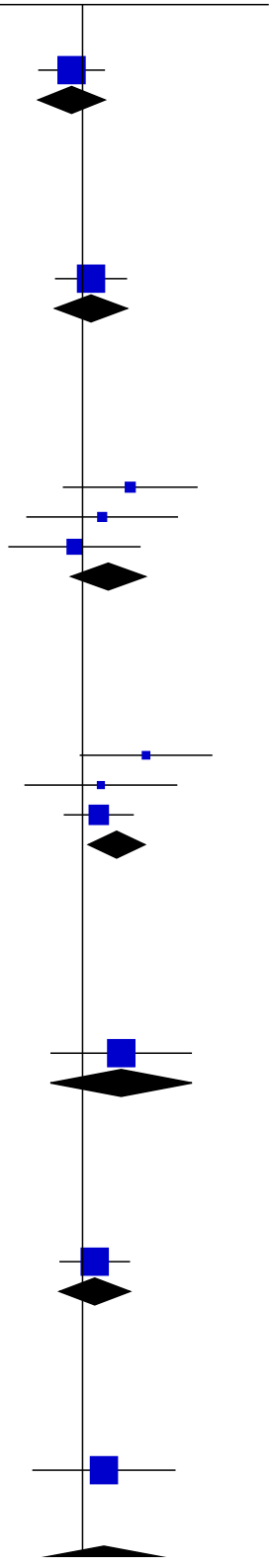


Footnotes

(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: $2\text{-}8x10_8$

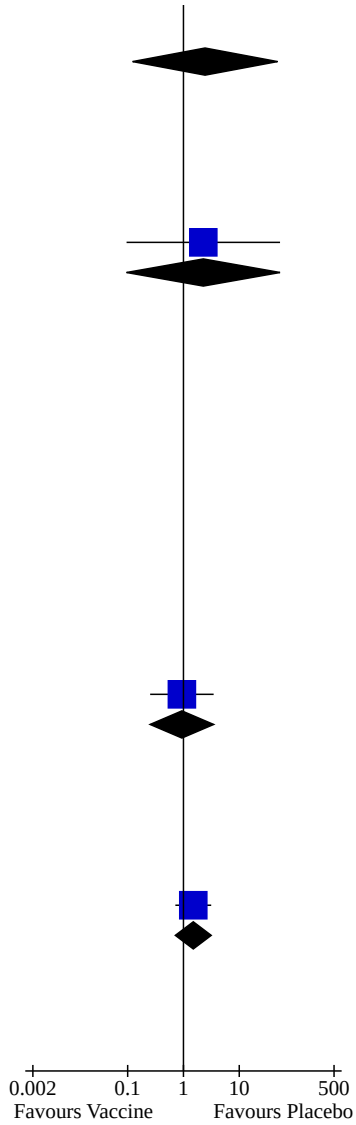
Analysis 9.2. Comparison 9: Live attenuated vaccines (all types) versus placebo - Safety outcomes, Outcome 2: Adverse events - Peru 15 versus placebo

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]**



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

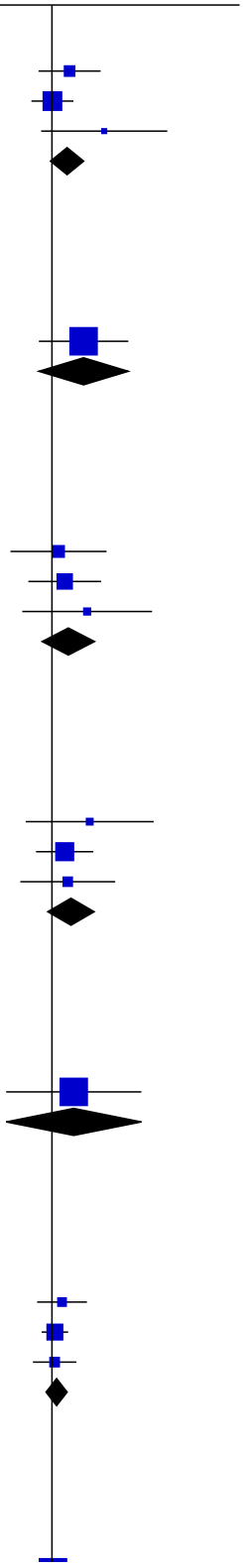
(2) Qadri 2005: Age 18 to 45 years, 4 days AE monitoring, all AEs are described as mild

(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

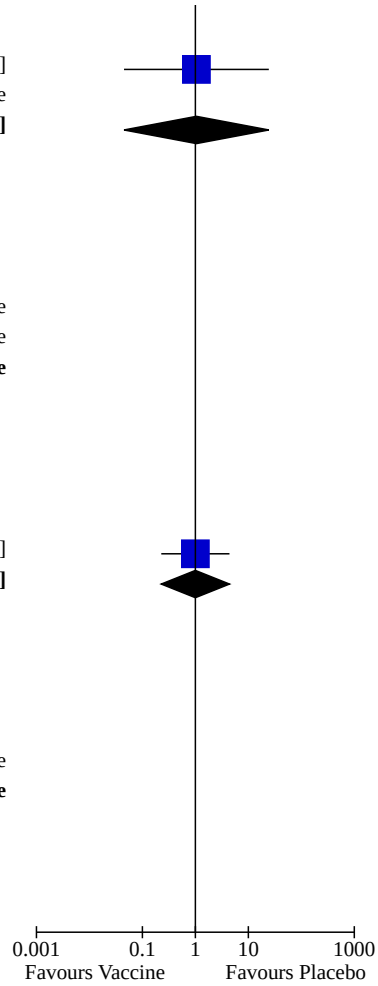
Analysis 9.3. Comparison 9: Live attenuated vaccines (all types) versus placebo - Safety outcomes, Outcome 3: Adverse events - VC638 versus placebo

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						



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

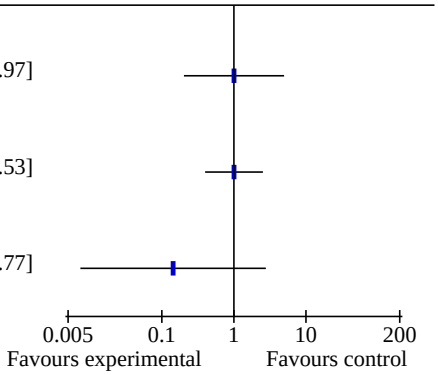
Comparison 10. Live attenuated CVD 103-HgR vaccine versus placebo - Subgroup analysis

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

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

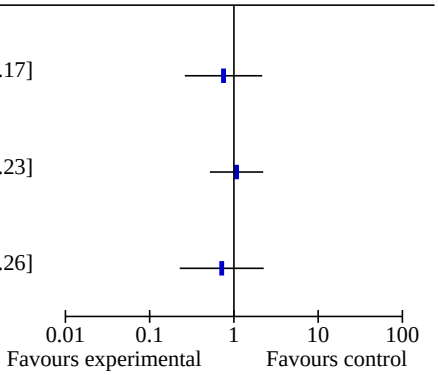
Analysis 10.1. Comparison 10: Live attenuated CVD 103-HgR vaccine versus placebo - Subgroup analysis, Outcome 1: Cases of cholera by age group (age 2-5 years)

Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Risk Ratio 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]



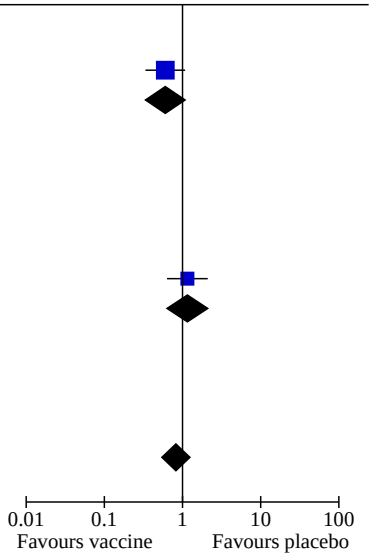
Analysis 10.2. Comparison 10: Live attenuated CVD 103-HgR vaccine versus placebo - Subgroup analysis, Outcome 2: Cases of confirmed cholera attending healthcare facilities (age over 5 years)

Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Risk Ratio 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]



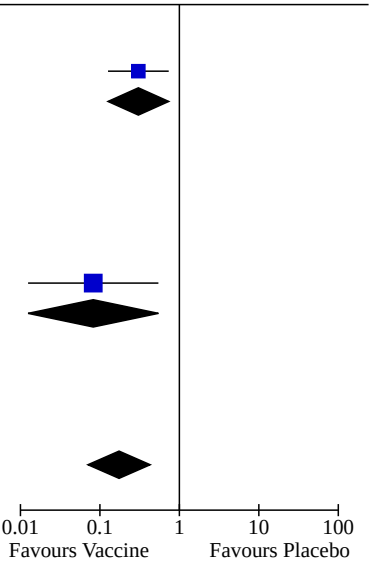
Analysis 10.3. Comparison 10: Live attenuated CVD 103-HgR vaccine versus placebo - Subgroup analysis, Outcome 3: Cases of cholera within four years and five months, by blood group

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%						

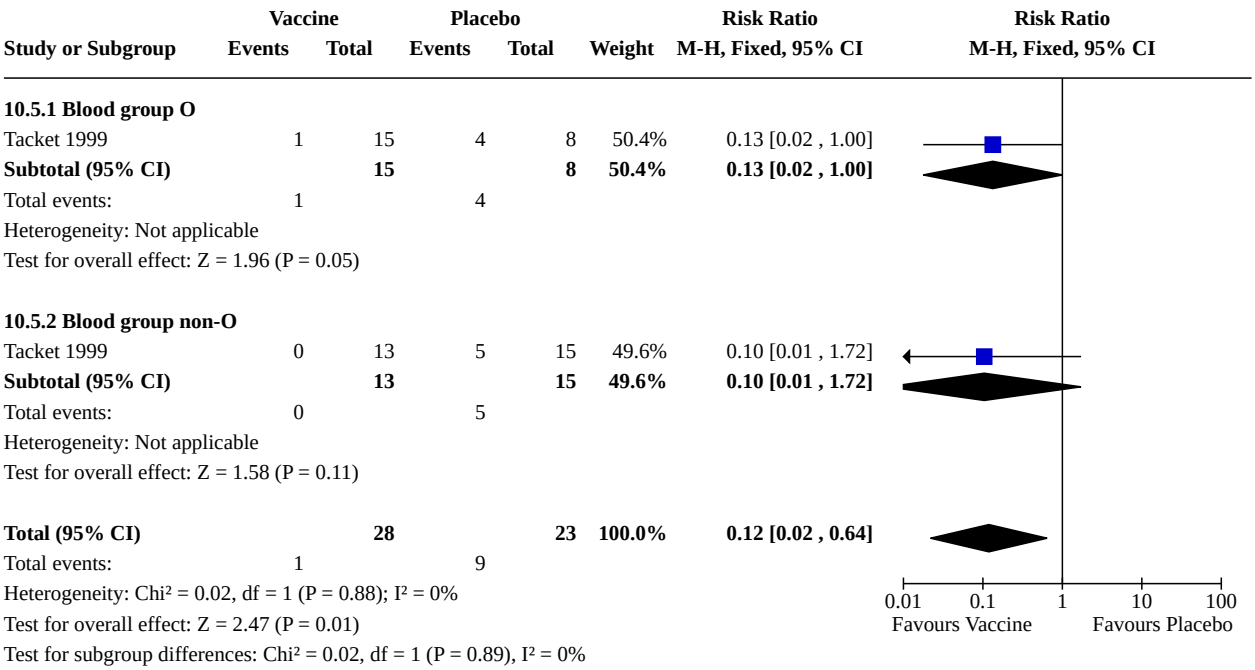


Analysis 10.4. Comparison 10: Live attenuated CVD 103-HgR vaccine versus placebo - Subgroup analysis, Outcome 4: Any diarrhoea following artifical challenge, by blood group

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%						



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

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: • 2.5 x 10^{10} heat-killed *V. cholerae* classical Inaba whole cells (strain Cairo 48) • 2.5 x 10^{10} heat-killed *V. cholerae* classical Ogawa whole cells (strain Cairo 50) • 2.5 x 10^{10} formalin-killed*V. cholerae* El Tor Inaba whole cells (strain Phil 6973) • 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: • 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: • 1 mg recombinant cholera B subunit
	Dosing schedule	Two doses, 2 weeks apart 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)

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 Taylor 2000 Peru: Adults and children aged 2 to 65 years
vWC **(ORCVAX®)**	**Composition**	Four strains of *V. cholerae* O1. As for WC except the2.5 x 10^{10} formalin-killed*V. cholerae* classical Ogawa whole cells (strain Cairo 50) are replaced with: • 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 **(Shanchol®)**	**Composition**	Three strains of *V. cholerae* O1 plus one strain of *V. cholerae* O139: • 600 ELISA units of LPS of formalin-killed *V. cholerae* O1 El Tor Inaba (strain Phil 6973), • 300 ELISA units of LPS of heat-killed *V. cholerae* O1 Classical Ogawa (strain Cairo 50), • 300 ELISA units of LPS of formalin-killed *V. cholerae* O1 Classical Ogawa (strain Cairo 50), • 300 ELISA units of LPS of heat-killed *V. cholerae* O1 Classical Ogawa (strain Cairo 48), and • 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 (Trade name)	Item	Vaccine composition, dosing and population used in the field trials
CVD103-HGR **(not currently available)**	**Composition**	Richie 2000 Indonesia: 5 x 10^{9} lyophilized organisms of a genetically modified *V. cholerae* O1 Classical Inaba (569B) 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 **Artificial challenge study**	Richie 2000 Indonesia: 67,508 participants Tacket 1999: 51 participants
	Population	Richie 2000 Indonesia: Age 2 to 41 years in Jakarta, Indonesia

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 **(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 **(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).

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