Vaccines for preventing typhoid fever (Review)

Anwar E, Goldberg E, Fraser A, Acosta CJ, Paul M, Leibovici L

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2014, Issue 1

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Vaccines for preventing typhoid fever

Elspeth Anwar[1], Elad Goldberg[2], Abigail Fraser[3], Camilo J Acosta[4], Mical Paul[5], Leonard Leibovici[2]

[1]Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK. [2]Department of Medicine E, Beilinson Hospital, Rabin Medical Center, Petah Tikva, Israel. [3]MRC Integrative Epidemiology Unit at the University of Bristol, University of Bristol, Oakfield House, Bristol, UK. [4]Merck Global Health Outcomes Vaccines, West Point, PA, USA. [5]Unit of Infectious Diseases, Rambam Health Care Center, Haifa, Israel and Sackler Faculty of Medicine, Tel Aviv, Israel

Contact address: Elspeth Anwar, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK. anware@liverpool.ac.uk.

Editorial group: Cochrane Infectious Diseases Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 1, 2014.
Review content assessed as up-to-date: 17 June 2013.

Citation: Anwar E, Goldberg E, Fraser A, Acosta CJ, Paul M, Leibovici L. Vaccines for preventing typhoid fever. *Cochrane Database of Systematic Reviews* 2014, Issue 1. Art. No.: CD001261. DOI: 10.1002/14651858.CD001261.pub3.

ABSTRACT

Background

Typhoid fever and paratyphoid fever continue to be important causes of illness and death, particularly among children and adolescents in south-central and southeast Asia. Two typhoid vaccines are commercially available, Ty21a (oral) and Vi polysaccharide (parenteral), but neither is used routinely. Other vaccines, such as a new, modified, conjugated Vi vaccine called Vi-rEPA, are in development.

Objectives

To evaluate the efficacy and adverse effects of vaccines used to prevent typhoid fever.

Search methods

In June 2013, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL, MEDLINE, EMBASE, LILACS, and *m*RCT. We also searched relevant conference proceedings up to 2013 and scanned the reference lists of all included trials.

Selection criteria

Randomized and quasi-randomized controlled trials (RCTs) comparing typhoid fever vaccines with other typhoid fever vaccines or with an inactive agent (placebo or vaccine for a different disease).

Data collection and analysis

Two review authors independently applied inclusion criteria and extracted data. We computed vaccine efficacy per year of follow-up and cumulative three-year efficacy, stratifying for vaccine type and dose. The outcome addressed was typhoid fever, defined as isolation of *Salmonella typhi* in blood. We calculated risk ratios (RRs) and efficacy (1-RR as a percentage) with 95% confidence intervals (CIs).

Main results

In total, 18 RCTs were included in this review; 12 evaluated efficacy (Ty21a: five trials; Vi polysaccharide: six trials; Vi-rEPA: one trial), and 11 reported on adverse events.

Ty21a vaccine (oral vaccine, three doses)

A three-dose schedule of Ty21a vaccine prevents around one-third to one-half of typhoid cases in the first two years after vaccination (Year 1: 35%, 95% CI 8% to 54%; Year 2: 58%, 95% CI 40% to 71%; one trial, 20,543 participants; *moderate quality evidence;* data taken from a single trial conducted in Indonesia in the 1980s). No benefit was detected in the third year after vaccination. Four additional cluster-RCTs have been conducted, but the study authors did not adjust for clustering.

Compared with placebo, this vaccine was not associated with more participants with vomiting, diarrhoea, nausea or abdominal pain (four trials, 2066 participants; *moderate quality evidence*) headache, or rash (two trials, 1190 participants; *moderate quality evidence*); however, fever (four trials, 2066 participants; *moderate quality evidence*) was more common in the vaccine group.

Vi polysaccharide vaccine (injection, one dose)

A single dose of Vi polysaccharide vaccine prevents around two-thirds of typhoid cases in the first year after vaccination (Year 1: 69%, 95% CI 63% to 74%; three trials, 99,979 participants; *high quality evidence*). In Year 2, the trial results were more variable, with the vaccine preventing between 45% and 69% of typhoid cases (Year 2: 59%, 95% CI 45% to 69%; four trials, 194,969 participants; *moderate quality evidence*). The three-year cumulative efficacy of the vaccine is around 55% (95% CI 30% to 70%; 11,384 participants, one trial; *moderate quality evidence*). These data are taken from a single trial in South Africa in the 1980s.

Compared with placebo, this vaccine was not associated with more participants with fever (four trials, 133,038 participants; *moderate quality evidence*) or erythema (three trials, 132,261 participants; *low quality evidence*); however, swelling (three trials, 1767 participants; *moderate quality evidence*) and pain at the injection site (one trial, 667 participants; *moderate quality evidence*) were more common in the vaccine group.

Vi-rEPA vaccine (two doses)

Administration of two doses of the Vi-rEPA vaccine prevents between 50% and 96% of typhoid cases during the first two years after vaccination (Year 1: 94%, 95% CI 75% to 99%; Year 2: 87%, 95% CI 56% to 96%; one trial, 12,008 participants; *moderate quality evidence*). These data are taken from a single trial with children 2 to 5 years of age conducted in Vietnam.

Compared with placebo, the first and second doses of this vaccine were not associated with increased risk of adverse events. The first dose of this vaccine was not associated with fever (2 studies, 12,209 participants; *low quality evidence*), erythema (two trials, 12,209 participants; *moderate quality evidence*) or swelling at the injection site (two trials, 12,209 participants; *moderate quality evidence*). The second dose of this vaccine was not associated with fever (two trials, 11,286 participants; *low quality evidence*), erythema (two trials, 11,286 participants; *moderate quality evidence*) and swelling at the injection site (two trials, 11,286 participants; *moderate quality evidence*).

Authors' conclusions

The licensed Ty21a and Vi polysaccharide vaccines are efficacious. The new and unlicensed Vi-rEPA vaccine is as efficacious and may confer longer immunity.

PLAIN LANGUAGE SUMMARY

Ty21a and Vi polysaccharide vaccines are effective in reducing typhoid fever; new vaccines are promising

Typhoid fever is a bacterial infection found mainly among children and adolescents in south and east Asia, Africa, Latin America and the Caribbean. Typhoid fever is spread by food, drink, or contaminated water. It is characterized by fever, abdominal symptoms, headache, loss of appetite, cough, weakness, sore throat, dizziness and muscle pains. The infection also sometimes causes psychosis and confusion. Mortality varies and can reach 10% of cases. Treatment normally consists of antibiotics, but problems with drug-resistant strains have been reported. Improved sanitation and food hygiene are important control measures. However, these are associated with socioeconomic progress that has been slow in most affected areas. Therefore vaccination is an effective way to try to prevent this disease. The review found 18 trials (17 with usable data): Six evaluated vaccine effectiveness only; six evaluated vaccine effectiveness and adverse events; and six provided data only on adverse events. The two major vaccines currently licensed for use, Ty21a and Vi polysaccharide, were effective in reducing typhoid fever; adverse events such as nausea, vomiting and fever were rare. Other vaccines, such as a new, modified, conjugated Vi vaccine called Vi-rEPA, are in development and appear promising. A vaccine that could be given to infants would be helpful as they are probably at increased risk of this infection.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [*Explanation*]

Ty21a vaccine (3 doses) compared with control; efficacy for preventing typhoid fever

Patient or population: adults and children aged 5 years of age and older
Settings: any
Intervention: Ty21a vaccine (3 doses)
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Ty21a vaccine				
Incidence of typhoid fever, Year 1	**Moderate**[1]		**RR 0.65** (0.46 to 0.92)	20,543 (1 study, 2 arms)	⊕⊕⊕◯ **moderate**[2,3,4,5]	Additional cluster-randomized studies have evaluated this vaccine but did not adjust for the effect of clustering and therefore were not included in the meta-analysis
	4 per 10,000	**3 per 10,000** (2 to 4)				
	High[1]					
	59 per 10,000	**38.4 per 10,000** (27.1 to 54.3)				
Incidence of typhoid fever, Year 2	**Moderate**[1]		**RR 0.42** (0.29 to 0.6)	20,543 (1 study, 2 arms)	⊕⊕⊕◯ **moderate**[2,4,5,6]	
	4 per 10,000	**1.7 per 10,000** (1.2 to 2.4)				
	High[1]					
	59 per 10,000	**24.8 per 10,000** (17.1 to 35.4)				
Serious adverse events	See comment	See comment	Not estimable	2620 (3 studies, 5 arms)	See comment	No serious adverse events were reported

Fever	**17 per 1000**	**25 per 1000** (14 to 45)	**RR 1.53** (0.86 to 2.72)	2066 (2 studies, 4 arms)	⊕⊕⊕◯ **moderate**[2,7,8]
Rash	**4 per 1000**	**8 per 1000** (2 to 28)	**RR 1.89** (0.56 to 6.43)	1190 (2 studies, 4 arms)	⊕⊕⊕◯ **moderate**[2,8,9]
Vomiting	**25 per 1000**	**15 per 1000** (7 to 31)	**RR 0.61** (0.3 to 1.24)	2066 (1 study, 2 arms)	⊕⊕⊕◯ **moderate**[2,8,10]
Any mild adverse event	**70 per 1000**	**117 per 1000** (72 to 191)	**RR 1.67** (1.03 to 2.72)	1360 (2 studies, 3 arms)	⊕⊕⊕◯ **moderate**[2,11,12]

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

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]The incidence of typhoid in a medium -risk setting is taken from the control group in a study from china (Yang 2001 CHN).The incidence of typhoid in a high-risk setting is taken from a study in India (Sur 2009 IND). This is consistent with the incidence levels described by a global epidemiological study (Crump 2004).
[2]No serious risk of bias detected.
[3]No serious inconsistency: The result was consistent across the two trials ($I^2 = 0$).
[4]Downgraded by 1 for indirectness: The vaccine has been evaluated only in trials from one endemic setting (Indonesia).
[5]No serious imprecision: The result is statistically significant with a narrow 95% confidence interval. The meta-analysis is adequately powered to detect this effect.
[6]No serious inconsistency: The result was consistent across the two trials ($I^2 = 1\%$).
[7]No serious inconsistencies: The results were consistent across the 5 trials ($I^2 = 0$).
[8]Downgraded by 1 for serious imprecision: The result is not statistically significant.
[9]No serious inconsistency: The results were consistent across the three trials ($I^2 = 0$).
[10]No serious inconsistency.
[11]Downgraded by 1 for indirectness: The vaccine has been evaluated only in trials from high-incidence settings (Indonesia and Thailand).
[12]No serious imprecision: The result is statistically significant with a narrow 95% confidence interval.

BACKGROUND

Description of the condition

Epidemiology

Typhoid fever remains an important global public health problem. It is estimated that typhoid fever has caused 21.7 million illnesses and 217,000 deaths worldwide (Crump 2004). However, this is likely to be a conservative estimate because availability of diagnostic testing and surveillance is limited, and the burden of typhoid fever is unknown in many developing countries (Crump 2010).

The highest burden of typhoid fever is seen in south-central and south-eastern Asia (Crump 2004). Recent large population-based surveillance studies conducted in five Asian countries (China, India, Indonesia, Pakistan and Vietnam) have confirmed the high incidence of typhoid fever in the region (Ochiai 2008). Typhoid fever incidence in sub-Saharan Africa is poorly described; historically, typhoid fever within the region has been thought to occur in the form of outbreaks rather than as endemic disease. However, a recent population-based surveillance study conducted in Kenya found a high incidence of typhoid fever among children in urban settings, with rates similar to those seen in south-central and south-eastern Asia (Breiman 2012). Typhoid fever is rare in industrialized nations, although travellers to endemic countries are at risk of acquiring the disease (Bennish 1995).

Until recently, the common view was that typhoid fever mainly affects children of school age and adults. However, it is now recognized that typhoid fever is an important cause of morbidity among younger children in areas of high incidence (Ochiai 2008; Sinha 1999; Saha 2001).

Clinical features

Typhoid fever is a systemic infection caused by the Gram-negative bacterium *Salmonella enterica* serotype *typhi* (*S. typhi*). *S. typhi* is spread by food, drink or water contaminated by faecal or urinary carriers excreting the bacteria. After ingestion, the bacteria spread from the intestine via the blood, where they multiply to the intestinal lymph nodes, liver and spleen. Typhoid fever is characterized by fever and abdominal symptoms. Nonspecific symptoms such as chills, perspiration, diarrhoea or constipation, headache, anorexia, cough, weakness, sore throat, dizziness and muscle pains are frequently present before the onset of fever in typhoid. Neuropsychiatric manifestations, including psychosis and confusion, occur in 5% to 10% of those with typhoid fever. Other symptoms include bradycardia, rose spots, hepatomegaly, and splenomegaly (Mandell 2005).

Complications occur in 10% to 15% of patients, usually in the third and fourth weeks of infection. The most important complications are gastrointestinal bleeding, intestinal perforation and typhoid encephalopathy. Gastrointestinal bleeding is the most common, occurring in up to 10% of patients (Parry 2002). Estimates of case-fatality rates in typhoid fever range from 1% to 4%; fatality rates in children younger than 4 years of age are 10 times higher than in older children. In untreated cases, the fatality rates may rise to 10% to 20% (Bhutta, 1996).

Diagnosis and treatment

Confirmation of typhoid fever requires isolation of *S. typhi* from blood, bone marrow, stool or duodenal fluid; blood culture is the most common method of diagnosis. The Widal test identifies the agglutinating antibodies against the O (somatic) and H (flagellar) *S. typhi* antigens, which appear a week to 10 days after disease onset. However, the high numbers of false-positive and false-negative Widal test results limit its clinical usefulness (Bhan 2005).

Typhoid fever is treated with antibiotics. Increased case-fatality rates have been associated with multidrug-resistant strains and delays in antimicrobial therapy. Chloramphenicol was for a long time the preferred treatment for typhoid fever, but owing to substantial relapse rates and the development of bacterial resistance during the 1970s and 1980s, this drug was widely replaced by ampicillin and co-trimoxazole. More recently, increasing resistance to the latter antibiotics has prompted the use of quinolone derivatives and third-generation cephalosporins (WHO 2008).

Potential control measures

As humans are the only source of infection and because of the route of transmission, improved sanitation and food hygiene are important control measures. However, these measures are associated with socioeconomic progress that has been slow in most endemic areas. Furthermore, achieving control of typhoid fever by antimicrobial treatment alone requires well-functioning medical services and is hindered by the increasing problem of antibiotic-resistant *S. typhi.* Therefore vaccination against typhoid fever is a key control measure in high-risk areas (WHO 2008). In addition to the populations residing in areas in which typhoid fever is endemic, travellers to these regions as well as household contacts of typhoid fever carriers and laboratory workers may benefit from an effective vaccine (Parry 2002).

Description of the intervention

Typhoid vaccines

Vaccination against typhoid fever is a key control measure; however, although they have been evaluated among populations in endemic middle- and low-income countries, typhoid fever vaccines have been used predominantly among travellers from high-

income countries. This situation is changing, thanks to the availability of high-quality burden of disease data from endemic countries (Ochiai 2008) and to the experience of typhoid vaccination programs in Thailand, China, Vietnam and India (DeRoeck, 2008), and of vaccine demonstration projects in five Asian countries (Ochiai, 2007). A 2008 World Health Organization (WHO) position paper on the use of typhoid vaccines concluded that given the continued high burden of disease and increasing antibiotic resistance, countries should consider the programmatic use of typhoid vaccines for controlling endemic disease (WHO 2008). Despite this recommendation, very few typhoid endemic countries have implemented a typhoid vaccination programme (Maurice, 2012).

Two typhoid vaccines are currently available internationally: the live oral Ty21a vaccine (an attenuated strain of *S. typhi*) and the parenteral Vi polysaccharide (based on the purified capsular polysaccharide *S. typhi* Vi antigen).

Researchers are working to develop a low-cost typhoid vaccine that is effective in children younger than two years, and that can therefore be incorporated into the infant EPI (Expanded Programme on Immunization) schedule. Typhoid vaccine development is currently moving in two main directions: the development of Vi conjugate vaccines, and the development of an improved live oral vaccine (WHO 2008).

Inactivated whole-cell typhoid vaccine

Vaccines of this type were introduced in 1896 (WHO 2005). Their efficacy was established only in 1960 in controlled trials in Yugoslavia, the Soviet Union, Poland and Guyana. The 1998 version of this Cochrane Review demonstrated that two doses of this type of vaccine resulted in 73% efficacy over three years (95% confidence interval 65% to 80%) (Engels 1998a). Different methods of inactivating cells of *S. typhi* have been used to prepare these vaccines: acetone-inactivated, alcohol-inactivated or heat-inactivated and phenol preserved. In field trials, the vaccine has been associated with fever and systemic reactions in 9% to 34% of recipients, and with short absences from work or school in 2% to 17% of cases (WHO 2000). Therefore, the inactivated whole-cell typhoid vaccine is considered unsuitable for use as a public health vaccine, and, although licensed, it is no longer available for use (Garmory 2002). Consequently, we have not included killed whole-cell vaccines in this update.

Ty2la vaccine

This live oral vaccine is available as an enteric-coated capsule or liquid formulation. It is given in three doses every other day and is approved for use in children at least 5 years of age. It elicits protection that starts 10 to 14 days after the third dose. Travellers should be revaccinated annually, and those living in disease endemic areas every three years. A theoretical question associated with the Ty21a vaccine is whether it reverts to virulence; however, such hypothetical effects have never been documented in any of the multiple large field trials conducted (WHO 2008).

The 2007 version of this Cochrane review found that compared with placebo, the TY21a vaccine provided statistically significant protection over the first three years following vaccination, and that this vaccine was not associated with an increased rate of mild adverse events (Fraser 2007a).

Vi polysaccharide vaccine

The Vi polysaccharide vaccine is given as a single parenteral dose. Protection begins seven days after injection, and maximum protection is reached 28 days after injection, when the highest antibody concentration is attained (Garmory 2002). This vaccine is approved for persons of 2 years of age and older. Revaccination every three years is recommended.

The 2007 version of this Cochrane review found that this vaccine provided protection in Year 1 and in Year 2 but not in Year 3 (Fraser 2007a).

Vi-rEPA vaccine

A new, modified Vi vaccine conjugated to a nontoxic recombinant *Pseudomonas aeruginosa* exotoxin A (rEPA) has been evaluated in a randomized controlled trial (RCT) among children 2 to 5 years of age. This vaccine (Vi-rEPA) has the potential of being immunogenic in infants younger than age 2 (Parry 2002). However, this prototype vaccine is not yet licensed.

Why it is important to do this review

This update of the 2007 Cochrane Review (Fraser 2007a) provides a more accurate assessment of the efficacy and safety of vaccines to prevent typhoid fever by incorporating data from new trials. We would have included head-on comparisons of vaccines had these been conducted.

OBJECTIVES

To evaluate the efficacy and adverse effects of vaccines used to prevent typhoid fever.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized controlled trials.

Types of participants

Adults and children.

Types of interventions

Intervention

- Typhoid fever vaccines (live oral vaccine Ty2la or genetic modifications of this strain, Vi polysaccharide vaccine, and Vi conjugate vaccine).

Control

- Other typhoid fever vaccines or inactive agents (placebo or vaccine for a different disease).

Excluded

- Trials evaluating killed whole-cell vaccines, because these vaccines are no longer in use. Trials assessing only adverse events but not efficacy (the number of typhoid fever cases prevented) of experimental vaccines that have not yet been evaluated for efficacy. We excluded trials that reported only on adverse events while comparing different brands of the same type of typhoid vaccine.

Types of outcome measures

Primary outcomes

Cases of typhoid fever

Cases of typhoid fever were defined by isolation of *S. typhi* from a blood culture.

Secondary outcomes

Adverse events

Serious adverse events (leading to death, requiring inpatient hospitalization or prolonged existing hospitalization, life threatening, or resulting in persistent or significant disability or incapacity). Other adverse events (eg fever, erythema at injection site, vomiting, diarrhoea).

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press and in progress).

Databases

We searched the following databases using the search terms and strategy described in Appendix 1: Cochrane Infectious Diseases Group Specialized Register (June 2013); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2013); MEDLINE (1966 to June 2013); EMBASE (1974 to June 2013); and LILACS (1982 to June 2013). We also searched the *meta*Register of Controlled Trials (*m*RCT) using 'typhoid' and 'vaccine' as search terms. We searched the Internet for new drug application (NDA) documents of the US Food and Drug Administration, which may include unpublished studies.

Conference proceedings

We searched the following conference proceedings for relevant abstracts: Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC; 1995 to 2013); European Congress of Clinical Microbiology and Infectious Diseases (ECCMID; 2001 to 2013); and the Annual Meeting of the Infectious Diseases Society of America (IDSA; 2001 to 2013).

Reference lists

We checked the reference lists of the included trials.

Data collection and analysis

We used standard methodological procedures as expected by The Cochrane Collaboration.

Selection of studies

We (E Anwar, E Goldberg and M Paul) independently inspected titles and abstracts identified by the literature search to identify potentially relevant publications. Potentially relevant articles, according to at least one review author, were obtained in full-text format. We applied the inclusion criteria for the final decision regarding eligibility. We also checked that trials were independent, that is, we looked for multiple publications of the same trial and made sure that we included each trial only once. We resolved disagreements by discussion and consensus. Reasons for excluding studies from the review were documented. We attempted to contact trial authors for clarification if it was unclear whether a potentially relevant trial was eligible for the review.

Data extraction and management

We (E Anwar and E Goldberg) independently extracted data into a standard form; a third review author (M Paul) extracted the data in cases of disagreement. We discussed data extraction, documented decisions and, when necessary, contacted the trial authors for clarification or additional details. E Anwar entered data into Review Manager 5. We aimed to extract data according to an intention-to-treat analysis. If a discrepancy was noted in the number randomly assigned and the numbers analyzed in each treatment group, we reported this information. We recorded the surveillance method used to assess outcomes in each trial, categorizing it as active (staff entry into the field to identify cases or establishment of additional study clinics), intermediate (reliance on existing clinics and encouragement to evaluate participants for typhoid fever) or passive (no increase in surveillance). We also recorded the unit of randomization and indicated whether trials were adjusted for cluster-randomization in the analysis.

For dichotomous outcome measures, we recorded the number of participants experiencing the event and the number analyzed in each treatment group. For trials randomly assigned using clusters (cluster-RCTs) we extracted cluster-adjusted risk ratios when available; we also recorded the number of clusters in the trial, the average size of clusters and the unit of randomization (eg, household or institution). The statistical methods used to analyze the trial results were documented, along with details describing whether these methods were adjusted for clustering or for other co-variables.

Assessment of risk of bias in included studies

We (E Anwar and E Goldberg) independently assessed the risk of bias in included trials; in cases of disagreement, we consulted a third review author (M Paul). We took an individual component approach to quality assessment by using five variables: generation of allocation sequence; allocation concealment; blinding of participants and investigators; inclusion of all randomly assigned participants in the analysis; and reporting of all stated outcomes. We categorized generation of the allocation sequence and allocation concealment as adequate, unclear, or inadequate by using the approach described in Jüni 2001. We recorded whether trials used single, double or no blinding, and whether all randomly assigned participants were included in the results. We classified inclusion of all randomly assigned participants in the analysis as adequate if at least 90% and as inadequate if less than 90%.

Data synthesis

If a single reference included more than one trial, we labelled the trials separately using a letter (eg, Wang 1997a CHN and Wang 1997b CHN); if a single trial compared several vaccine arms with a control arm, we labelled the arms separately using a roman numeral (eg, Black 1990i CHL and Black 1990ii CHL). To avoid including data for controls more than once in the same comparison, we divided the placebo group into equal parts while assuming equal incidence in these groups.

We combined dichotomous data from trials that randomly assigned individuals by using risk ratios (RRs) and presented them with 95% confidence intervals (CIs). We interpreted the results as efficacy, defined as 1-RR and expressed as a percentage. We pooled cluster-RCT data that had been adjusted for clustering with data from trials that randomly assigned individuals (individual-RCTs) using the generic inverse variance method. When the results of a cluster-RCT had not been adjusted for clustering, we did not pool the data but presented the data in the additional table section.

We explored the following potential sources of heterogeneity in subgroup analyses: number of doses; length of follow-up; and vaccine type (Ty21a vaccine, Vi polysaccharide vaccine or Vi-rEPA) and age (if data were available). We rounded to the nearest year when trials included follow-up for only part of a year.

We calculated cumulative three-year efficacy, defined as efficacy for the entire three-year period, by vaccine type, as above. We also recorded cumulative data on vaccine efficacy for longer than three years of follow-up, if available. We analyzed efficacy per year and cumulative efficacy, as they provide different information. Analyses per year show whether the effect of the vaccine decreases over time, and cumulative efficacy demonstrates efficacy overall, for a given period, regardless of whether changes over time occurred within this period.

We extracted data on adverse events from trials comparing a typhoid fever vaccine with placebo, and from trials comparing a typhoid fever vaccine with a different typhoid fever vaccine. When the occurrence of adverse events was reported after each of several doses, we extracted only the occurrence after the first dose. Similarly, when reports provided estimates of the incidence of adverse events for different time points after vaccination, we presented the data corresponding to 24 hours after vaccination.

We assessed heterogeneity by inspecting the forest plots to detect overlapping confidence intervals and by applying the Chi^2 test with a P-value of 0.10 indicating statistical significance and the I^2 statistic with a value of 50% used to denote moderate levels of heterogeneity. The random-effects model was used throughout the review.

We calculated number needed to treat for an additional beneficial outcome (NNTB) (1/reduction in risk of typhoid fever attributable to vaccination) for each type of vaccine based on the cumulative 2.5- to 3-year point estimate and the incidence of typhoid fever in control groups of trials assessing the given vaccination.

Quality of evidence

The quality of evidence across each outcome measure was assessed using the GRADE approach. The quality rating across studies has one of four levels: high, moderate, low or very low. Randomized trials are initially categorized as high quality but can be downgraded after assessment of five criteria: risk of bias, consistency,

directness, imprecision and publication bias (Guyatt 2008). The main results of the review and the quality assessments are displayed in the 'Summary of findings' tables.

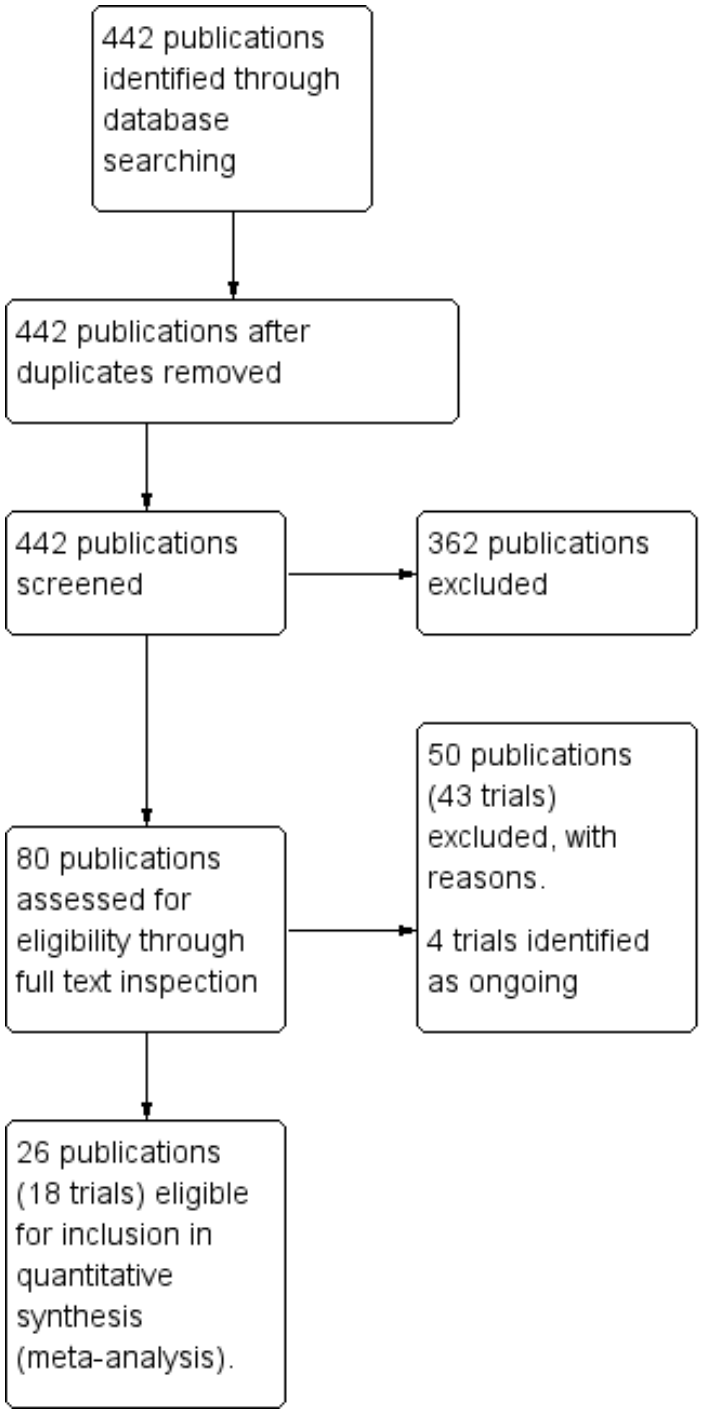
RESULTS

Description of studies

Results of the search

Four hundred forty-two potentially relevant publications were identified, and after screening, 80 publications were retrieved for full-text inspection. See Figure 1 for the study flow diagram. Five trials were identified as currently ongoing (see Characteristics of ongoing studies).

Figure 1. Study flow diagram.



Included studies

Altogether, 26 publications (18 trials-12 individual-RCTs and six cluster-RCTs) met the inclusion criteria (see details in Characteristics of included studies table).

This review update includes four new trials that were not included in the previous review: three of the new trials evaluated the Vi polysaccharide vaccine, two trials reported on efficacy and adverse events (Khan 2012 PAK; Sur 2009 IND) and one trial reported adverse events only (Zhou 2007 CHN). One trial evaluated adverse events associated with the Vi-rEPA vaccine (Thiem 2011 VNM). All of the newly included trials were conducted in Asia.

Excluded studies

A total of 50 publications (43 trials) were excluded from the review. For details of excluded trials and reasons for their exclusion, see the Characteristics of excluded studies table.

Outcomes

Data on the primary outcome, cases of typhoid fever, were derived from 12 trials:

- Five trials of Ty21a (Black 1990i CHL; Black 1990ii CHL; Levine 1987i CHL; Levine 1987ii CHL; Levine 1987iii CHL; Levine 1987iv CHL; Levine 1990i CHL; Levine 1990ii CHL; Simanjuntak 1991i IDN; Simanjuntak 1991ii IDN; Wahdan 1980a EGY);
- Six trials of Vi polysaccharide (Acharya 1987 NPL; Khan 2012 PAK; Klugman 1987 ZAF; Sur 2009 IND; Wang 1997a CHN; Yang 2001 CHN); and
- One Vi-rEPA trial (Lin 2001 VNM).

Data on the secondary outcome, adverse events, were taken from 11 trials:

- Three trials of Ty21a (Levine 1986i CHL; Levine 1986ii CHL; Olanratmanee 1992 THA; Simanjuntak 1991ii IDN);
- Six trials of Vi polysaccharide (Keitel 1994 USA; Khan 2012 PAK; Sur 2009 IND; Wang 1997a CHN; Yang 2001 CHN; Zhou 2007 CHN); and
- Two trials of Vi-rEPA (Lin 2001 VNM; Thiem 2011 VNM).

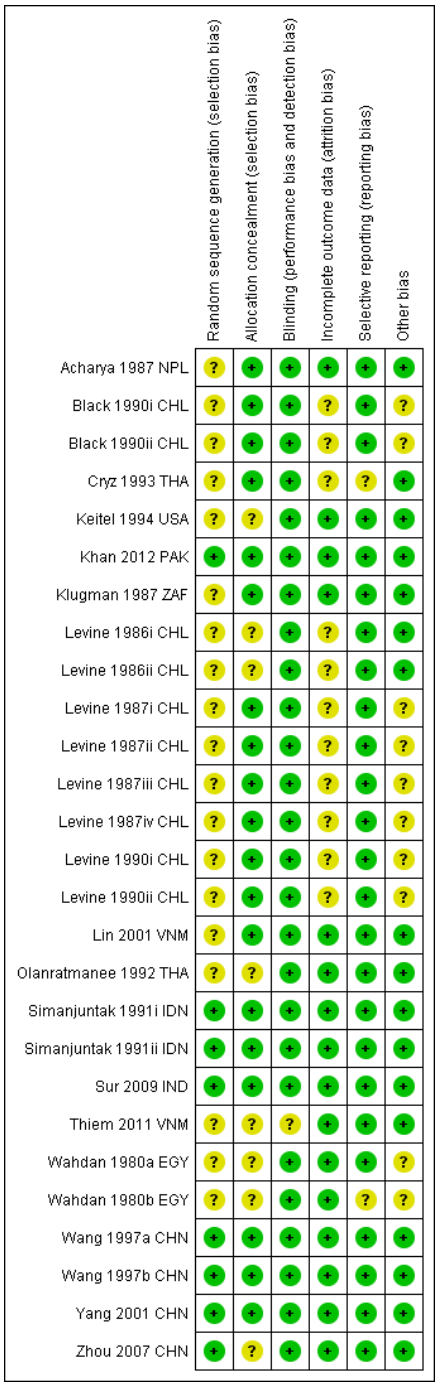
One additional trial assessed the Ty21a vaccine and reported on adverse events but did not provide the number of participants per study arm (Cryz 1993 THA); therefore results of this trial were not included in the meta-analysis.

All efficacy trials and all but one adverse event trial (Keitel 1994 USA) were performed in countries in which typhoid fever is endemic; Chile four trials, China three trials, Vietnam two trials, Thailand two trials, Egypt one trial, India one trial, Indonesia one trial, Nepal one trial, Pakistan one trial and South Africa one trial. None of the trials evaluated vaccine efficacy in travellers from developed countries. None of the trials compared the efficacy of different types of typhoid vaccines.

Risk of bias in included studies

See Figure 2 for a summary of the assessment and the ' Characteristics of included studies' for further details on the reasons for review authors' judgements.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Efficacy trials

Five of the 12 efficacy trials reported adequate randomization procedures (Khan 2012 PAK; Simanjuntak 1991i IDN; Simanjuntak 1991ii IDN; Sur 2009 IND; Wang 1997a CHN; Wang 1997b CHN; Yang 2001 CHN). In the other seven trials, insufficient information was supplied to permit judgement. All but one trial (Klugman 1987 ZAF) used adequate methods to conceal allocation.

Adverse event trials

Six of the 12 trials looking at adverse events reported adequate randomization procedures (Khan 2012 PAK; Simanjuntak 1991i IDN; Simanjuntak 1991ii IDN; Sur 2009 IND; Wang 1997a CHN; Wang 1997b CHN; Yang 2001 CHN; Zhou 2007 CHN). Six of 12 trials used adequate methods to conceal allocation (Khan 2012 PAK; Lin 2001 VNM; Simanjuntak 1991i IDN; Simanjuntak 1991ii IDN; Sur 2009 IND; Wang 1997a CHN; Wang 1997b CHN; Yang 2001 CHN), but in the other trials, insufficient information was supplied to permit judgement.

Blinding

Efficacy trials

All but two trials used double blinding. Two cluster-randomized trials (Khan 2012 PAK; Sur 2009 IND) could not guarantee blinding of researchers or participants, as they used vaccines that were packaged differently and therefore did not look identical. However, both trials tried to minimize this effect by assigning each vaccination team to only one vaccine, identifying the vaccines only by code and not informing local research staff members or participants of the assignment of the code or the vaccine.

Adverse event trials

All but three trials used double blinding. Two trials (Khan 2012 PAK; Sur 2009 IND) used vaccines that did not look identical, as outlined above, and one trial (Thiem 2011 VNM) did not state whether blinding had taken place.

Incomplete outcome data

Efficacy trials

Nine of 12 trials were assessed as adequate in terms of including all randomly assigned participants in the analysis. In three trials (Black 1990i CHL; Black 1990ii CHL; Levine 1987i CHL; Levine 1987ii CHL; Levine 1987iii CHL; Levine 1987iv CHL; Levine 1990i CHL; Levine 1990ii CHL), no reasons for missing data were provided.

Adverse event trials

Ten of 12 trails were assessed as adequate in terms of including all randomly assigned participants in the analysis or providing reasons for missing outcome data. Two trials were unclear on this issue (Cryz 1993 THA; Levine 1986i CHL; Levine 1986ii CHL). One additional trial assessed the Ty21a vaccine and reported on adverse events but did not provide the number of participants per study arm (Cryz 1993 THA); therefore results of this trial were not included in the meta-analysis.

Selective reporting

Efficacy trials

All 12 trials reported on expected outcomes.

Adverse event trials

All 12 trials reported on expected outcomes.

Other potential sources of bias

Efficacy trials

Four of the six cluster-RCTs provided data on the efficacy of the Ty21a vaccine (Black 1990i CHL;; Levine 1987i CHL; Levine 1990i CHL; ; Wahdan 1980a EGY). However, these four cluster-RCTs, all of which randomly assigned by classroom, did not adjust for clustering in their results; therefore we could not include their results in the meta-analyses.

The two remaining cluster-RCTs included within the review provided data on the efficacy of the Vi polysaccharide vaccine (Khan 2012 PAK; Sur 2009 IND). Both of these trials randomly assigned by geographic clusters. Study authors were contacted to gather unpublished cluster-adjusted data for inclusion within the meta-analysis.

Adverse event trials

Two cluster-RCTs provided data on adverse events associated with the Vi polysaccharide vaccine (Khan 2012 PAK; Sur 2009 IND); however, these cluster-RCTs did not adjust for clustering in their results and therefore were not included in the meta-analyses.

Effects of interventions

See: **Summary of findings for the main comparison** Ty21a vaccine (three doses) compared with control; efficacy for preventing typhoid fever; **Summary of findings 2** Vi polysaccharide vaccine (one dose) compared with control; efficacy for preventing typhoid fever; **Summary of findings 3** Vi-rEPA vaccine (two doses) compared with control; efficacy for preventing typhoid fever

TY21a vaccine

Efficacy

This vaccine has been evaluated in one three-arm RCT (Simanjuntak 1991i IDN) and in four cluster-RCTs. The cluster-RCTs did not adjust analyses for the effect of clustering; therefore any protective effect is likely overestimated (Black 1990ii CHL; Levine 1987i CHL; Levine 1987ii CHL; Levine 1987iii CHL; Levine 1987iv CHL; Wahdan 1980a EGY, Levine 1990i CHL. Levine 1990ii CHL). We could not include these studies in the meta-analysis.

A three-dose schedule of Ty21a vaccine provided vaccine efficacy of 35% at Year 1 (95% CI 8% to 54%; 20,543 participants; Analysis 1.1), 58% at Year 2 (95% CI 40% to 71%; 20,543 participants; Analysis 1.2) and 46% at Year 3, although this finding was not statistically significant (95% CI -6% to 72%; 20,543 participants; Analysis 1.3). The cumulative efficacy of the Ty21a vaccine over 2.5 to 3 years was 48% (95% CI 34% to 58%; 20,543 participants; Analysis 1.4). A comparison of cumulative efficacy between the liquid formulation and the enteric capsules showed no statistically significant difference (10,215 participants; Simanjuntak 1991ii IDN; Analysis 2.1).

Results of the four unadjusted cluster-RCTs for the three-dose schedule of Ty21a vaccine liquid formulation or enteric capsules were similar to the individual-RCT results and are presented in Table 1. Cumulative efficacy of the three-dose schedule of Ty21a vaccine for over three years is available from two of the unadjusted cluster-RCTs (Levine 1987ii CHL; Levine 1990i CHL). Cumulative efficacy was 79% at five years (95% CI 65% to 87%; Table 2) and 62% at seven years (95% CI 48% to 73%; Table 2).

We were unable to conduct subgroup analysis by age, as trials evaluating the efficacy of the Ty21a vaccine did not stratify results by age.

Adverse events

None of the individual- or cluster-randomized trials report any serious adverse events (leading to death, requiring inpatient hospitalization or prolonged existing hospitalization, life threatening or resulting in persistent or significant disability or incapacity).

Compared with placebo, the Ty21a vaccine (both preparations) was not associated with an increased rate of vomiting (two trials/four arms, 2066 participants; Analysis 3.2), diarrhoea (two trials/four arms, 2066 participants; Analysis 3.3), nausea or abdominal pain (two trials/four arms, 2066 participants; Analysis 3.4), headache (one trial/two arms, 1190 participants; Analysis 3.5) or rash (one trial/two arms, 1190 participants; Analysis 3.6) compared with control. However, fever (RR 1.84, 95% CI 1.02 to 3.05; two trials/four arms, 2066 participants) was more common after vaccine delivery. A pooled analysis of two individual-RCTs showed a marginal increase in risk of any mild adverse events (RR 1.67, 95% CI 1.03 to 2.72; two trials/three arms, 1360 participants; Analysis 3.7).

Vi polysaccharide vaccine

Efficacy

The efficacy of this vaccine has been evaluated in four individually randomized RCTs (Acharya 1987 NPL; Klugman 1987 ZAF; Wang 1997a CHN; Yang 2001 CHN) and in two cluster-RCTs (Khan 2012 PAK; Sur 2009 IND). We contacted the cluster-randomized study authors to obtain unpublished cluster-adjusted results for efficacy at Year 2 following vaccination. We were therefore able to pool the results from the individually randomized RCTs and the cluster-adjusted RCTs using the generic inverse variance method.

The efficacy of the Vi polysaccharide vaccine was 69% at Year 1 (95% CI 63% to 74%; three trials, 99,797 participants; Analysis 4.1), 59% at Year 2 (95% CI 45% to 69%; four trials, 194,969 participants; Analysis 4.1) and 50% at Year 3 based on a single trial (95% CI 22% to 68%, 11,384 participants; Analysis 4.1). Cumulative efficacy at 2.5 to 3 years, based on the same single trial (Klugman 1987 ZAF), was 55% (95% CI 30% to 70%; 11,384 participants; Analysis 4.2).

Two of the trials used the Widal test (as well as a positive culture) to detect cases of typhoid fever (Wang 1997a CHN; Yang 2001 CHN). Results of the Widal test were not included in the meta-analysis. Both trials followed participants for six years, and their combined results demonstrated that protection was significant in each of the first two years but not in Years 3 to 6 separately. Three-year cumulative efficacy was 69% (95% CI 50% to 81%), and combined efficacy for Years 4 through 6 was 11% (95% CI -76% to 55%) (analyses not shown).

Three of the trials conducted subgroup analysis by age: one individual-RCT (Yang 2001 CHN) and two cluster-RCTs (Khan

2012 PAK; Sur 2009 IND). However, the individual-RCT (Yang 2001 CHN) included very small numbers in each age group; the two cluster-RCTs (Khan 2012 PAK; Sur 2009 IND) did not adjust for clustering and presented their results in the form of hazard ratios rather than risk ratios (with effectiveness of vaccination estimated as [1-hazard ratio] × 100%). We were therefore unable to conduct subgroup analysis by age. Unadjusted results by age from the two cluster-RCTs are presented in Table 3. The cluster-randomized trial conducted in India (Sur 2009 IND) found that compared with control, the Vi polysaccharide vaccine provided significant protection for children 2 to 5 years of age two years after vaccination (efficacy 59%, 95% CI 18% to 79%). However, contrary to these results, the cluster-randomized trial conducted in Pakistan (Khan 2012 PAK) showed no protection among children between two and five years of age compared with placebo at two years after vaccination (efficacy -30%, 95% CI -183% to 40%).

Adverse events

No trials reported any serious adverse events (leading to death, requiring inpatient hospitalization or prolonged existing hospitalization, life threatening, or resulting in persistent or significant disability or incapacity).

Overall, no statistically significant difference was noted between vaccine and placebo in the incidence rate of fever (four trials, 133,038 participants; Analysis 5.1) or erythema (three trials, 132,261 participants; Analysis 5.2). However, swelling (RR 6.06, 95% CI 1.07 to 34.22; three trials, 1767 participants; Analysis 5.3) and pain at the injection site (RR 7.98, 95% CI 3.69 to 17.24; one trial, 667 participants; Analysis 5.4) were more common after delivery of the Vi polysaccharide vaccine.

Two cluster-RCTs presented data on adverse events for a subgroup of participants. These data were not adjusted for clustering and therefore could not be included within the meta-analysis; results were similar to the individual-RCT results, with erythema and pain at the injection site reported more commonly in the vaccine group (Table 4).

Vi-rEPA vaccine

Efficacy

The efficacy of this vaccine has been evaluated by one trial in children 2 to 5 years of age conducted in Vietnam (Lin 2001 VNM). The efficacy of the Vi-rEPA vaccine was 94% at Year 1 (95% CI 75% to 99%; 12,008 participants; Analysis 6.1) and 87% at Year 2 (95% CI 56% to 96%; 12,008 participants; Analysis 6.1). The cumulative efficacy of the Vi-rEPA vaccine after 3.8 years was 89% (95% CI 76% to 97%; 12,008 participants).

The efficacy of this vaccine has been evaluated only in children 2 to 5 years of age; we were therefore unable to conduct subgroup analysis by age.

Adverse events

No trials reported any serious adverse events (leading to death, requiring inpatient hospitalization or prolonged existing hospitalization, life threatening or resulting in persistent or significant disability or incapacity).

Two trials evaluated adverse events associated with this vaccine (Lin 2001 VNM; Thiem 2011 VNM). Investigators reported no statistically significant difference between the vaccine and placebo for the incidence of fever after doses 1 and 2 (Analysis 7.1; Analysis 7.2), erythema after doses 1 and 2 (Analysis 7.3; Analysis 7.4) or swelling after doses 1 and 2 (Analysis 7.5; Analysis 7.6).

Heterogeneity

In most comparisons that included several trials, the degree of heterogeneity was not substantial (ie, I^2 < 50% and Chi^2 test with P value > 0.10). However, because of the limited number of trials included in each comparison, we were unable to conclude why a greater degree of heterogeneity in trial results was apparent in some comparisons.

Sensitivity analyses

We performed sensitivity analyses for trials for which the control arm was split in the main analyses and found that the results were not altered (analyses not shown). As most comparisons included few trials, we could not perform sensitivity analyses by trial methodological quality (risk of bias). No difference was noted in adverse event results from trials that did and did not evaluate efficacy, although no formal testing was undertaken.

Number needed to treat for an additional beneficial outcome (NNTB) to prevent one case of typhoid fever

Ty21a vaccine

Based on the results of one individual-RCT, the liquid formulation of the Ty21a vaccine had a three-year cumulative protective efficacy of 53% (95% CI 34% to 67%; Simanjuntak 1991i IDN; Analysis 1.4). The incidence rate in the control group was 2021/100,000 with a corresponding NNTB of 93 (95% CI 74 to 145). The enteric capsule formulation of the Ty21a vaccine had three-year cumulative protective efficacy of 42% (95% CI 21% to 58%; Simanjuntak 1991ii IDN; Analysis 1.4). The incidence in the control group was 2031/100,000, and the corresponding NNTB was 237 (95% CI 86 to 119)

Vi polysaccharide vaccine

The Vi polysaccharide vaccine has a 2.5- to 3-year cumulative protective efficacy of 55% (95% CI 30% to 70%; Klugman 1987 ZAF; Analysis 3.2) with an incidence rate of 1160/100,000. From these data, we estimated the NNTB to be 192 (95% CI 124 to 288).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Vi polysaccharide vaccine (1 dose) compared with control; efficacy for preventing typhoid fever

Patient or population: adults and children of 2 years of age and older
Settings: any
Intervention: Vi polysaccharide vaccine (1 dose)
Comparison: control; efficacy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control; efficacy	Vi polysaccharide vaccine (1 dose)				
Incidence of typhoid fever-Year 1 Blood culture	**Moderate**[1]		**RR 0.31** (0.26 to 0.37)	99,797 (3 studies)	⊕⊕⊕⊕ **high**[2,3,4,5]	
	4 per 10,000	**1.2 per 10,000** (1.0 to 1.5)				
	High[1]					
	51 per 10,000	**15.8 per 10,000** (13.3 to 18.9)				
Incidence of typhoid fever-Year 2	**Moderate**[1]		**RR 0.41** (0.31 to 0.55)	194,969 (4 studies)	⊕⊕⊕◯ **moderate**[2,6,7,5]	
	4 per 10,000	**1.6 per 10,000** (1.2 to 2.2)				
	High[1]					
	51 per 10,000	**20.9 per 10,000** (15.8 to 28.1)				

Serious adverse events	See comment	See comment	Not estimable	133,240 (4 studies)	See comment	No serious adverse events were reported
Fever	**5 per 1000**	**5 per 1000** (3 to 8)	**RR 0.93** (0.57 to 1.53)	133,038 (4 studies)	⊕⊕⊕◯ **moderate**[2,3,8,9]	
Erythema	**5 per 1000**	**6 per 1000** (2 to 22)	**RR 1.15** (0.33 to 4.03)	132,261 (3 studies)	⊕⊕⊕◯ **low**[2,10,9]	

*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; **RR:** Risk ratio.

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]The incidence of typhoid in a medium-risk setting is taken from the control group in a study from china (Yang 2001 CHN).The incidence of typhoid in a high-risk setting is taken from a study in India (Sur 2009 IND). This is consistent with the incidence levels described by a global epidemiological study (Crump 2004).
[2]No serious risk of bias detected.
[3]No serious inconsistency: The result was consistent across all three trials ($I^2 = 0\%$).
[4]No serious indirectness: The vaccine has been evaluated in trials from Nepal, South Africa and China. Of note, none of the trials were conducted in travellers from nonendemic settings, and all three trials excluded children younger than 2 years of age and pregnant women.
[5]No serious imprecision: The result is statistically significant with a narrow 95% CI. The meta-analysis is adequately powered to detect this effect.
[6]Downgraded by 1 for inconsistency: The magnitude of the protective effect varied between trials from 34% to 69% ($I^2 = 72\%$). The reasons for this are not clear; one potential factor may be the different age groups included in the trials, with the trial by (Khan 2012 PAK) suggesting lower protective effect in children <5 years of age.
[7]No serious indirectness: The vaccine has been evaluated in trials from endemic settings (India, Pakistan, China and South Africa).
[8]No serious indirectness: The vaccine has been evaluated in trials from endemic settings (China) and in one trial conducted in a nonendemic setting (USA).
[9]Downgraded by 1 for serious imprecision: The result is not statistically significant.
[10]Downgraded by 1 for inconsistency ($I^2 = 63\%$).

Vi-rEPA vaccine (2 doses) compared with control; efficacy for preventing typhoid fever

Patient or population: adults and children of 2 years of age and older
Settings: any
Intervention: Vi-rEPA vaccine (2 doses)
Comparison: control; efficacy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control; efficacy	Vi-rEPA vaccine (2 doses)				
Incidence of typhoid fever-Year 1 Follow-up: 1 year	**Moderate**[1]		**RR 0.06** (0.01 to 0.25)	12,008 (1 study)	⊕⊕⊕◯ **moderate**[2,3]	
	4 per 10,000	**024 per 10,000** (0.04 to 1)				
	High[1]					
	59 per 10,000	**3.5 per 10,000** (0.6 to 14.8)				
Incidence of typhoid fever-Year 2	**Moderate**[1]		**RR 0.13** (0.04 to 0.44)	12,008 (1 study)	⊕⊕⊕◯ **moderate**[3]	
	4 per 10,000	**0.52 per 10,000** (0.16 to 1.8)				
	High[1]					
	59 per 10,000	**7.7 per 10,000** (2.4 to 26.0)				
Serious adverse events	See comment	See comment	Not estimable	12,209 (2 studies)	See comment	No serious adverse events were reported

Fever after Vi-rEPA (dose1)	**9 per 1000**	**14 per 1000** (5 to 39)	**RR 1.55** (0.57 to 4.23)	12,209 (2 studies)	⊕⊕◯◯ **low**[4,5]
Erythema after Vi-rEPA (dose 1)	**0 per 1000**	**0 per 1000** (0 to 5)	**RR 3.03** (0.32 to 28.64)	12,209 (2 studies)	⊕⊕⊕◯ **moderate**[5]
Swelling at injection site after Vi-rEPA (dose 1)	**0 per 1000**	**0 per 1000** (0 to 2)	**RR 1.01** (0.15 to 7.03)	12,209 (2 studies)	⊕⊕⊕◯ **moderate**[5]

*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; **RR:** Risk ratio.

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]The incidence of typhoid in a medium -risk setting is taken from the control group in a study from china (Yang 2001 CHN).The incidence of typhoid in a high-risk setting is taken from a study in India (Sur 2009 IND). This is consistent with the incidence levels described by a global epidemiological study (Crump 2004).
[2]No serious risk of bias detected.
[3]Downgraded by 1 for indirectness: The vaccine has been evaluated by only one trial in children 2 to 5 years of age in a high-incidence setting (Vietnam).
[4]Downgraded by 1 for serious inconsistency: $I^2 = 89\%$.
[5]Downgraded by 1 for serious imprecision: The result is not statistically significant.

DISCUSSION

Summary of main results

Ty21a vaccine (three doses)

A three-dose schedule of Ty21a vaccine probably prevents around one-third to one-half of typhoid cases during the first two years after vaccination (Year 1: 35%, 95% CI 8% to 54%; Year 2: 58%, 95% CI 40% to 71%; one trial, 20,543 participants; *moderate quality evidence*). These data are taken from a single trial conducted in Indonesia in the 1980s. No statistically significant benefit was seen in the third year after vaccination. Four additional cluster-RCTs have been conducted, but the authors did not adjust for clustering.

Compared with placebo, this vaccine was not associated with more participants with vomiting, diarrhoea, nausea or abdominal pain (four trials, 2066 participants; *moderate quality evidence*) headache, or rash (two trials, 1190 participants; *moderate quality evidence*); however, fever (four trials, 2066 participants; *moderate quality evidence*) was more common in the vaccine group.

Vi polysaccharide vaccine (one dose)

A single dose of Vi polysaccharide vaccine prevents around two-thirds of typhoid cases in the first year after vaccination (Year 1: 69%, 95% CI 63% to 74%; three trials, 99,979 participants; *high quality evidence*). In Year 2, trial results were more variable, with the vaccine probably preventing between 45% and 69% of typhoid cases (Year 2: 59%, 95% CI 45% to 69%; 4 trials, 194,969 participants; *moderate quality evidence*). The three-year cumulative efficacy of the vaccine is probably around 55% (95% CI 30% to 70%; 11,384 participants, one trial; *moderate quality evidence*). These data were taken from a single trial conducted in South Africa in the 1980s.

Compared with placebo, this vaccine was not associated with an increased rate of fever (four trials, 133,038 participants; *moderate quality evidence*) or erythema (three trials, 132,261 participants; *low quality evidence*); however, swelling (three trials, 1767 participants; *moderate quality evidence*) and pain at the injection site (one trial, 667 participants; *moderate quality evidence*) were more common in the vaccine group.

Vi-rEPA vaccine (two doses)

Administration of two doses of the Vi-rEPA vaccine probably prevents between 50% and 96% of typhoid cases during the first two years after vaccination (Year 1: 94%, 95% CI 75% to 99%; Year 2: 87%, 95% CI 56% to 96%, one trial, 12,008 participants; *moderate quality evidence*). These data are taken from a single trial with children two to five years of age conducted in Vietnam.

Compared with placebo, the first and second doses of this vaccine were not associated with increased risk of adverse events. The first dose of this vaccine was not associated with fever (two trials, 12,209 participants; *low quality evidence)*, erythema (two trials, 12,209 participants; *moderate quality evidence)* or swelling at the injection site (two trials, 12,209 participants; moderate*quality evidence*). The second dose of this vaccine was not associated with fever (two trials, 11,286 participants; low *quality evidence*),*erythema* (two trials, 11,286 participants; *moderate quality evidence*)*and* swelling at the injection site (two trials, 11,286 participants; *moderate quality evidence*).

Overall completeness and applicability of evidence

In the absence of trials directly comparing different types of typhoid vaccines, we provide an indirect means of comparing the efficacy of different vaccines. The cumulative efficacy at 2.5 to 3 years for the Ty21a vaccine (3 doses) and the Vi polysaccharide vaccine was 48% (95% CI 34% to 58%) and 55% (95% CI 30% to 70%), respectively. The cumulative efficacy of the Vi-rEPA vaccine at 3.8 years was higher (89%, 95% CI 76% to 97%), but this vaccine is unlicensed. Adverse events were mild in nature and, for the most, were not significantly different between vaccine and placebo groups.

Ty21a vaccine (three doses)

Although the efficacy of the Ty21a vaccine was evaluated in five separate trials, four of these were cluster-RCTs that did not account for this design in the analysis and therefore were not included in the meta-analyses. In general, the cluster-RCTs suggested greater efficacy of the Ty21a vaccine, as would be expected in trials that do not adjust appropriately for the effect of clustering. The data for the efficacy of this vaccine therefore were derived from one three-arm individually randomized RCT conducted in Indonesia in the 1980s. Further evidence from other settings would be valuable in proving the generalizability of these findings.

None of the studies presented subgroup data by age. Therefore, we cannot report on efficacy of this vaccine in different age groups.

Vi polysaccharide vaccine (one dose)

Evidence available from four trials conducted in four different settings (two high-incidence settings: India and Pakistan; and two medium-incidence settings: China and South Africa) demonstrates that the Vi polysaccharide vaccine is efficacious for the first two years after vaccination. One trial from South Africa conducted in the 1980s provided efficacy data at three years.

Two recent cluster-RCTs presented unadjusted efficacy results stratified by age with contrasting results (presented in Table 3). The cluster-RCT conducted in India (Sur 2009 IND) found that

compared with control, the ViPS vaccine provided significant protection in children 2 to 5 years of age two years after vaccination. However, contrary to these results, the cluster-RCT conducted in Pakistan (Khan 2012 PAK) did not show any protection among children between two and five years of age compared with placebo. The reasons for the difference in effectiveness by age are unclear. The two trials differed in methodology, with the trial in India taking a mass vaccination approach (vaccinating the entire population) and the trial in Pakistan targeting only children. The trial conducted in India, which took a mass vaccination approach, demonstrated indirect protection (herd immunity) within the population under study; this was not seen in the trial in Pakistan, in which only children were vaccinated. It may be that this indirect protection led to reduced overall transmission within the intervention clusters and a reduced incidence of typhoid fever among young children compared with control clusters observed within the Indian trial.

Vi-rEPA vaccine (two doses)

Evidence of the efficacy of this vaccine is available from a single trial conducted in Vietnam (Lin 2001 VNM). This single study assessed efficacy of the vaccine only in children two to five years of age; therefore vaccine efficacy in different settings and age groups is unknown.

Quality of the evidence

We assessed the quality of evidence provided by the randomized studies using the GRADE approach; these assessments are presented in Summary of findings for the main comparison, Summary of findings 2 and Summary of findings 3.

Ty21a vaccine (three doses)

Evidence obtained for the protective efficacy of the Ty21a vaccine was judged to be of moderate quality. The quality was downgraded for indirectness-this vaccine has been evaluated in only one setting (Indonesia), and studies from elsewhere would be important before this result can be widely generalized.

Vi polysaccharide vaccine (one dose)

Evidence obtained for the protective efficacy of the Vi polysaccharide vaccine was judged to be of high quality at Year 1 and of moderate quality at Year 2. At Year 2, the quality was downgraded for inconsistency-the magnitude of the protective effect varied between trials from 34% to 69% (I^2 = 72%). The reason for this may be the different efficacy of the vaccine within different age groups, with one cluster trial (Khan 2012 PAK) finding that compared with control, the vaccine did not provide significant protection to children between 2 and 5 years of age.

Vi-rEPA vaccine (two doses)

Evidence obtained for the protective efficacy of the Vi-rEPA vaccine was judged to be of moderate quality. The quality was downgraded for indirectness-the vaccine has been evaluated only in children 2 to 5 years of age in one high-incidence setting (Vietnam), and studies of participants of different ages conducted elsewhere would be important before this result can be widely generalized. The quality of the evidence obtained for the adverse event of fever was downgraded for inconsistency (I^2 = 89% Year 1; I^2 = 85% Year 2). The reason for this heterogeneity is unclear, as both trials were conducted among children younger than 5 years in Vietnam. Further investigation of the potential adverse events of this vaccine is warranted.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the available evidence, the currently licensed Ty21a and Vi polysaccharide vaccines are efficacious and safe public health measures for preventing typhoid fever. Factors such as costs, availability and convenience of administration may determine which vaccine is chosen for use.

Implications for research

An effective typhoid vaccine is needed for young children. Neither the Vi polysaccharide vaccine nor the Ty21a vaccine is licensed for children younger than 2 years of age. Given the finding that typhoid fever affects infants (Saha 2001; Sinha 1999), development of a vaccine suitable for this age group is required. Future trials should be sufficiently powered to present results stratified by age group. This would mean that vaccine efficacy in different groups could be analyzed and would ensure that vaccine delivery can be targeted appropriately (eg, via a school-based programme or through the expanded programme of vaccination (EPI)).

None of the included trials compared different types of vaccines used to prevent typhoid fever. Such future comparisons may be helpful in allowing direct conclusions regarding the relative efficacy of the vaccines, although such evidence would not necessarily promote the introduction of vaccines against typhoid fever to new settings and would require substantial resources.

Future trials should conduct analyses suited to their design; cluster-randomization should be accounted for in sample size calculations and in analyses of results.

ACKNOWLEDGEMENTS

We thank the Cochrane Infectious Diseases Group for support and assistance provided. The editorial base for the Cochrane Infectious Diseases Group is funded by the UK Department for International Development (DFID) for the benefit of developing countries.

REFERENCES

References to studies included in this review

Acharya 1987 NPL *{published data only}*
Acharya IL, Lowe CU, Thapa R, Gurubacharya VL, Shrestha MB, Cadoz M, et al.Prevention of typhoid fever in Nepal with the Vi capsular polysaccharide of Salmonella typhi: a preliminary report. *New England Journal of Medicine* 1987;**317**(18):1101–4.

Black 1990i CHL *{published data only}*
* Black RE, Levine MM, Ferreccio C, Clements ML, Lanata C, Rooney J, et al.Efficacy of one or two doses of Ty21a Salmonella typhi vaccine in enteric coated capsules in a controlled field trial. *Vaccine* 1990;**8**(1):81–4.
Levine MM, Ferreccio C, Black RE, Lagos R, San Martin O, Blackwelder WC. Ty21a live oral typhoid vaccine and prevention of paratyphoid fever caused by Salmonella enterica Serovar Paratyphi B. *Clinical Infectious Diseases* 2007;**45(Suppl 1)**:S24–28.

Black 1990ii CHL *{published data only}*
See Black 1990i: different arm of same trial.

Cryz 1993 THA *{published data only}*
Cryz SJ Jr, Vanprapar N, Thisyakorn U, Olanratmanee T, Losonsky G, Levine MM, et al.Safety and immunogenicity of Salmonella typhi Ty21a vaccine in young Thai children. *Infection and Immunity* 1993;**61**(3):1149–51.

Keitel 1994 USA *{published data only}*
Keitel WA, Bond NL, Zahradnik JM, Cramton TA, Robbins JB. Clinical and serological responses following primary and booster immunization with Salmonella typhi Vi capsular polysaccharide vaccines. *Vaccine* 1994;**12**(3): 195–9.

Khan 2012 PAK *{published and unpublished data}*
Khan I, Soofi S, Ochiai R, Habib M, Sahito S, Nizami S, et al.Effectiveness of Vi capsular polysaccharide vaccine among children: a cluster randomised trial in Karachi, Pakistan. *Vaccine* 2012;**30**(36):5389–95.

Klugman 1987 ZAF *{published data only}*
* Klugman KP, Gilbertson IT, Koornhof HJ, Robbins JB, Schneerson R, Schulz D, et al.Protective activity of Vi capsular polysaccharide vaccine against typhoid fever. *Lancet* 1987;**2**(8569):1165–9.
Klugman KP, Koornhof HJ, Robbins JB, Le Cam NN. Immunogenicity, efficacy and serological correlate of protection of Salmonella typhi Vi capsular polysaccharide vaccine three years after immunization. *Vaccine* 1996;**14**(5): 435–8.

Levine 1986i CHL *{published data only}*
Levine MM, Black RE, Ferreccio C, Clements ML, Lanata C, Rooney J, et al.The efficacy of attenuated Salmonella typhi oral vaccine strain TY21A evaluated in controlled field trials. In: Holmgren J, Lindberg A, Möllby R editor (s). *Development of Vaccines and Drugs Against Diarrhea. 11th Noble Conference, Stockholm, 1985*. Lund, Sweden: Studentlitteratur, 1986:90–101.

Levine 1986ii CHL *{published data only}*
See Levine 1986i: different arm of same trial.

Levine 1987i CHL *{published data only}*
Germanier R, Levine MM. The live oral typhoid vaccine Ty21a: recent field trial results. *Collana Monografica* 1986;**3** (1-2):19–22.
Levine MM, Ferreccio C, Abrego P, Martin OS, Ortiz E, Cryz S. Duration of efficacy of Ty21a, attenuated Salmonella typhi live oral vaccine. *Vaccine* 1999;**17(Suppl 2)**:22–7.
* Levine MM, Ferreccio C, Black RE, Germanier R. Large-scale field trial of Ty21a live oral typhoid vaccine in enteric-coated capsule formulation. *Lancet* 1987;**1**(8541):1049–52.
Levine MM, Ferreccio C, Black RE, Lagos R, San Martin O, Blackwelder WC. Ty21a live oral typhoid vaccine and prevention of paratyphoid fever caused by Salmonella enterica Serovar Paratyphi B. *Clinical Infectious Diseases* 2007;**45(Suppl 1)**:S24–28.
Levine MM, Tacket CO, Herrington D, Losonsky G, Murphy J, Ferreccio C. The current status of typhoid vaccine development and clinical trials with typhoid vaccines. *Southeast Asian Journal of Tropical Medicine and Public Health* 1988;**19**(3):459–69.
Levine MM, Taylor DN, Ferreccio C. Typhoid vaccines come of age. *Pediatric Infectious Disease Journal* 1989;**8**(6): 374–81.

Levine 1987ii CHL *{published data only}*
See Levine 1987i: different arm of same trial.

Levine 1987iii CHL *{published data only}*
See Levine 1987i: different arm of same trial.

Levine 1987iv CHL *{published data only}*
See Levine 1987i: different arm of same trial.

Levine 1990i CHL *{published data only}*
Levine MM, Ferreccio C, Abrego P, Martin OS, Ortiz E, Cryz S. Duration of efficacy of Ty21a, attenuated Salmonella typhi live oral vaccine. *Vaccine* 1999;**17(Suppl 2)**:22–7.
* Levine MM, Ferreccio C, Cryz S, Ortiz E. Comparison of enteric-coated capsules and liquid formulation of Ty21a

typhoid vaccine in randomised controlled field trial. *Lancet* 1990;**336**(8720):891–4.

Levine 1990ii CHL *{published data only}*
See Levine 1990i: different arm of same trial.

Lin 2001 VNM *{published data only}*
* Lin FY, Ho VA, Khiem HB, Trach DD, Bay PV, Thanh TC, et al.The efficacy of a Salmonella typhi Vi conjugate vaccine in two-to-five-year-old children. *New England Journal of Medicine* 2001;**344**(17):1263–9.
Mai NL, Phan VB, Vo AH, Tran CT, Lin FY, Bryla DA, et al.Persistent efficacy of Vi conjugate vaccine against typhoid fever in young children. *New England Journal of Medicine* 2003;**349**(14):1390–1.

Olanratmanee 1992 THA *{published data only}*
Olanratmanee T, Levine M, Losonsky G, Thisyakorn V, Cryz SJ Jr. Safety and immunogenicity of Salmonella typhi Ty21a liquid formulation vaccine in 4- to 6-year-old Thai children. *Journal of Infectious Diseases* 1992;**166**(2):451–2.

Simanjuntak 1991i IDN *{published data only}*
Simanjuntak CH, Paleologo FP, Punjabi NH, Darmowigoto R, Soeprawoto, Totosudirjo H, et al.Oral immunisation against typhoid fever in Indonesia with Ty21a vaccine. *Lancet* 1991;**338**(8774):1055–9.

Simanjuntak 1991ii IDN *{published data only}*
See Simanjuntak 1991i: different arm of same trial.

Sur 2009 IND *{published and unpublished data}*
Sur D, Ochiai RL, Bhattacharya SK, et al.A cluster-randomized effectiveness trial of Vi typhoid vaccine in India. *New England Journal of Medicine* 2009;**361**(4):335–344.

Thiem 2011 VNM *{published data only}*
Thiem VD, Lin FY, Canh DG, Canh do G, Son NH, et al.The Vi conjugate typhoid vaccine is safe, elicits protective levels of IgG anti-Vi, and is compatible with routine infant vaccines. *Clinical and Vaccine Immunology* 2011;**18**(5): 730–5.

Wahdan 1980a EGY *{published data only}*
Wahdan MH, Sérié C, Cerisier Y, Sallam S, Germanier R. A controlled field trial of live Salmonella typhi strain Ty 21a oral vaccine against typhoid: three-year results. *Journal of Infectious Diseases* 1982;**145**(3):292–5.
* Wahdan MH, Sérié C, Germanier R, Lackany A, Cerisier Y, Guerin N, et al.A controlled field trial of live oral typhoid vaccine Ty21a. *Bulletin of the World Health Organization* 1980;**58**(3):469–74.

Wahdan 1980b EGY *{published data only}*
Wahdan MH, Sérié C, Cerisier Y, Sallam S, Germanier R. A controlled field trial of live Salmonella typhi strain Ty 21a oral vaccine against typhoid: three year results. *Journal of Infectious Diseases* 1982;**145**(3):292–5.
* Wahdan MH, Sérié C, Germanier R, Lackany A, Cerisier Y, Guerin N, et al.A controlled field trial of live oral typhoid vaccine Ty21a. *Bulletin of the World Health Organization* 1980;**58**(3):469–74.

Wang 1997a CHN *{published data only}*
Acosta CJ, Hong-Hui Y, Ning W, Qion G, Qun D, Xiaolei M, et al.Efficacy of a locally produced, Chinese Vi polysaccharide typhoid fever vaccine during six years of follow-up. *Vaccine* 2005;**23**(48-9):5618–23.
* Wang ZG, Zhou WZ, Shi J. Efficacy and side effects following immunization with Salmonella typhi Vi capsular polysaccharide vaccine. *Zhonghua Liu Xing Bing Xue Za Zhi* 1997;**18**(1):26–9.

Wang 1997b CHN *{published data only}*
Wang ZG, Zhou WZ, Shi J. Efficacy and side effects following immunization with Salmonella typhi Vi capsular polysaccharide vaccine. *Zhonghua Liu Xing Bing Xue Za Zhi* 1997;**18**(1):26–9.

Yang 2001 CHN *{published data only}*
Acosta CJ, Hong-Hui Y, Ning W, Qion G, Qun D, Xiaolei M, et al.Efficacy of a locally produced, Chinese Vi polysaccharide typhoid fever vaccine during six years of follow-up. *Vaccine* 2005;**23**(48-9):5618–23.
* Yang HH, Wu CG, Xie GZ, Gu QW, Wang BR, Wang LY, et al.Efficacy trial of Vi polysaccharide vaccine against typhoid fever in south-western China. *Bulletin of the World Health Organization* 2001;**79**(7):625–31.

Zhou 2007 CHN *{published data only}*
Zhou WZ, Koo HW, Wang XY, et al.Revaccination with locally-produced Vi typhoid polysaccharide vaccine among Chinese school-aged children: safety and immunogenicity findings. *The Paediatric Infectious Disease Journal* 2007;**26** (11):1001–5.

References to studies excluded from this review

Ali 2011 *{published data only}*
Ali M, Sur D, Kim DR, Kanungo S, Bhattacharya SK, Manna B, et al.Impact of Vi vaccination on spatial patterns of typhoid fever in the slums of Kolkata, India. *Vaccine* 2011;**29**(48):9051–6.

Arya 1997 *{published data only}*
Arya SC. Efficacy of Salmonella typhi Vi capsular polysaccharide vaccine in South Africa. *Vaccine* 1997;**15**(2): 244.

Ashcroft 1967 *{published data only}*
Ashcroft MT, Ritchie JM, Nicholson CC. Controlled field trial in British Guiana school children of heat-killed phenolized and acetone-killed lyophilized vaccines. *American Journal of Hygiene* 1964;**79**:196–206.
* Ashcroft MT, Singh B, Nicholson CC, Ritchie JM, Sobryan E, Williams F. A seven-year field trial of two typhoid vaccines in Guyana. *Lancet* 1967;**2**(7525):1056–9.
Kasi AM. A controlled field trial of acetone-dried and inactivated and heat-phenol-inactivated typhoid vaccines in British Guiana. *Bulletin of the World Health Organization* 1964;**30**:631–4.

Black 1983 *{published data only}*
Black R, Levine MM, Young C, Rooney J, Levine S, Clements ML, et al.Immunogenicity of Ty21a attenuated "Salmonella typhi" given with sodium bicarbonate or in enteric-coated capsules. *Developments in Biological Standardization* 1983;**53**:9–14.

Bumann 2001 *{published data only}*

Bumann D, Metzger WG, Mansouri E, Palme O, Wendland M, Hurwitz R, et al.Safety and immunogenicity of live recombinant Salmonella enterica serovar Typhi Ty21a expressing urease A and B from Helicobacter pylori in human volunteers. *Vaccine* 2001;**20**(5-6):845–52.

Cahn 2004 *{published data only}*

Canh DG, Lin FY, Thiem VD, Trach DD, Trong ND, Mao ND, et al.Effect of dosage on immunogenicity of a Vi conjugate vaccine injected twice into 2- to 5-year-old Vietnamese children. *Infection and Immunity* 2004;**72**(11): 6586–8.

Chuttani 1977 *{published data only}*

Chuttani CS. Controlled field trials of three different oral killed typhoid vaccines in India. *Developments in Biological Standardization* 1976;**33**:98–101.

* Chuttani CS, Prakash K, Gupta P, Grover V, Kumar A. Controlled field trial of a high-dose oral killed typhoid vaccine in India. *Bulletin of the World Health Organization* 1977;**55**(5):643–4.

Chuttani CS, Prakash K, Vergese A, Gupta P, Chawla RK, Grover V, et al.Ineffectiveness of an oral killed typhoid vaccine in a field trial. *Bulletin of the World Health Organization* 1973;**48**(6):754–5.

Chuttani CS, Prakash K, Vergese A, Sharma U, Singha P, Ray BG. Effectiveness of oral killed typhoid vaccine. *Bulletin of the World Health Organization* 1971;**45**(4): 445–50.

Cordero-Yap 2001 *{published data only}*

Cordero-Yap L, Rivera RG, Dispo AP, Mallabo J. Evaluation of a new Vi polysaccharide typhoid vaccine in children aged 2-5 years. BioDrugs 2001; Vol. 15(Suppl 1):27.

Cryz 1995 *{published data only}*

Cryz SJ Jr, Que JU, Levine MM, Wiedermann G, Kollaritsch H. Safety and immunogenicity of a live oral bivalent typhoid fever (Salmonella typhi Ty21a)-cholera (Vibrio cholerae CVD 103-HgR) vaccine in healthy adults. *Infection and Immunity* 1995;**63**(4):1336–9.

Cumberland 1992 *{published data only}*

Cumberland NS, St Clair Roberts J, Arnold WS, Patel RK, Bowker CH. Typhoid Vi: a less reactogenic vaccine. *Journal of International Medical Research* 1992;**20**(3):247–53.

Ferreccio 1989 *{published data only}*

Ferreccio C, Levine MM, Rodriguez H, Contreras R. Comparative efficacy of two, three, or four doses of TY21a live oral typhoid vaccine in enteric-coated capsules: a field trial in an endemic area. *Journal of Infectious Diseases* 1989; **159**(4):766–9.

Hejfec 1965 *{published data only}*

* Hejfec LB. Results of the study of typhoid vaccines in four controlled field trials in the USSR. *Bulletin of the World Health Organization* 1965;**32**:1–14.

Khasanov MI, Kheifets LB, Salmin LV. A controlled field trial of the typhoid component of polyvalent enteric vaccine (NIISI polyvaccine). *Bulletin of the World Health Organization* 1962;**26**:371–9.

Hejfec 1966 *{published data only}*

Hejfec LB. Results of the study of typhoid vaccines in four controlled field trials in the USSR. *Bulletin of the World Health Organization* 1965;**32**:1–14.

* Hejfec LB, Salmin LV, Lejtman MZ, Kuz'minova ML, Vasil'eva AV, Levina LA, et al.A controlled field trial and laboratory study of five typhoid vaccines in the USSR. *Bulletin of the World Health Organization* 1966;**34**(3): 321–39.

Hejfec 1968 *{published data only}*

Hejfec LB, Levina LA, Kuz'minova ML, Salmin LV, Slavina AM, Vasil'eva AV. Controlled field trials of paratyphoid B vaccine and evaluation of the effectiveness of a single administration of typhoid vaccine. *Bulletin of the World Health Organization* 1968;**38**(6):907–15.

Hejfec 1969 *{published data only}*

Hejfec LB, Levina LA, Kuz'minova ML, Slavina AM, Drozd AK, Tonojan IA, et al.A controlled field trial to evaluate the protective capacity of a single dose of acetone-killed agar-grown and heat-killed broth-grown typhoid vaccines. *Bulletin of the World Health Organization* 1969;**40**(6): 903–7.

Hejfec 1976 *{published data only}*

Hejfec LB, Levina LA, Salmin LB, Antonova AA, Segal LS, Kuzminova ML, et al.Controlled field trials of killed oral typhoid and paratyphoid B vaccines and cell-free, chemical aerosol typhoid vaccine. *Developments in Biological Standardization* 1976;**33**:93–7.

Hien 2010 *{published data only}*

Hien TT, Dung NT, Truong NT, Van NTT, Chau TNB, Van Hoang NM, et al.A randomised trial evaluating the safety and immunogenicity of the novel single oral dose typhoid vaccine M01ZH09 in healthy Vietnamese children. *PloS one* 2010;**5**(7):e11778.

Hohmann 1996a *{published data only}*

Hohmann EL, Oletta CA, Killeen KP, Miller SI. phoP/phoQ-deleted Salmonella typhi (Ty800) is a safe and immunogenic single-dose typhoid fever vaccine in volunteers. *Journal of Infectious Diseases* 1996;**173**(6): 1408–14.

Hohmann 1996b *{published data only}*

Hohmann EL, Oletta CA, Miller SI. Evaluation of a phoP/phoQ-deleted, aroA-deleted live oral Salmonella typhi vaccine strain in human volunteers. *Vaccine* 1996;**14**(1): 19–24.

Kantele 2013 *{published data only}*

Kantele A, Pakkanen SH, Karttunen R, Kantele JM. Head-to-head comparison of humoral immune responses to Vi capsular polysaccharide and salmonella typhi Ty21a typhoid vaccine-a randomised trial. *PLoS One* 2013;**8**(4):e60583.

Keddy 1999 *{published data only}*

Keddy KH, Klugman KP, Hansford CF, Blondeau C, Bouveret le Cam NN. Persistence of antibodies to the Salmonella typhi Vi capsular polysaccharide vaccine in South African school children ten years after immunization. *Vaccine* 1999;**17**(2):110–3.

Khan 2007 *{published data only}*
Khan S, Chatfield S, Stratford R, Bedwell J, Bentely M, Sulsh S, et al.Ability of SPI2 mutant of S. typhi to effectively induce antibody responses to the mucosal antigen enterotoxigenic E. coli heat labile toxin B subunit after oral delivery to humans. *Vaccine* 2007;**25**(21):4175–82.

Khoo 1995 *{published data only}*
Khoo SH, St Clair Roberts J, Mandal BK. Safety and efficacy of combined meningococcal and typhoid vaccine. *BMJ* 1995;**310**(6984):908–9.

Kirkpatrick 2006 *{published data only}*
Kirkpatrick B, McKenzie R, O'Neill J, Larsson C, Bourgeois A, Shimko J, et al.Evaluation of Salmonella enterica serovar Typhi (Ty2 aroCssaV) M01ZH09, with a defined mutation in the Salmonella pathogenicity island 2, as a live, oral typhoid vaccine in human volunteers. *Vaccine* 2006;**24**(2): 116–23.

Lebacq 2001 *{published data only}*
Lebacq E. Comparative tolerability and immunogenicity of Typherix or Typhim Vi in healthy adults: 0, 12-month and 0, 24-month administration. *BioDrugs* 2001;**15(Suppl 1)**: 5–12.

Levin 1975 *{published data only}*
Levin DM, Wong KH, Reynolds HY, Sutton A, Northrup RS. Vi antigen from Salmonella typhosa and immunity against typhoid fever. 11. Safety and antigenicity in humans. *Infection and Immunity* 1975;**12**(6):1290–4.

Lyon 2010 *{published data only}*
Lyon CE, Sadigh KS, Carmolli MP, Harro C, Sheldon E, Lindow JC, et al.In a randomized, double-blinded, placebo-controlled trial, the single oral dose typhoid vaccine, M01ZH09, is safe and immunogenic at doses up to 1.7 × 10(10) colony-forming units. *Vaccine* 2010;**28**(20):3602–8.

Murphy 1991 *{published data only}*
Murphy JR, Grez L, Schlesinger L, Ferreccio C, Baqar S, Munoz C, et al.Salmonella typhi Ty21a vaccine for young children. *Infection and Immunity* 1991;**59**(11):4291–3.

Nisini 1993 *{published data only}*
Nisini R, Biselli R, Matricardi PM, Fattorossi A, D'Amelio R. Clinical and immunological response to typhoid vaccination with parenteral or oral vaccines in two groups of 30 recruits. *Vaccine* 1993;**11**(5):582–6.

Panchanathan 2001 *{published data only}*
Panchanathan V, Kumar S, Yeap W, Devi S, Ismail R, Sarijan S, et al.Comparison of safety and immunogenicity of a Vi polysaccharide typhoid vaccine with a whole-cell killed vaccine in Malaysian Air Force recruits. *Bulletin of the World Health Organization* 2001;**79**(9):811–7.

Polish committee 1966 *{published data only}*
Polish Typhoid Committee. Controlled field trials and laboratory studies on the effectiveness of typhoid vaccines in Poland, 1961-64. *Bulletin of the World Health Organization* 1966;**34**(2):211–22.

Sabitha 2004 *{published data only}*
Sabitha P, Prabha Adhikari MR, Chowdary A, Prabhu M, Soofi M, Shetty M, et al.Comparison of the immunogenicity and safety of two different brands of Salmonella typhi Vi capsular polysaccharide vaccine. *Indian Journal of Medical Sciences* 2004;**58**(4):141–9.

Tacket 1992 *{published data only}*
Tacket CO, Hone DM, Curtiss R 3rd, Kelly SM, Losonsky G, Guers L, et al.Comparison of the safety and immunogenicity of delta aroC delta aroD and delta cya delta crp Salmonella typhi strains in adult volunteers. *Infection and Immunity* 1992;**60**(2):536–41.

Tacket 1997 *{published data only}*
Tacket CO, Sztein MB, Losonsky GA, Wasserman SS, Nataro JP, Edelman R, et al.Safety of live oral Salmonella typhi vaccine strains with deletions in htrA and aroC aroD and immune response in humans. *Infection and Immunity* 1997;**65**(2):452–6.

Tacket 2000 *{published data only}*
Tacket CO, Sztein MB, Wasserman SS, Losonsky G, Kotloff KL, Wyant TL, et al.Phase 2 clinical trial of attenuated Salmonella enterica serovar typhi oral live vector vaccine CVD 908-htrA in U.S. volunteers. *Infection and immunity* 2000;**68**(3):1196–201.

Tapa 1975 *{published data only}*
Tapa S, Cvjetanovic B. Controlled field trial on the effectiveness of one and two doses of acetone-inactivated and dried vaccine. *Bulletin of the World Health Organization* 1975;**52**(1):75–80.

Thiem 2006 *{published data only}*
Thiem VD, Danovaro-Holliday MC, Canh do G, Son ND, Hoa NT, Thuy DT, et al.The feasibility of a school-based VI polysaccharide vaccine mass immunization campaign in Hue City, central Vietnam: streamlining a typhoid fever preventive strategy. *The Southeast Asian Journal of Tropical Medicine and Public Health* 2006;**37**(3):515–22.

van Damme 2011 *{published data only}*
van Damme P, Kafeja F, Anemona A, Basile V, Hilbert AK, De Coster I, et al.Safety, immunogenicity and dose ranging of a new Vi-CRM(1)(9)(7) conjugate vaccine against typhoid fever: randomized clinical testing in healthy adults. *PLoS One* 2011;**6**(9):e25398.

Wahdan 1975 *{published data only}*
Wahdan MH, Sippel JE, Mikhail IA, Rahka AE, Anderson ES, Sparks HA, et al.Controlled field trial of a typhoid vaccine prepared with a nonmotile mutant of Salmonella typhi Ty2. *Bulletin of the World Health Organization* 1975; **52**(1):69–73.

Wahid 2011 *{published data only}*
Wahid R, Pasetti MF, Maciel M Jr, Simon JK, Tacket CO, Levine MM, et al.Oral priming with Salmonella Typhi vaccine strain CVD 909 followed by parenteral boost with the S. Typhi Vi capsular polysaccharide vaccine induces CD27+IgD-S. Typhi-specific IgA and IgG B memory cells in humans. *Clinical Immunology* 2011;**138**(2):187–200.

Yang 2005 *{published data only}*
Yang J, Acosta CJ, Si GA, Zeng J, Li CY, Liang DB, et al.A mass vaccination campaign targeting adults and children

to prevent typhoid fever in Hechi; expanding the use of Vi polysaccharide vaccine in Southeast China: a cluster-randomized trial. *BMC Public Health* 2005;**5**(1):49.

Yang 2009 ***{published data only}***
Yang J, Ye Q, Dong BQ. Immediate adverse reaction after mass vaccination of groups A+C meningococcal polysaccharide vaccine. *Chinese Journal of Biologicals* 2009; **7**:699–701.

Yug Ty Comm 1962 ***{published data only}***
* Yugoslav Typhoid Commission. A controlled field trial of the effectiveness of phenol and alcohol typhoid vaccines: final report. *Bulletin of the World Health Organization* 1962; **26**:357–69.
Yugoslav Typhoid Commission. Field and laboratory studies with typhoid vaccines. A preliminary report. *Bulletin of the World Health Organization* 1957;**16**:897–910.

Yug Ty Comm 1964 ***{published data only}***
Yugoslav Typhoid Commission. A controlled field trial of the effectiveness of acetone-dried and inactivated and heat-phenol-inactivated typhoid vaccines in Yugoslavia. *Bulletin of the World Health Organization* 1964;**30**:623–30.

Zhou 2008 CHN ***{published data only}***
Zhou W-Z, Zeng M, Pan H-X. Adverse reaction and immune effect of typhoid Vi polysaccharide vaccine.. *Chinese Journal of Biologicals* 2008;**21**(5):425–7.

References to ongoing studies

Chinnasami ***{unpublished data only}***
Chinnasami B (overall contact). A clinical trial to study the optimal use of conjugate typhoid vaccine-single dose vs two doses. *CTRI identifier: CTRI/2010/091/003031*.

Darton 2012 ***{unpublished data only}***
Darton T, Pollard A (overall contacts). Understanding Typhoid Disease After Vaccination: A Single Centre, Randomised, Doubleblind, Placebo Controlled Study to Evaluate M01ZH09 in a Healthy Adult Challenge Model, Using Ty21a Vaccine as a Positive Control. NCT Identifier: NCT01405521.

House 2011 ***{unpublished data only}***
House H (Overall contact). A phase II, single-centre, randomised, single-blind, study to evaluate Vi-CRM197 against historical unvaccinated controls in a healthy adult challenge model, with a Vi-PS vaccine control arm-Understanding immunity after typhoid vaccination. EUCTR Identifier: EUCTR2011-003653-26-GB.

Mitra 2012 ***{unpublished data only}***
Mitra M (Overall contact). Incidence of typhoid fever as observed over 1 year in children aged 6 months-12 years after receiving conjugated typhoid vaccine (Peda Typh TM) versus a similar non-vaccinated group in the same locality in Kolkata. *CTRI Identifier: CTRI/2012/06/002719*.

Additional references

Bennish 1995
Bennish ML. Immunization against Salmonella typhi. *Infectious Diseases in Clinical Practice* 1995;**4**:114–22.

Bhan 2005
Bhan MK, Bahl R, Bhatnagar S. Typhoid and paratyphoid fever. *Lancet* 2005;**366**(9487):749–62.

Bhutta, 1996
Bhutta ZA. Impact of age and drug resistance on mortality in typhoid fever. *Archives of Diseases of Childhood* 1996;**75** (3):214–7.

Breiman 2012
Breiman R, Cosmas L, Njuguna H, Audi A, Olack B, Ochieng J. Population-based incidence of typhoid fever in an urban informal settlement and a rural area in Kenya: implications for typhoid vaccine use in Africa. *PLoS One* 2012;**7**(1):e29119.

Crump 2004
Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. *Bulletin of the World Health Organization* 2004;**82**(5):346–53.

Crump 2010
Crump J, Mintz E. Global trends in typhoid and paratyphoid fever. *Clinical Infectious Disease* 2010;**50**(2): 241–6.

DeRoeck, 2008
Deroeck D, Ochiai L, Yang J, Anh D, Alag V, Clemens J. Typhoid vaccination: the Asian experience. *Vaccines* 2008;**7** (5):547–60.

Garmory 2002
Garmory HS, Brown KA, Titball RW. Salmonella vaccines for use in humans: present and future perspectives. *FEMS Microbiology Reviews* 2002;**26**(4):339–53.

Guyatt 2008
Guyatt GH, Oxman AD, Vist GE, Kunz R, Falek-Ytter Y, Alonso-Coello P, et al.GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924–6.

Higgins 2006
Higgins JPT, Green S, editors. Highly sensitive search strategies for identifying reports of randomized controlled trials in MEDLINE. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]; Appendix 5b. www.cochrane.org/resources/handbook/hbook.htm (accessed 1 December 2006).

Jüni 2001
Jüni P, Altman DG, Egger M. Systematic reviews in healthcare: assessing the quality of controlled trials. *BMJ* 2001;**323**(7303):42–6.

Mandell 2005
Mandell GL, Bennett JE, Dolin R, editors. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*. 6th Edition. New York: Elsevier/ Churchill Livingstone, 2005.

Maurice, 2012
Maurice J. A first step in bringing typhoid fever out of the closet. *The Lancet* 2012;**379**:699–700.

Ochiai 2008
Ochiai RL, Acosta CJ, Danovaro-Holliday MC, Baiqing D, Bhattacharya SK, Agtini MD, et al.A study of typhoid fever in five Asian countries: disease burden and implications for controls. *Bulletin of the World Health Organisation* 2008;**86**(4):260–8.

Ochiai, 2007
Ochiai L, Acosta C, Agtini M, Bhattacharya S, Bhutta Z, Do C, et al.The use of typhoid vaccines in Asia: the DOMI experience. *Clinical Infectious Diseases* 2007;**45**((Suppl 1)): S34–38.

Parry 2002
Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid fever. *New England Journal of Medicine* 2002;**347**(22):1770–82.

Review Manager 5
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

Saha 2001
Saha SK, Baqui AH, Hanif M, Darmstadt GL, Ruhulamin M, Nagatake T, et al.Typhoid fever in Bangladesh: implications for vaccination policy. *Pediatric Infectious Disease Journal* 2001;**20**(5):521–4.

Sinha 1999
Sinha A, Sazawal S, Kumar R, Sood S, Reddaiah VP, Singh B, et al.Typhoid fever in children aged less than 5 years. *Lancet* 1999;**354**(9180):734–7.

WHO 2000
World Health Organization. Typhoid vaccines: WHO position paper. *Weekly Epidemiological Record* 2000;**75**(32): 257–64.

WHO 2005
Initiative for Vaccines Research, World Health Organization. 1. Diarrhoeal diseases [www.who.int/vaccine˙research/documents/Diarrhoeal˙Diseases.pdf]. *State of the Art of Vaccine Research and Development [WHO/IVB/05.XX]*. Geneva: World Health Organization, 2005.

WHO 2008
World Health Organisation. Typhoid vaccine: WHO position paper. *Weekly Epidemiological Record* 2008;**83**(6): 49–60.

References to other published versions of this review

Engels 1998a
Engels EA, Lau J. Vaccines for preventing typhoid fever. *Cochrane Database of Systematic Reviews* 1998, Issue 4. [DOI: 10.1002/14651858.CD001261]

Engels 1998b
Engels EA, Falagas MA, Lau J, Bennish ML. Typhoid fever vaccines: a meta-analysis of efficacy and toxicity studies. *BMJ* 1998;**316**(7125):110–6.

Fraser 2007a
Fraser A, Goldberg E, Acosta CJ, Paul M, Leibovici L. Vaccines for preventing typhoid fever. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art No: CD001261. [DOI: 10.1002/14651858.CD001261.pub2]

Fraser 2007b
Fraser A, Paul M, Goldberg E, Acosta CJ, Leibovici L. Typhoid fever vaccines: systematic review and meta-analysis of randomised controlled trials. *Vaccine* 2007;**25**(45): 7848–57.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Acharya 1987 NPL

Methods	Design: individual-RCT Active surveillance for efficacy (health workers visited vaccinees every 2 days; in case of a fever lasting longer than 3 days, a blood sample was taken) and adverse events (health workers examined vaccinees on days 1 to 3 post-vaccination)
Participants	Number: 6907 Inclusion criteria: age 5 to 44 years Exclusion criteria: children age < 2 years; fever or acute illness; pregnancy
Interventions	1. Capsular polysaccharide of *S. typhi,* Vi: 25 µg Vi in 0.5 mL; 3457 participants 2. Pneumococcal vaccine: 25 µg; 3450 participants Route and schedule: intramuscular injection; 1 dose Concomitant medication: not specified
Outcomes	1. Typhoid fever cases (*S. typhi* bacteraemia) 2. Adverse events
Notes	Location: 5 villages near Kathmandu, Nepal Socioeconomic description: rural, low income Setting: home Date: 1986 to 1988 No demographic information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized, random arrangement of syringes in packages of 10. Insufficient information about the sequence generation process provided to permit judgement
Allocation concealment (selection bias)	Low risk	Sequentially numbered vaccines of identical appearance
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Inclusion of randomized assigned participants in analysis: 100%
Selective reporting (reporting bias)	Low risk	All expected outcomes reported on

Acharya 1987 NPL (*Continued*)

Other bias	Low risk	None

Black 1990i CHL

Methods	Design: cluster (classroom)-RCT Intermediate surveillance for efficacy: enteric fever and isolation of *S. typhi* from blood or bone marrow in clinics and local hospital during the study (5-year follow-up)
Participants	Number: 54,925 participants Number of classrooms: 3655 Inclusion criteria: age 5 to 22 years Exclusion criteria: no details
Interventions	1. Lyophilized attenuated *S. typhi* strain Ty21a: enteric-coated capsule containing 2-5 × 10^9 viable Ty21a; 27,620 participants 2. Placebo: in enteric-coated capsule; 27,305 participants Route and schedule: oral; 2 doses, 1 week apart Concomitant medication: not specified
Outcomes	1. Typhoid fever cases (*S. typhi* bacteraemia or in bone marrow)
Notes	Location: northern area of Santiago, Chile Socioeconomic description: no details Setting: school Date: 1982 to 1987 No demographic information

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Generation of allocation sequence: unclear
Allocation concealment (selection bias)	Low risk	Allocation concealment: central (WHO). Sequentially numbered vaccines of identical appearance
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Of 91,954 participating children, 82,543 received all assigned doses. No reason for missing data provided
Selective reporting (reporting bias)	Low risk	All expected outcomes reported on

Black 1990i CHL (*Continued*)

Other bias	Unclear risk	Unclear whether data were adjusted for clustering

Black 1990ii CHL

Methods	See Black 1990i CHL (Black 1990ii CHL is a different arm of the same trial)
Participants	Details as for Black 1990i CHL, except number: 54,923
Interventions	1. Lyophilized attenuated *S. typhi* strain Ty21a: enteric-coated capsule containing 2-5 × 10^9 viable Ty21a; 27,618 participants 2. Placebo: in enteric-coated capsule; 27,305 participants Route and schedule: oral; 1 dose (2nd dose contained placebo in all participants) Concomitant medication: not specified
Outcomes	Details as for Black 1990i CHL
Notes	Details as for Black 1990i CHL

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Details as for Black 1990i CHL
Allocation concealment (selection bias)	Low risk	Details as for Black 1990i CHL
Blinding (performance bias and detection bias) All outcomes	Low risk	Details as for Black 1990i CHL
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details as for Black 1990i CHL
Selective reporting (reporting bias)	Low risk	Details as for Black 1990i CHL
Other bias	Unclear risk	Details as for Black 1990i CHL

Cryz 1993 THA

Methods	Design: individual-RCT
Participants	Number: 634 Inclusion criteria: children 2 to 6 years old with no history of typhoid fever Exclusion criteria: no details

Cryz 1993 THA (*Continued*)

Interventions	1. Ty21a liquid formulation 2. Placebo Route and schedule: oral solution; 3 doses
Outcomes	1. Adverse events 2. Immunogenicity
Notes	Location: Thailand Socioeconomic description: no details Date: no details No demographic details

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Generation of the allocation sequence: unclear
Allocation concealment (selection bias)	Low risk	Sequentially numbered vaccines of identical appearance
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Inclusion of randomly assigned participants in analysis: unclear
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Low risk	None

Keitel 1994 USA

Methods	Design: individual-RCT Active surveillance for adverse events: local and systemic symptoms before and at 24 and 48 hours after inoculation; fever and symptoms at 6 to 9 hours, days 1, 2, 7, 14 and 28 after inoculation
Participants	Number: 323 Inclusion criteria: age 8 to 40 years; healthy; no previous typhoid vaccination Exclusion criteria: no details
Interventions	1. Capsular polysaccharide of *S. typhi*, Vi vaccine (freeze-dried preparation and liquid preparation): 25 µg Vi in 0.5 mL; 237 participants 2. Placebo: 86 participants Route and schedule: intramuscular injection; 1 dose Concomitant medication: not specified

Keitel 1994 USA (*Continued*)

Outcomes	1. Adverse events 2. Immunogenicity
Notes	Location: Houston, Texas, USA Socioeconomic description: urban, high income Setting: clinic Date: no information No demographic information Results presented jointly for 3 separate trials

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Generation of allocation sequence: unclear
Allocation concealment (selection bias)	Unclear risk	Allocation concealment: unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Inclusion of randomly assigned participants in analysis: 100%
Selective reporting (reporting bias)	Low risk	All outcomes reported on
Other bias	Low risk	none

Khan 2012 PAK

Methods	Design: Cluster (geographic clusters)-RCT Intermediate surveillance for efficacy: Participants were identified through three study health centres during study period (2 years) Surveillance for adverse events: All participants were visited 30 minutes after vaccination, a subgroup of 240 participants were visited 3 days after vaccination and an adverse event form was completed
Participants	51,965 participants 120 geographic clusters using the Geographic Information System (GIS) imagery (60 clusters in each study arm) Inclusion criteria: children between the ages of 2 and 16 years Exclusion criteria: married female children older than 12 years of age were not included to avoid inadvertent immunization of pregnant women. Recent history of fever

Khan 2012 PAK (*Continued*)

Interventions	Single-dose capsular polysaccharide of *S. typhi*, Vi vaccine (dose 25 mcg) or hepatitis A vaccine (dose 720 IU) Route and schedule: single intramuscular injection, Vi vaccine or hepatitis A vaccine
Outcomes	1. Typhoid fever cases (*S. typhi* bacteraemia) 2. Indirect protection from typhoid fever 3. Adverse events
Notes	Location: Karachi, Pakistan Socioeconomic description: low socioeconomic urban squatter settlements Date: 2002 and 2007 Setting: vaccination centres and health centres

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A table of random numbers was used
Allocation concealment (selection bias)	Low risk	Vaccine identified by code, code assignment held centrally
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and investigators blinded- vaccines identified only by code. One vaccine administered per cluster
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reason for missing data given (migration, dying from other causes) and balanced across groups
Selective reporting (reporting bias)	Low risk	Study protocol not available but published study reports on both primary and secondary outcome
Other bias	Low risk	No recruitment bias, no baseline imbalance, no loss of clusters, analysis adjusted for clustering using generalized estimating equation

Klugman 1987 ZAF

Methods	Design: individual-RCT Active surveillance for efficacy: blood cultures if febrile with no obvious clinical cause

Klugman 1987 ZAF (*Continued*)

Participants	Number: 11,384 Inclusion criteria: 5 to 15 years Exclusion criteria: no details
Interventions	1. Capsular polysaccharide of *S. typhi*, Vi vaccine: 25 µg Vi; 5692 participants 2. Meningococcal vaccine: 25 µg Vi; 5692 participants Route and schedule: intramuscular injection; 1 dose Concomitant medication: not specified
Outcomes	1. Typhoid fever cases (*S. typhi* bacteraemia) 2. Immunogenicity
Notes	Location: eastern Transvaal area of South Africa Socioeconomic description: no details Setting: school Date: 1985 to 1988 No demographic information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization process unclear
Allocation concealment (selection bias)	Low risk	Sequentially numbered vaccines of identical appearance. Code held by independent observers
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind. Vaccines identical in appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Inclusion of randomized assigned participants in analysis: 100%
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	None

Levine 1986i CHL

Methods	Design: individual-RCT Active surveillance for adverse events: no further details

Levine 1986i CHL (*Continued*)

Participants	Number: 539 Inclusion criteria: adults, no details Exclusion criteria: no details
Interventions	1. Enteric-coated capsules *S. typhi* Ty21a vaccine: 172 participants 2. Placebo: 367 participants Route and schedule: oral capsules; 3 doses Concomitant medication: not specified
Outcomes	1. Adverse events
Notes	Location: Chile Socioeconomic description: no details Setting: no details Date: no details No demographic information

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Generation of allocation sequence: unclear
Allocation concealment (selection bias)	Unclear risk	Allocation concealment: unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding: double blind (no details)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Inclusion of randomly assigned participants in analysis: unclear
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	None

Levine 1986ii CHL

Methods	See Levine 1986i CHL (Levine 1986ii CHL is a different arm of the same trial with separate placebo group)
Participants	Number: 337 Inclusion criteria: children, no details Exclusion criteria: no details

Levine 1986ii CHL (*Continued*)

Interventions	1. *S. typhi* Ty21a vaccine in milk with NaHCO3S: 172 participants 2. Placebo: 172 participants Route and schedule: oral capsules; 3 doses Concomitant medication: not specified
Outcomes	Details as for Levine 1986i CHL
Notes	Details as for Levine 1986i CHL

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details as for Levine 1986i CHL
Allocation concealment (selection bias)	Unclear risk	Details as for Levine 1986i CHL
Blinding (performance bias and detection bias) All outcomes	Low risk	Details as for Levine 1986i CHL
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details as for Levine 1986i CHL
Selective reporting (reporting bias)	Low risk	Details as for Levine 1986i CHL
Other bias	Low risk	Details as for Levine 1986i CHL

Levine 1987i CHL

Methods	Design: cluster (classroom)-RCT Intermediate surveillance for efficacy: enteric fever and isolation of *S. typhi* from blood, bone marrow or bile-stained duodenal fluid in the hospital or in clinics during the trial (3 years)
Participants	Number: 27,074 Number of classrooms: 4312 Inclusion criteria: age 6 to 21 years; parental consent; no further details Exclusion criteria: no details
Interventions	1. Enteric capsules of *S. typhi*, Ty21a vaccine: 21,598 participants 2. Placebo: 5476 participants (placebo group divided into 4 equal groups for the comparison) Route and schedule: oral capsules; 3 doses given 21 days apart Concomitant medication: not specified
Outcomes	1. Typhoid fever cases (*S. typhi* bacteraemia, in bone marrow or in duodenal fluid)

Levine 1987i CHL (*Continued*)

Notes	Location: Chile socioeconomic description: no details Setting: school Date: 1983 to 1986 No demographic information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Generation of allocation sequence: unclear
Allocation concealment (selection bias)	Low risk	Sequentially numbered vaccines of identical appearance
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Inclusion of randomly assigned participants in analysis: 78% (109,594/141,127) of enrolled children received 3 doses and included in results. No reason for missing data given
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Unclear risk	Analysis not adjusted for clustering

Levine 1987ii CHL

Methods	See Levine 1987i CHL (Levine 1987ii CHL is a different arm of the same trial) Details as for Levine 1987i CHL, except blinding: placebo given in a similar regimen, but not mentioned if identical to gelatin or enteric capsules
Participants	Details as for Levine 1987i CHL, except number: 27,647
Interventions	1. Enteric capsules of *S. typhi*, Ty21a vaccine: 22,170 participants 2. Placebo: 5477 participants (placebo group divided into 4 equal groups for the comparison) Route and schedule: oral capsules; 3 doses given 2 days apart Concomitant medication: not specified
Outcomes	Details as for Levine 1987i CHL
Notes	Details as for Levine 1987i CHL

Levine 1987ii CHL (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Details as for Levine 1987i CHL
Allocation concealment (selection bias)	Low risk	Details as for Levine 1987i CHL
Blinding (performance bias and detection bias) All outcomes	Low risk	Details as for Levine 1987i CHL
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details as for Levine 1987i CHL
Selective reporting (reporting bias)	Low risk	Details as for Levine 1987i CHL
Other bias	Unclear risk	Details as for Levine 1987i CHL

Levine 1987iii CHL

Methods	See Levine 1987i CHL (Levine 1987iii CHL is a different arm of the same trial)
Participants	Details as for Levine 1987i CHL, except number: 27,017
Interventions	Details as for Levine 1987i CHL, except: 1. Gelatin capsules of *S. typhi*, Ty21a vaccine: 21,541 2. Placebo: 5476 (placebo group divided into 4 equal groups for the comparison)
Outcomes	Details as for Levine 1987i CHL
Notes	Details as for Levine 1987i CHL

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Details as for Levine 1987i CHL
Allocation concealment (selection bias)	Low risk	Details as for Levine 1987i CHL
Blinding (performance bias and detection bias) All outcomes	Low risk	Details as for Levine 1987i CHL

Levine 1987iii CHL (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details as for Levine 1987i CHL
Selective reporting (reporting bias)	Low risk	Details as for Levine 1987i CHL
Other bias	Unclear risk	Details as for Levine 1987i CHL

Levine 1987iv CHL

Methods	See Levine 1987i CHL (Levine 1987iv CHL is a different arm of the same trial) Details as for Levine 1987i CHL, except blinding: placebo given in a similar regimen, but not mentioned whether identical to gelatin or enteric capsules
Participants	Details as for Levine 1987i CHL, except number: 27,856
Interventions	1. Gelatin capsules of *S. typhi*, Ty21a vaccine: 22,379 participants 2. Placebo: 5477 participants (placebo group divided into 4 equal groups for the comparison) Route and schedule: oral capsules; 3 doses given 2 days apart Concomitant medication: not specified
Outcomes	Details as for Levine 1987i CHL
Notes	Details as for Levine 1987i CHL

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Details as for Levine 1987i CHL
Allocation concealment (selection bias)	Low risk	Details as for Levine 1987i CHL
Blinding (performance bias and detection bias) All outcomes	Low risk	Details as for Levine 1987i CHL
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details as for Levine 1987i CHL
Selective reporting (reporting bias)	Low risk	Details as for Levine 1987i CHL
Other bias	Unclear risk	Details as for Levine 1987i CHL

Levine 1990i CHL

Methods	Design: cluster (classroom)-RCT Intermediate surveillance for efficacy: enteric fever and isolation of *S. typhi* from blood, bone marrow or bile-stained duodenal fluid in the hospital or in clinics during the study (5 years)
Participants	Number: 42,073 Number of classes: 5423 Inclusion criteria: 5 to 19 years old; parental consent; no further details Exclusion criteria: no details
Interventions	1. Liquid formulation of *S. typhi*, Ty21a vaccine: 36,623 participants 2. Placebo: 5450 participants Route and schedule: oral solution; 3 doses given 2 days apart Concomitant medication: not specified
Outcomes	1. Typhoid fever cases (*S. typhi* bacteraemia, in bone marrow or in duodenal fluid)
Notes	Location: Chile Socioeconomic description: no details Setting: school Date: 1986 to 1991 No demographic information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Generation of allocation sequence: unclear
Allocation concealment (selection bias)	Low risk	Sequentially numbered vaccines of identical appearance. Code kept at WHO
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind. Identical packets and capsules
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Inclusion of randomly assigned participants in analysis: 85% (81,621/95,910 children who received at least 1 dose) received all 3 doses and included in results. No reason for missing data given
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Unclear risk	Analysis not adjusted for clustering; however, authors state, "analysis of cases by class after three years of follow-up showed no clustering"

Levine 1990ii CHL

Methods	See Levine 1990i CHL (Levine 1990ii CHL is a different arm of the same trial) Details as for Levine 1990i CHL, except intermediate surveillance for efficacy for 3 years
Participants	Details as for Levine 1990i CHL, except number: 39,548
Interventions	Details as for Levine 1990i CHL, except: 1. Enteric capsules of *S. typhi*, Ty21a vaccine: 34,696 participants 2. Placebo: 4852 participants
Outcomes	Details as for Levine 1990i CHL
Notes	Details as for Levine 1990i CHL

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Details as for Levine 1990i CHL
Allocation concealment (selection bias)	Low risk	Details as for Levine 1990i CHL
Blinding (performance bias and detection bias) All outcomes	Low risk	Details as for Levine 1990i CHL
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details as for Levine 1990i CHL
Selective reporting (reporting bias)	Low risk	Details as for Levine 1990i CHL
Other bias	Unclear risk	Details as for Levine 1990i CHL

Lin 2001 VNM

Methods	Design: individual-RCT Active surveillance for efficacy and adverse events: weekly history; temperature; blood cultures and serology if febrile during the trial (27 months); review of bacteriological records in the provincial hospital Passive surveillance: 19 additional months
Participants	Number: 12,008 Inclusion criteria: age 2 to 5 years; no further details Exclusion criteria: illnesses that required ongoing medical care; fever > 37.5 °C at first injection

Lin 2001 VNM (*Continued*)

Interventions	1. Vi-rEPA vaccine; capsular polysaccharide of *S. typhi*, Vi, bound to a nontoxic recombinant protein that is antigenically identical to *Pseudomonas aeruginosa* exotoxin A; 22 µg Vi in 0.5 mL; 5991 participants 2. Placebo: 6017 participants Route and schedule: intramuscular injection; 2 doses, 6 weeks apart Concomitant medication: not specified
Outcomes	1. Typhoid fever cases (*S. typhi* bacteraemia) 2. Adverse events 3. Immunogenicity Subgroups for gender, age and study year
Notes	Location: Dong Thap Province, Mekong Delta, Vietnam Socioeconomic description: rural; low income Setting: home Date: 1998 to 2000 Sex, age at vaccination, household composition and size and interval between the 2 injections similar in both groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Identical looking vaccine and placebo were randomly numbered 0 to 9 and packaged in packets of 10; however, unclear how randomization sequence generated
Allocation concealment (selection bias)	Low risk	Code identifying identical-looking vaccine and placebo was kept at the central pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind. Vaccine and placebo vials indistinguishable
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Inclusion of randomly assigned participants in analysis: 100%
Selective reporting (reporting bias)	Low risk	All expected outcomes reported on
Other bias	Low risk	None

Olanratmanee 1992 THA

Methods	Design: individual-RCT Active surveillance for adverse events: 1.5 hours of observation and parental reporting via adverse event report sheet
Participants	Number: 170 Inclusion criteria: age 4 to 6 years; no further details Exclusion criteria: no details
Interventions	1. Liquid formulation of *S. typhi*, TY21a: 88 participants 2. Placebo: 82 participants Route and schedule: oral solution; 3 doses, alternate days Concomitant medication: not specified
Outcomes	1. Adverse events 2. Immunogenicity
Notes	Location: Thailand Socioeconomic description: no details Setting: clinic Date: no details No demographic information

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Generation of allocation sequence: not mentioned
Allocation concealment (selection bias)	Unclear risk	Allocation concealment: no information
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind. Identical vaccine and placebo packages
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Inclusion of randomly assigned participants in analysis: 100%
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	None

Simanjuntak 1991i IDN

Methods	Design: individual-RCT Intermediate surveillance for efficacy: isolation of *S. typhi* from blood during trial (2.5 years) Surveillance for adverse events: questionnaires collected from 588 individuals
Participants	Number: 10,212 Inclusion criteria: age 3 to 44 years; no further details Exclusion criteria: pregnant women; febrile illness
Interventions	1. Liquid formulation of *S. typhi*, Ty21a: 5066 participants 2. Placebo: 5146 participants Route and schedule: oral solution; 3 doses, 1 week apart Concomitant medication: not specified Note Simanjuntak 1991ii IDN is a different arm of the same trial (see below for further details). Simanjuntak 1991i IDN and Simanjuntak 1991ii IDN had different placebo groups
Outcomes	1. Typhoid fever cases (*S. typhi* bacteraemia) 2. Adverse events Subgroups for age and study year
Notes	Location: Plaju and Sungai Gerong, Sumatra, Indonesia Socioeconomic description: no details Setting: clinic Date: 1986 to 1989 Sex, age at vaccination, residence in a compound, history of typhoid vaccination and level of education similar in both groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Generation of allocation sequence: computer-generated table of random numbers
Allocation concealment (selection bias)	Low risk	Identical vaccine and placebo
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind. Identical vaccine and placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	93% of participants (20,543/22,001) received 3 doses and included in results. Missing outcome data balanced across intervention and control groups
Selective reporting (reporting bias)	Low risk	All expected outcomes reported on

Simanjuntak 1991i IDN (*Continued*)

Other bias	Low risk	None

Simanjuntak 1991ii IDN

Methods	See Simanjuntak 1991i IDN (Simanjuntak 1991ii IDN is a different arm of the same trial) Details as for Levine 1990i CHL, except surveillance for adverse events: questionnaires collected from 602 individuals
Participants	Details as for Simanjuntak 1991i IDN, except number: 10,331
Interventions	1. Enteric capsules of *S. typhi*, Ty21a: 5209 participants 2. Placebo: 5122 participants Route and schedule: oral capsules; 3 doses, 1 week apart Concomitant medication: not specified Note Simanjuntak 1991i IDN is a different arm of the same trial (see below for further details). Simanjuntak 1991i IDN and Simanjuntak 1991ii IDN had different placebo groups
Outcomes	Details as for Simanjuntak 1991i IDN
Notes	Details as for Simanjuntak 1991i IDN

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Details as for Simanjuntak 1991i IDN
Allocation concealment (selection bias)	Low risk	Details as for Simanjuntak 1991i IDN
Blinding (performance bias and detection bias) All outcomes	Low risk	Details as for Simanjuntak 1991i IDN
Incomplete outcome data (attrition bias) All outcomes	Low risk	Details as for Simanjuntak 1991i IDN
Selective reporting (reporting bias)	Low risk	Details as for Simanjuntak 1991i IDN
Other bias	Low risk	Details as for Simanjuntak 1991i IDN

Sur 2009 IND

Methods	Design: cluster (geographic clusters)-RCT Active surveillance for efficacy: five study clinics were established to conduct surveillance for febrile illnesses and to refer participants with severe disease for hospital care during study period (2 years) Surveillance period adverse events: all participants 30 minutes after vaccination, subgroup of 320 participants for 3 consecutive days, passive surveillance for adverse events for 1 month at all study clinics and hospitals
Participants	37,673 participants 80 contiguous geographic clusters (40 clusters in each study group) Inclusion criteria: 24 months of age and older, no reported fever or had an axillary temperature not greater than 37.5 °C at time of administration Exclusion criteria: not stated
Interventions	Single-dose capsular polysaccharide of *S. typhi*, Vi vaccine (dose 25 mcg) or inactivated hepatitis A vaccine (dose 720 IU for children 2 to 18, 1440 IU for adults) Route and schedule: single intramuscular injection, Vi vaccine or inactivated hepatitis A vaccine
Outcomes	1. Typhoid fever cases (*S. typhi* bacteraemia) 2. Indirect protection from typhoid fever 3. Adverse events
Notes	Location: Kolkata, India Socioeconomic description: slum-dwelling residents The clusters were stratified according to ward and the number of residents who were 18 years of age or younger (< 200 vs ≥ 200 persons) and the number of residents who were older than 18 years (< 500 vs ≥ 500 persons), resulting in eight strata Date: November 2004 to December 2006 Setting: vaccination centres set up for each cluster and health clinics

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Used a table of random numbers to assign half the 80 clusters to each vaccine"
Allocation concealment (selection bias)	Low risk	"The vaccines were labelled only with code letters." However, two vaccines were not packaged in an identical fashion. Attempts to minimize this bias unlikely to have affected the findings of the trial
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and study personnel blind. Not stated whether outcome assessors were blinded

Sur 2009 IND (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for missing data given (migration, dying from other causes) and balanced across groups
Selective reporting (reporting bias)	Low risk	Study protocol not available but published study reports on both primary and secondary outcomes
Other bias	Low risk	No recruitment bias, no baseline imbalance, no loss of clusters, analysis adjusted for clustering using generalized estimating equation

Thiem 2011 VNM

Methods	Design: individual-RCT Active surveillance adverse events: Participants were observed at the clinic for 30 minutes after injection. They were visited by the commune health staff 6, 24 and 48 hours after each vaccination for measurement of temperature and inspection of the injection sites
Participants	301 full-term infants Inclusion criteria: full-term, birth weight > 2500 g Exclusion criteria: born to mothers with serious medical problems
Interventions	Three arms: Vi-r EPA and expanded programme on immunization (EPI) versus Hib-TT and EPI versus EPI only Route and schedule: intramuscular injection, infants vaccinated at 2, 4, 6 and 12 months
Outcomes	1. Adverse events
Notes	Location: Thanh Thuy District, Phu Tho Province, Vietnam Socioeconomic description: rural area Date: not stated Setting: community health centre and district hospital

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Thiem 2011 VNM (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	318 infants were randomly assigned. 301 infants received the first injection, 294 the second, 283 the third and 167 the fourth of either Vi-rEPA or Hib-TT. Reasons for missing data given
Selective reporting (reporting bias)	Low risk	Expected outcomes reported on
Other bias	Low risk	None

Wahdan 1980a EGY

Methods	Design: cluster (classroom)-RCT Intermediate surveillance for efficacy: isolation of *S. typhi* from blood in the hospital during the study (3 years) Surveillance for adverse events: no details
Participants	Number: 32,388 Inclusion criteria: age 6 to 7 years; no further details Exclusion criteria: no details
Interventions	1. Liquid formulation of *S. typhi*, Ty21a: 16,486 participants 2. Placebo: 15,902 participants Route and schedule: oral solution; 3 doses, alternate days Concomitant medication: not specified
Outcomes	1. Typhoid fever cases (*S. typhi* bacteraemia) 2. Adverse events
Notes	Location: Alexandria, Egypt Socioeconomic description: no details Setting: school Date: 1978 to 1981 No demographic information

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Generation of allocation sequence: unclear
Allocation concealment (selection bias)	Unclear risk	Vaccine and placebo identical. Allocation concealment unclear

Wahdan 1980a EGY (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Vaccine and placebo identical
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Inclusion of randomly assigned participants in analysis: 100%
Selective reporting (reporting bias)	Low risk	All expected outcomes reported on
Other bias	Unclear risk	Analysis not adjustment for clustering

Wahdan 1980b EGY

Methods	Design: cluster (classroom)-RCT Surveillance for adverse events: no details
Participants	Number: 884 Inclusion criteria: age 6 to 7 years; no further details Exclusion criteria: no details
Interventions	1. Liquid formulation of *S. typhi*, Ty21a: 413 participants 2. Placebo: 471 participants Route and schedule: oral solution; 3 doses, alternate days Concomitant medication: not specified
Outcomes	1. Adverse events
Notes	Location: Alexandria, Egypt Socioeconomic description: no details Setting: school Date: 1978 No demographic information

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Generation of allocation sequence: unclear
Allocation concealment (selection bias)	Unclear risk	Vaccine and placebo identical. Allocation concealment unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	Vaccine and placebo identical

Wahdan 1980b EGY (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Inclusion of randomly assigned participants in analysis: 100%
Selective reporting (reporting bias)	Unclear risk	All expected outcomes reported on
Other bias	Unclear risk	Analysis not adjusted for clustering

Wang 1997a CHN

Methods	Design: individual-RCT Passive surveillance for efficacy: signs and symptoms of typhoid fever; blood cultures and serum Widal's test (1 year)
Participants	Number: 81,506 Inclusion criteria: age 5 to 55 years; healthy Exclusion criteria: history of liver, kidney or heart disease; hypertension; acute infection; psychiatric disease; allergic history; prior typhoid infection; pregnancy; prior typhoid vaccination in the last 2 years
Interventions	1. Capsular polysaccharide of *S. typhi*, Vi vaccine: 30 µg Vi: 41,118 participants 2. Meningococcal vaccine: 40,388 participants Route and schedule: intramuscular injection; 1 dose Concomitant medication: not specified
Outcomes	1. Typhoid fever cases (*S. typhi* bacteraemia) 2. Adverse reactions Subgroups for age and gender
Notes	Location: Baoying County, Jiangsu Province, China Socioeconomic description: no details Setting: no details Date: 1994 to 1995 No demographic information

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Generation of allocation sequence: computer-generated random numbers ?
Allocation concealment (selection bias)	Low risk	Allocation concealment: code concealed from field workers and study population

Wang 1997a CHN (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind. Identical vaccine and placebo vials
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Inclusion of randomly assigned participants in analysis: 100%
Selective reporting (reporting bias)	Low risk	All expected outcomes reported on
Other bias	Low risk	None

Wang 1997b CHN

Methods	Design: individual-RCT Surveillance for adverse events: fever and local symptoms checked before immunization, and 6 to 8, 24 and 48 hours after immunization
Participants	Number: 777 Inclusion criteria: > 6 years old; healthy Exclusion criteria: no details
Interventions	1. Capsular polysaccharide of *S. typhi*, Vi vaccine: 30 µg Vi; 384 participants 2. Meningococcal vaccine: 393 participants Route and schedule: intramuscular injection; 1 dose Concomitant medication: not specified
Outcomes	1. Adverse reactions
Notes	Location: Baoying County, Jiangsu Province, China Socioeconomic description: no details Setting: no details Date: 1994 No demographic information

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Generation of allocation sequence: computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Allocation concealment: code concealed from field workers and study population
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind. Vaccine and placebo identical

Wang 1997b CHN (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	None

Yang 2001 CHN

Methods	Design: individual-RCT Passive surveillance for efficacy: clinical symptoms; positive blood cultures and serum Widal's test during trial (1.6 years) Surveillance for adverse events: parental reporting of adverse effects in 3 schools
Participants	Number: 131,271 Inclusion criteria: healthy children age 3 to 19 years and adults age < 51 years Exclusion criteria: chronic disease; under medication; pregnancy
Interventions	1. Capsular polysaccharide of *S. typhi*, Vi vaccine: 30 µg Vi; 65,287 participants 2. Placebo: 65,984 participants Route and schedule: hypodermically; 1 dose Concomitant medication: not specified
Outcomes	1. Typhoid fever cases (*S. typhi* bacteraemia) 2. Adverse events Subgroups for age, profession and sex
Notes	Location: County of Quan, north-eastern part of Guangxi Zhuang Autonomous Region, southern China Socioeconomic description: no details Setting: clinic Date: 1995 to 1996 Age, sex and profession similar in both groups

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Generation of allocation sequence: unique serial number to each participant; having an even or an odd number determined allocation to vaccine or placebo
Allocation concealment (selection bias)	Low risk	Allocation concealment: code concealed from field workers and study population

Yang 2001 CHN (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	None

Zhou 2007 CHN

Methods	Design: individual-RCT Active surveillance for adverse events: All participants were observed for 2 hours at the vaccination site after administration of the study agent and were visited by trained clinicians on days 1, 2, 3 and 28
Participants	Number: 667 Inclusion criteria: school children ages 9 to 14 who have previously received a primary dose of Vi vaccine, no signs or symptoms consistent with an infection within the 2 weeks before injection, no history of typhoid fever and axillary temperature of 37.5 °C on the day of the planned injection Exclusion criteria: no previous primary dose of Vi vaccine, signs or symptoms of infection within the 2 weeks before injection, history of typhoid fever or axillary temperature higher than 37.5 °C on day of planned injection
Interventions	1. Capsular polysaccharide of *S. typhi*, Vi vaccine to previously vaccinated children (revaccination), 334 participants 2. Placebo (normal saline), 333 participants Route and schedule: intramuscular injection, one dose
Outcomes	1. Adverse events
Notes	Location: Suzhou, Jiangsu, China Socioecomic description: no details Setting: school Date: 2002

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Computer generated random numbers"

Zhou 2007 CHN (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind-blinding of participants and study personnel. Vaccine and placebo identical
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	None

Cluster-RCT: randomized controlled trial that randomly assigned clusters (eg, classrooms); ELISA: enzyme-linked immunosorbent assay; individual-RCT: randomized controlled trial that randomly assigned individual participants; WHO: World Health Organization.

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

Study	Reason for exclusion
Ali 2011	No relevant outcome measures
Arya 1997	Letter; not an RCT
Ashcroft 1967	Evaluated the inactivated whole-cell vaccine, which is no longer in use
Black 1983	No relevant outcome measures
Bumann 2001	Evaluated experimental live-attenuated oral vaccine candidates; no efficacy trials of this vaccine
Cahn 2004	Study arms randomly assigned to receive different doses of same vaccine
Chuttani 1977	Evaluated the inactivated whole-cell vaccine, which is no longer in use
Cordero-Yap 2001	Compared 2 Vi polysaccharide vaccines made by 2 different companies
Cryz 1995	No relevant control group
Cumberland 1992	Evaluated Vi vaccine versus inactivated whole-cell vaccine, which is no longer in use
Ferreccio 1989	RCT compared different doses of the Ty21a vaccine

(*Continued*)

Hejfec 1965	Two separate randomized trials, described together; none of the chemical subunit vaccines that were studied are in use
Hejfec 1966	Evaluated the inactivated whole-cell vaccine, which is no longer in use
Hejfec 1968	Evaluated the inactivated whole-cell vaccine, which is no longer in use
Hejfec 1969	Evaluated the inactivated whole-cell vaccine, which is no longer in use
Hejfec 1976	Evaluated the inactivated whole-cell vaccine, which is no longer in use
Hien 2010	Evaluated adverse events of new M01ZH09 vaccine, no efficacy trials of this vaccine
Hohmann 1996a	No random allocation
Hohmann 1996b	No random allocation
Kantele 2013	No relevant outcome measures
Keddy 1999	No relevant outcome measures
Khan 2007	Nonrandomized study
Khoo 1995	Evaluated safety of Vi vaccine compared with meningococcal vaccine or combination
Kirkpatrick 2006	Evaluated adverse events of new M01ZH09 vaccine; no efficacy trials of this vaccine
Lebacq 2001	Evaluated different brands of Vi vaccine
Levin 1975	No random allocation; compared Vi with inactivated whole-cell vaccine, which is no longer in use
Lyon 2010	Evaluated adverse events of new M01ZH09 vaccine; no efficacy trials of this vaccine
Murphy 1991	No random allocation to vaccine and placebo arms
Nisini 1993	No random allocation
Panchanathan 2001	Compared Vi vaccine with inactivated whole-cell vaccine, which is no longer in use
Polish committee 1966	Evaluated the inactivated whole-cell vaccine, which is no longer in use
Sabitha 2004	Compared 2 brands of Vi vaccine
Tacket 1992	Evaluated experimental live-attenuated oral vaccine candidates; no efficacy trials of these vaccines
Tacket 1997	Evaluated experimental live-attenuated oral vaccine candidates; no efficacy trials of these vaccines

(*Continued*)

Tacket 2000	Evaluated experimental live-attenuated oral vaccine candidates; no efficacy trials of these vaccines
Tapa 1975	Evaluated the inactivated whole-cell vaccine, which is no longer in use
Thiem 2006	No relevant outcome measures
van Damme 2011	Evaluated adverse events of new conjugate vaccine (Vi-CRM); no efficacy trials of this vaccine
Wahdan 1975	Quasi-RCT evaluating the inactivated whole-cell vaccine, which is no longer in use
Wahid 2011	No relevant outcome measures
Yang 2005	No relevant outcome measures
Yang 2009	Safety only, evaluated different brands of same vaccine
Yug Ty Comm 1962	Evaluated the inactivated whole-cell vaccine, which is no longer in use
Yug Ty Comm 1964	Evaluated the inactivated whole-cell vaccine, which is no longer in use
Zhou 2008 CHN	Safety only; evaluated different brands of same vaccine

RCT: randomized controlled trial.

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

Chinnasami

Trial name or title	A Clinical Trial to Study the Optimal Use of Conjugate Typhoid Vaccine-Single Dose vs Two Doses
Methods	
Participants	400 healthy children between 6 months and 5 years of age
Interventions	1. Conjugated typhoid vaccination: two doses at two-month intervals, each dose 0.5 mL 2. Conjugated typhoid vaccination: single dose, dose 0.5 mL
Outcomes	Seroconversion rate
Starting date	December 2012
Contact information	Dr Bilal Chinnasami balajictriumphants@gmail.com

Chinnasami (*Continued*)

Notes	Location: Tamil Nadu, India Clinical Trials Registry-India: CTRI/2010/091/003031

Darton 2012

Trial name or title	Understanding Typhoid Disease After Vaccination: A Single Centre, Randomised, Doubleblind, Placebo Controlled Study to Evaluate M01ZH09 in a Healthy Adult Challenge Model, Using Ty21a Vaccine as a Positive Control
Methods	
Participants	99 adults ages 18 to 60 years and in good health
Interventions	1. M10ZH09 vaccine 2. Ty21a vaccine 3. Vaccine placebo
Outcomes	Diagnosis of typhoid fever (2 weeks after typhoid challenge)
Starting date	July 2011
Contact information	Thomas Darton 01865857420
Notes	Location: Oxford, United Kingdom National Clinical Trials identifier: NCT01405521

House 2011

Trial name or title	A Phase II, Single-centre, Randomised, Single-blind Study to Evaluate Vi-CRM197 Against Historical Unvaccinated Controls in a Healthy Adult Challenge Model, With a Vi-PS Vaccine Control Arm-Understanding Immunity After Typhoid Vaccination
Methods	
Participants	36 adults ages 18 to 60 years and in good health
Interventions	1. Vi-CRM197 conjugate vaccine 2. Vi-PS control arm
Outcomes	Main objective: Using an established model of human typhoid infection, in which healthy adults are deliberately infected with typhoid-causing bacteria, we will determine how effective a new typhoid vaccine (Vi-CRM197, Novartis Vaccine Institute for Global Health) is in preventing infection Primary end point(s): the proportion of participants developing typhoid fever after challenge with *S. typhi* (Quailes strain) given 28 days after vaccination with NVGH Vi-CRM197 vaccine
Starting date	December 2011

House 2011 (*Continued*)

Contact information	Ms Heather House heather.house@admin.ox.ac.uk
Notes	Location: Oxford, United Kingdom EU Clinical Trials Registration identifier: EUCTR2011-003653-26-GB

Mitra 2012

Trial name or title	Incidence of Typhoid Fever as Observed Over 1 Year in Children Aged 6 Months-12 Years After Receiving Conjugated Typhoid Vaccine (Peda Typh TM) Versus a Similar Non-vaccinated Group in the Same Locality in Kolkata
Methods	
Participants	2000 healthy children and teenagers of both sexes from 6 months to 12 years of age
Interventions	1. Vi-Tetanus toxoid conjugated typhoid vaccine (Peda Typh TM) 2. Nil
Outcomes	Incidence of typhoid fever and paratyphoid fever in the vaccinated and non vaccinated groups
Starting date	July 2012
Contact information	Dr Monjori Mitra monjorim@medclinsearch.com
Notes	Location: Kolkata, India Clinical Trials Registry-India: CTRI/2012/06/002719

DATA AND ANALYSES

Comparison 1. Ty21a vaccine (three doses) vs control; efficacy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of typhoid fever, Year 1	2	20543	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.46, 0.92]
1.1 Enteric capsules	1	10331	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.45, 1.15]
1.2 Liquid formulation	1	10212	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.35, 0.96]
2 Incidence of typhoid fever, Year 2	2	20543	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.29, 0.60]
2.1 Enteric capsules	1	10331	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.30, 0.79]
2.2 Liquid formulation	1	10212	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.20, 0.59]
3 Incidence of typhoid fever, Year 3	2	20543	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.28, 1.06]
3.1 Enteric capsules	1	10331	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.18, 1.31]
3.2 Liquid formulation	1	10212	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.23, 1.50]
4 Cumulative incidence of typhoid fever at 2.5 to 3 years	2	20543	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.42, 0.66]
4.1 Enteric capsules	1	10331	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.42, 0.79]
4.2 Liquid formulation	1	10212	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.33, 0.66]

Comparison 2. Ty21a vaccine: liquid formulation vs enteric capsules (3 doses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cumulative incidence of typhoid fever at 2.5 to 3 years	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 3. Ty21a vaccine vs control; adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fever	4	2066	Risk Ratio (M-H, Random, 95% CI)	1.84 [1.02, 3.31]
1.1 Enteric capsules	2	1141	Risk Ratio (M-H, Random, 95% CI)	2.72 [1.06, 6.96]
1.2 Liquid formulation	1	588	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.61, 3.03]
1.3 In milk with sodium bicarbonate	1	337	Risk Ratio (M-H, Random, 95% CI)	2.08 [0.19, 22.77]
2 Vomiting	4	2066	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.43, 3.05]
2.1 Enteric capsules	2	1141	Risk Ratio (M-H, Random, 95% CI)	1.92 [0.13, 27.74]
2.2 Liquid formulation	1	588	Risk Ratio (M-H, Random, 95% CI)	1.91 [0.37, 9.79]

2.3 In milk with sodium bicarbonate	1	337	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.33, 1.31]
3 Diarrhoea	4	2066	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.52, 1.24]
3.1 Enteric capsules	2	1141	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.57, 2.58]
3.2 Liquid formulation	1	588	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.34, 1.49]
3.3 In milk with sodium bicarbonate	1	337	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.29, 1.30]
4 Nausea or abdominal pain	4	2066	Risk Ratio (M-H, Random, 95% CI)	1.70 [0.77, 3.75]
4.1 Enteric capsules	2	1141	Risk Ratio (M-H, Random, 95% CI)	2.92 [1.53, 5.57]
4.2 Liquid formulation	1	588	Risk Ratio (M-H, Random, 95% CI)	1.84 [0.90, 3.77]
4.3 In milk with sodium bicarbonate	1	337	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.39, 1.13]
5 Headache	2	1190	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.76, 2.27]
5.1 Enteric capsules	1	602	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.64, 3.07]
5.2 Liquid formulation	1	588	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.57, 2.65]
6 Rash	2	1190	Risk Ratio (M-H, Random, 95% CI)	2.94 [0.61, 14.12]
6.1 Enteric capsules	1	602	Risk Ratio (M-H, Random, 95% CI)	2.81 [0.29, 26.83]
6.2 Liquid formulation	1	588	Risk Ratio (M-H, Random, 95% CI)	3.06 [0.34, 27.24]
7 Any mild adverse event	3	1360	Risk Ratio (M-H, Random, 95% CI)	1.67 [1.03, 2.72]
7.1 Enteric capsules	1	602	Risk Ratio (M-H, Random, 95% CI)	1.78 [1.08, 2.95]
7.2 Liquid formulation	2	758	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.06, 8.55]
8 Serious adverse events	5	2236	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.1 Enteric capsules	2	1141	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Liquid formulation	2	758	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.3 In milk with sodium bicarbonate	1	337	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 4. Vi polysaccharide vaccine (one dose) vs control; efficacy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of typhoid fever	6		Risk Ratio (Random, 95% CI)	Subtotals only
1.1 Year 1	3	99797	Risk Ratio (Random, 95% CI)	0.31 [0.26, 0.37]
1.2 Year 2	4	194969	Risk Ratio (Random, 95% CI)	0.41 [0.31, 0.55]
1.3 Year 3	1	11384	Risk Ratio (Random, 95% CI)	0.50 [0.32, 0.78]
2 Cumulative incidence of typhoid fever at 2.5 to 3 years	1	11384	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.30, 0.70]

Comparison 5. Vi polysaccharide vaccine vs control; adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fever	4	133038	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.85, 1.14]
2 Erythema	3	132261	Risk Ratio (M-H, Random, 95% CI)	3.04 [0.45, 20.30]
3 Swelling at injection site	3	1767	Risk Ratio (M-H, Random, 95% CI)	6.06 [1.07, 34.22]
4 Pain at injection site	1	667	Risk Ratio (M-H, Random, 95% CI)	7.98 [3.69, 17.24]
5 Serious adverse events	4	133038	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 6. Vi-rEPA vaccine (two doses) vs control; efficacy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of typhoid fever	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Year 1	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Year 2	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 7. Vi-rEPA vaccine vs control; adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fever after Vi-rEPA (dose1)	2	12209	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.57, 4.23]
2 Fever after Vi-rEPA (dose 2)	2	11286	Risk Ratio (M-H, Random, 95% CI)	2.29 [0.56, 9.46]
3 Erythema after Vi-rEPA (dose 1)	2	12209	Risk Ratio (M-H, Random, 95% CI)	3.03 [0.32, 28.64]
4 Erythema after Vi-rEPA (dose 2)	2	11286	Risk Ratio (M-H, Random, 95% CI)	2.01 [0.18, 22.21]
5 Swelling at injection site after Vi-rEPA (dose 1)	2	12209	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.15, 7.03]
6 Swelling at injection site after Vi-rEPA (dose 2)	2	11286	Risk Ratio (M-H, Random, 95% CI)	5.27 [0.26, 106.74]
7 Serious adverse events	2	12209	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Ty21a vaccine (three doses) vs control; efficacy, Outcome 1 Incidence of typhoid fever, Year 1.

Review: Vaccines for preventing typhoid fever

Comparison: 1 Ty21a vaccine (three doses) vs control; efficacy

Outcome: 1 Incidence of typhoid fever, Year 1

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Enteric capsules					
Simanjuntak 1991ii IDN	30/5209	41/5122		53.2 %	0.72 [0.45, 1.15]
Subtotal (95% CI)	**5209**	**5122**		**53.2 %**	**0.72 [0.45, 1.15]**
Total events: 30 (Vaccine), 41 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.37 (P = 0.17)					
2 Liquid formulation					
Simanjuntak 1991i IDN	24/5066	42/5146		46.8 %	0.58 [0.35, 0.96]
Subtotal (95% CI)	**5066**	**5146**		**46.8 %**	**0.58 [0.35, 0.96]**
Total events: 24 (Vaccine), 42 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.13 (P = 0.033)					
Total (95% CI)	**10275**	**10268**		**100.0 %**	**0.65 [0.46, 0.92]**
Total events: 54 (Vaccine), 83 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.38, df = 1 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 2.46 (P = 0.014)					
Test for subgroup differences: Chi^2 = 0.38, df = 1 (P = 0.54), I^2 =0.0%					

Analysis 1.2. Comparison 1 Ty21a vaccine (three doses) vs control; efficacy, Outcome 2 Incidence of typhoid fever, Year 2.

Review: Vaccines for preventing typhoid fever

Comparison: 1 Ty21a vaccine (three doses) vs control; efficacy

Outcome: 2 Incidence of typhoid fever, Year 2

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Enteric capsules					
Simanjuntak 1991ii IDN	25/5209	50/5122		56.6 %	0.49 [0.30, 0.79]
Subtotal (95% CI)	**5209**	**5122**		**56.6 %**	**0.49 [0.30, 0.79]**
Total events: 25 (Vaccine), 50 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.91 (P = 0.0036)					
2 Liquid formulation					
Simanjuntak 1991i IDN	17/5066	51/5146		43.4 %	0.34 [0.20, 0.59]
Subtotal (95% CI)	**5066**	**5146**		**43.4 %**	**0.34 [0.20, 0.59]**
Total events: 17 (Vaccine), 51 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.88 (P = 0.00011)					
Total (95% CI)	**10275**	**10268**		**100.0 %**	**0.42 [0.29, 0.60]**
Total events: 42 (Vaccine), 101 (Control)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.01, df = 1 (P = 0.31); I^2 =1%					
Test for overall effect: Z = 4.71 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 1.01, df = 1 (P = 0.31), I^2 =1%					

Analysis 1.3. Comparison 1 Ty21a vaccine (three doses) vs control; efficacy, Outcome 3 Incidence of typhoid fever, Year 3.

Review: Vaccines for preventing typhoid fever

Comparison: 1 Ty21a vaccine (three doses) vs control; efficacy

Outcome: 3 Incidence of typhoid fever, Year 3

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Enteric capsules					
Simanjuntak 1991ii IDN	6/5209	12/5122		47.5 %	0.49 [0.18, 1.31]
Subtotal (95% CI)	**5209**	**5122**		**47.5 %**	**0.49 [0.18, 1.31]**
Total events: 6 (Vaccine), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.42 (P = 0.16)					
2 Liquid formulation					
Simanjuntak 1991i IDN	7/5066	12/5146		52.5 %	0.59 [0.23, 1.50]
Subtotal (95% CI)	**5066**	**5146**		**52.5 %**	**0.59 [0.23, 1.50]**
Total events: 7 (Vaccine), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.10 (P = 0.27)					
Total (95% CI)	**10275**	**10268**		**100.0 %**	**0.54 [0.28, 1.06]**
Total events: 13 (Vaccine), 24 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.07, df = 1 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 1.78 (P = 0.076)					
Test for subgroup differences: Chi^2 = 0.07, df = 1 (P = 0.79), I^2 =0.0%					

Analysis 1.4. Comparison 1 Ty21a vaccine (three doses) vs control; efficacy, Outcome 4 Cumulative incidence of typhoid fever at 2.5 to 3 years.

Review: Vaccines for preventing typhoid fever

Comparison: 1 Ty21a vaccine (three doses) vs control; efficacy

Outcome: 4 Cumulative incidence of typhoid fever at 2.5 to 3 years

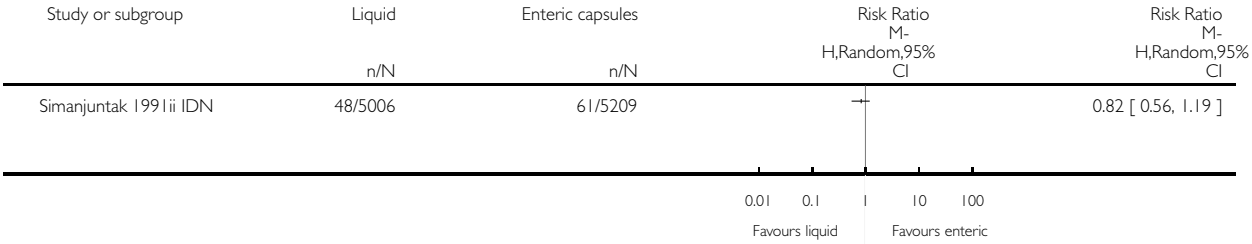
Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Enteric capsules					
Simanjuntak 1991ii IDN	61/5209	104/5122		54.0 %	0.58 [0.42, 0.79]
Subtotal (95% CI)	**5209**	**5122**		**54.0 %**	**0.58 [0.42, 0.79]**
Total events: 61 (Vaccine), 104 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.44 (P = 0.00059)					
2 Liquid formulation					
Simanjuntak 1991i IDN	48/5066	104/5146		46.0 %	0.47 [0.33, 0.66]
Subtotal (95% CI)	**5066**	**5146**		**46.0 %**	**0.47 [0.33, 0.66]**
Total events: 48 (Vaccine), 104 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.37 (P = 0.000012)					
Total (95% CI)	**10275**	**10268**		**100.0 %**	**0.52 [0.42, 0.66]**
Total events: 109 (Vaccine), 208 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.77, df = 1 (P = 0.38); I^2 =0.0%					
Test for overall effect: Z = 5.49 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.77, df = 1 (P = 0.38), I^2 =0.0%					

Analysis 2.1. Comparison 2 Ty21a vaccine: liquid formulation vs enteric capsules (3 doses), Outcome 1 Cumulative incidence of typhoid fever at 2.5 to 3 years.

Review: Vaccines for preventing typhoid fever

Comparison: 2 Ty21a vaccine: liquid formulation vs enteric capsules (3 doses)

Outcome: 1 Cumulative incidence of typhoid fever at 2.5 to 3 years

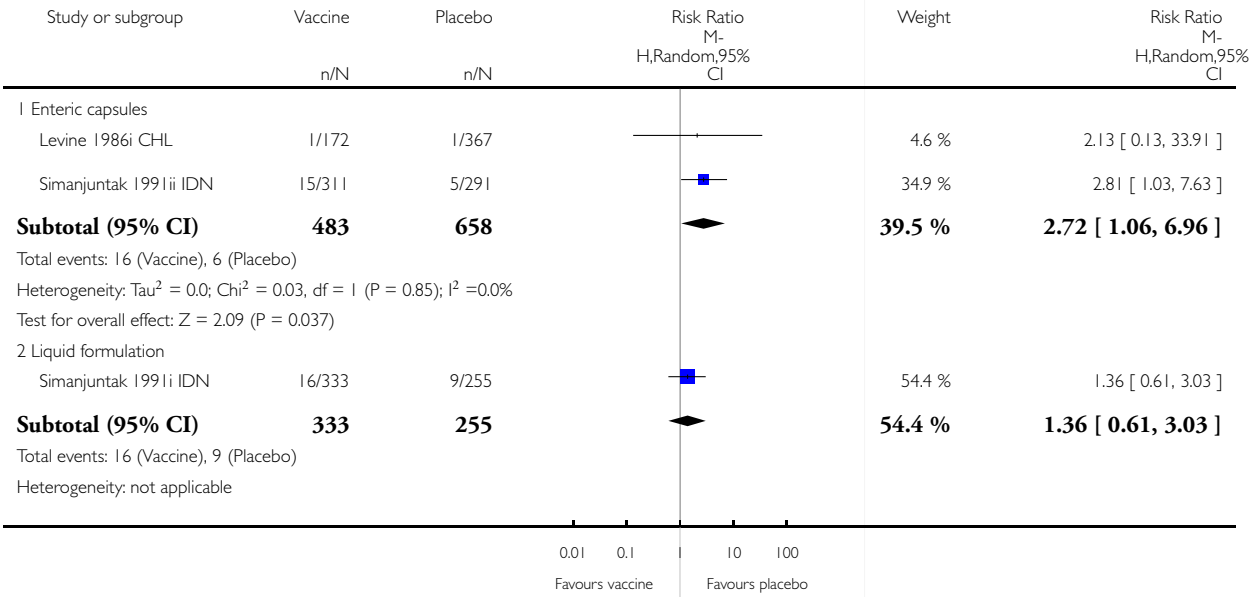


Analysis 3.1. Comparison 3 Ty21a vaccine vs control; adverse events, Outcome 1 Fever.

Review: Vaccines for preventing typhoid fever

Comparison: 3 Ty21a vaccine vs control; adverse events

Outcome: 1 Fever



(*Continued . . .*)

(. . . *Continued*)

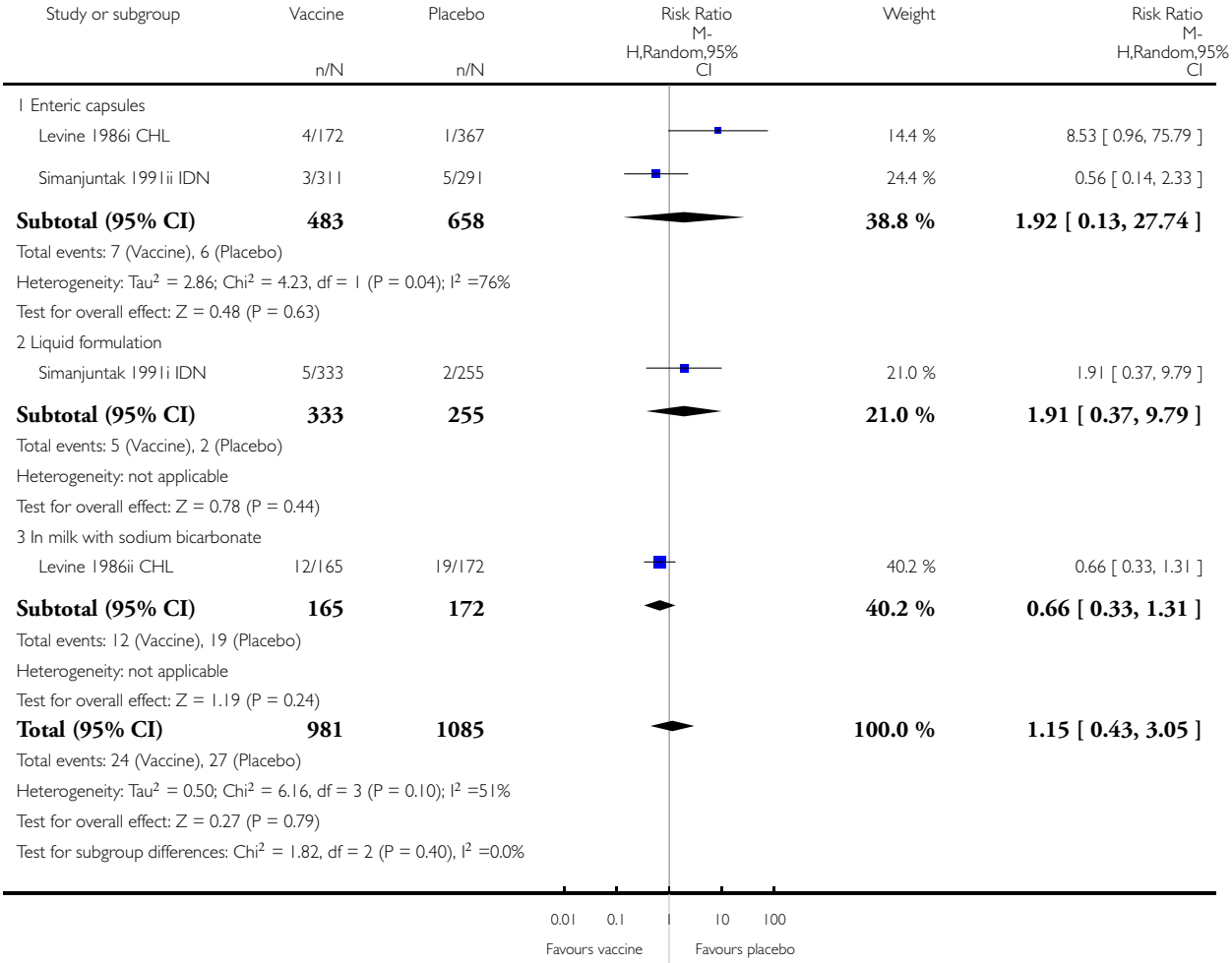
Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 0.76 (P = 0.45)					
3 In milk with sodium bicarbonate					
Levine 1986ii CHL	2/165	1/172		6.1 %	2.08 [0.19, 22.77]
Subtotal (95% CI)	**165**	**172**		**6.1 %**	**2.08 [0.19, 22.77]**
Total events: 2 (Vaccine), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.60 (P = 0.55)					
Total (95% CI)	**981**	**1085**		**100.0 %**	**1.84 [1.02, 3.31]**
Total events: 34 (Vaccine), 16 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.26$, df = 3 (P = 0.74); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.02 (P = 0.044)					
Test for subgroup differences: $Chi^2 = 1.22$, df = 2 (P = 0.54), $I^2 = 0.0\%$					

Analysis 3.2. Comparison 3 Ty21a vaccine vs control; adverse events, Outcome 2 Vomiting.

Review: Vaccines for preventing typhoid fever

Comparison: 3 Ty21a vaccine vs control; adverse events

Outcome: 2 Vomiting

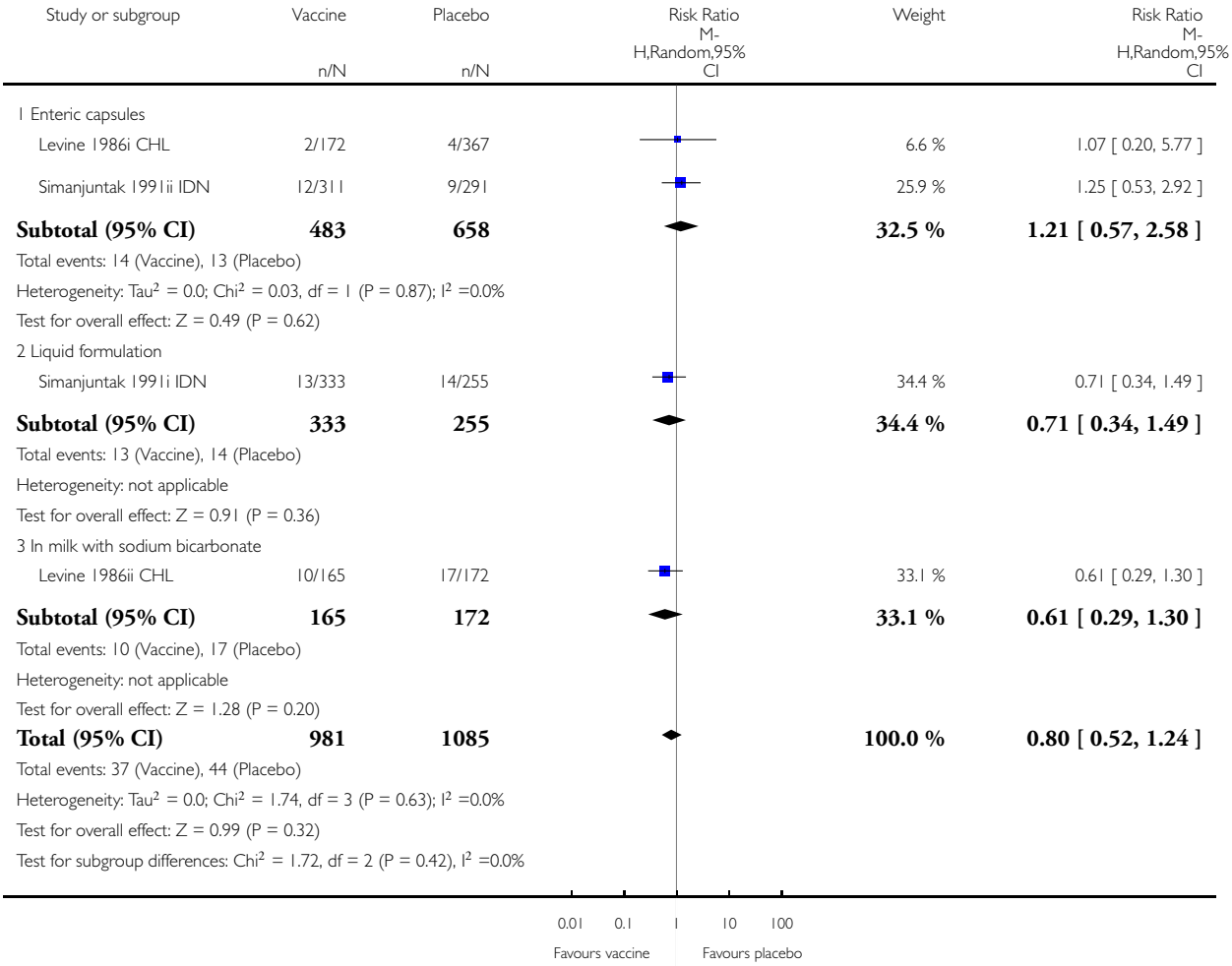


Analysis 3.3. Comparison 3 Ty21a vaccine vs control; adverse events, Outcome 3 Diarrhoea.

Review: Vaccines for preventing typhoid fever

Comparison: 3 Ty21a vaccine vs control; adverse events

Outcome: 3 Diarrhoea

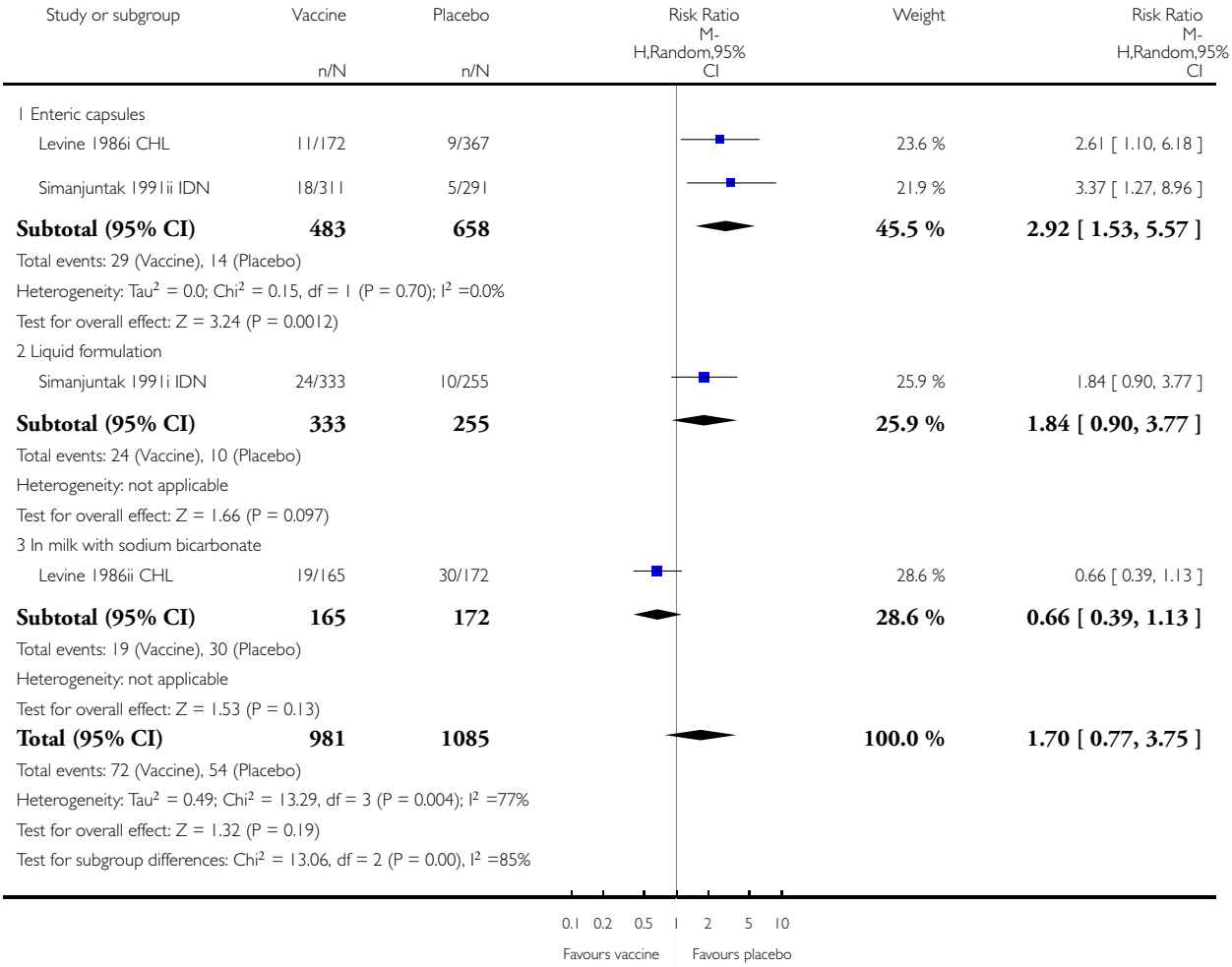


Analysis 3.4. Comparison 3 Ty21a vaccine vs control; adverse events, Outcome 4 Nausea or abdominal pain.

Review: Vaccines for preventing typhoid fever

Comparison: 3 Ty21a vaccine vs control; adverse events

Outcome: 4 Nausea or abdominal pain

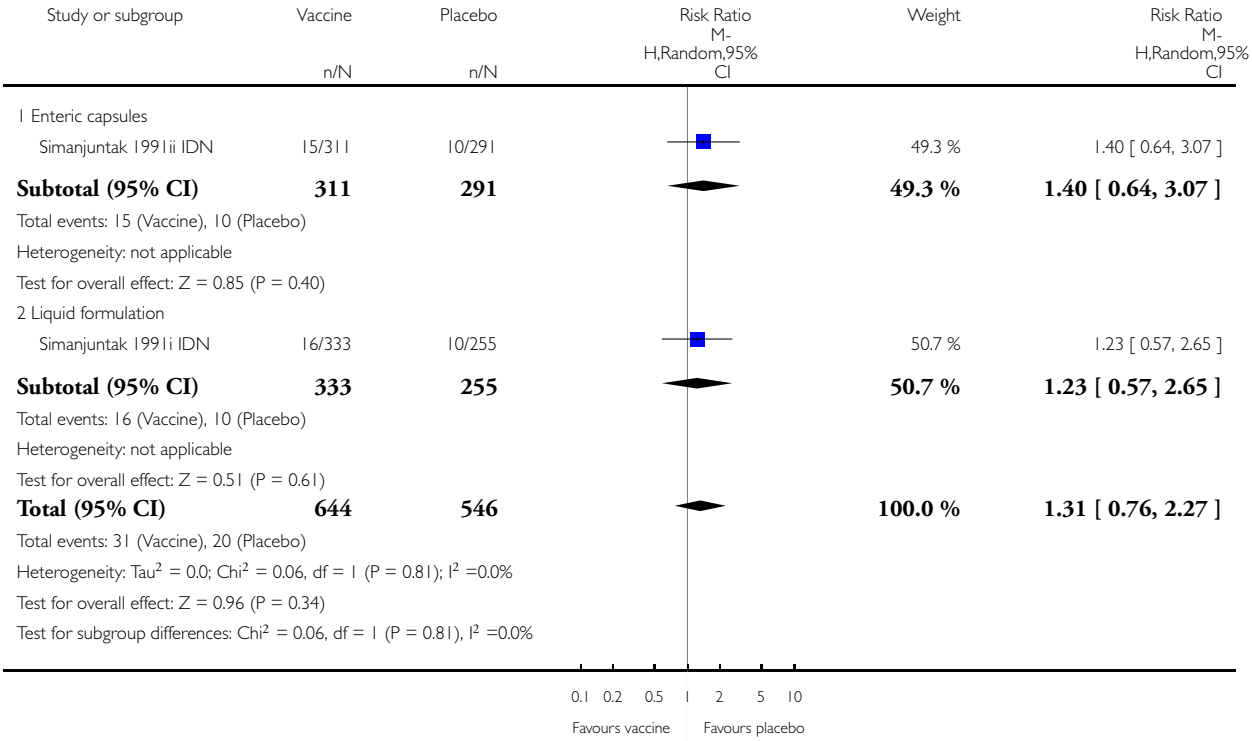


Analysis 3.5. Comparison 3 Ty21a vaccine vs control; adverse events, Outcome 5 Headache.

Review: Vaccines for preventing typhoid fever

Comparison: 3 Ty21a vaccine vs control; adverse events

Outcome: 5 Headache

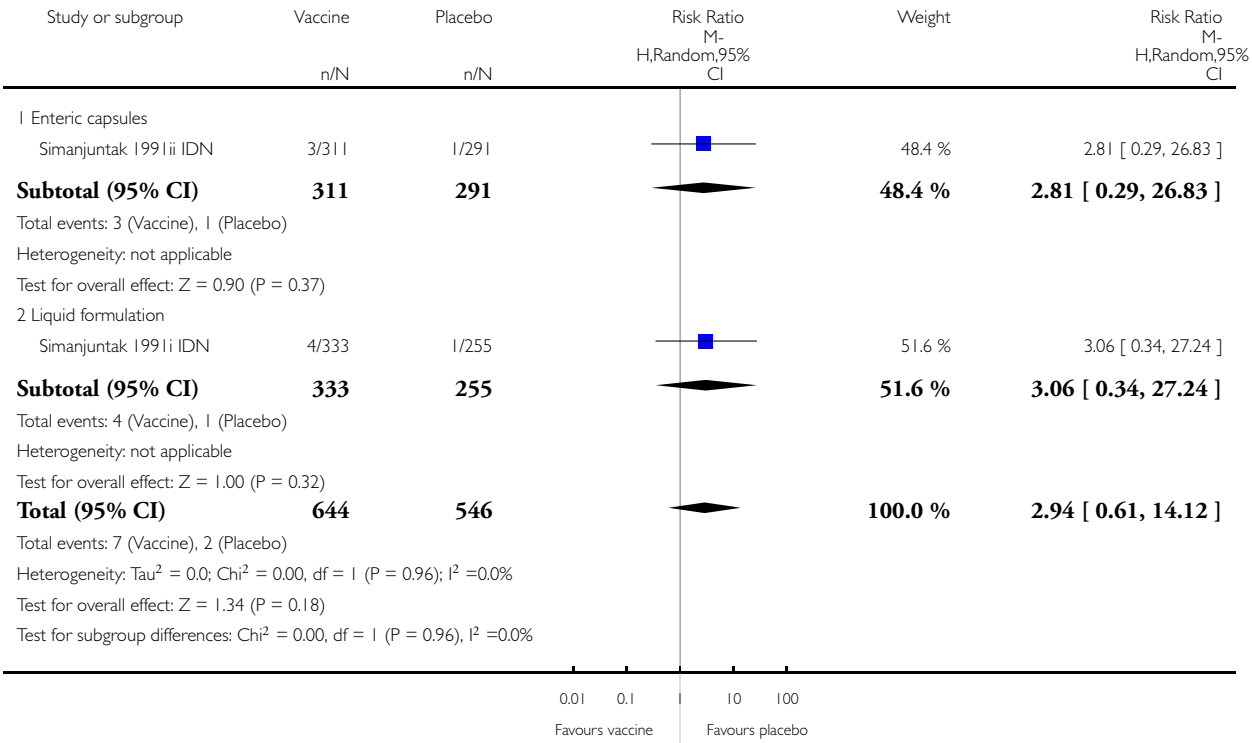


Analysis 3.6. Comparison 3 Ty21a vaccine vs control; adverse events, Outcome 6 Rash.

Review: Vaccines for preventing typhoid fever

Comparison: 3 Ty21a vaccine vs control; adverse events

Outcome: 6 Rash

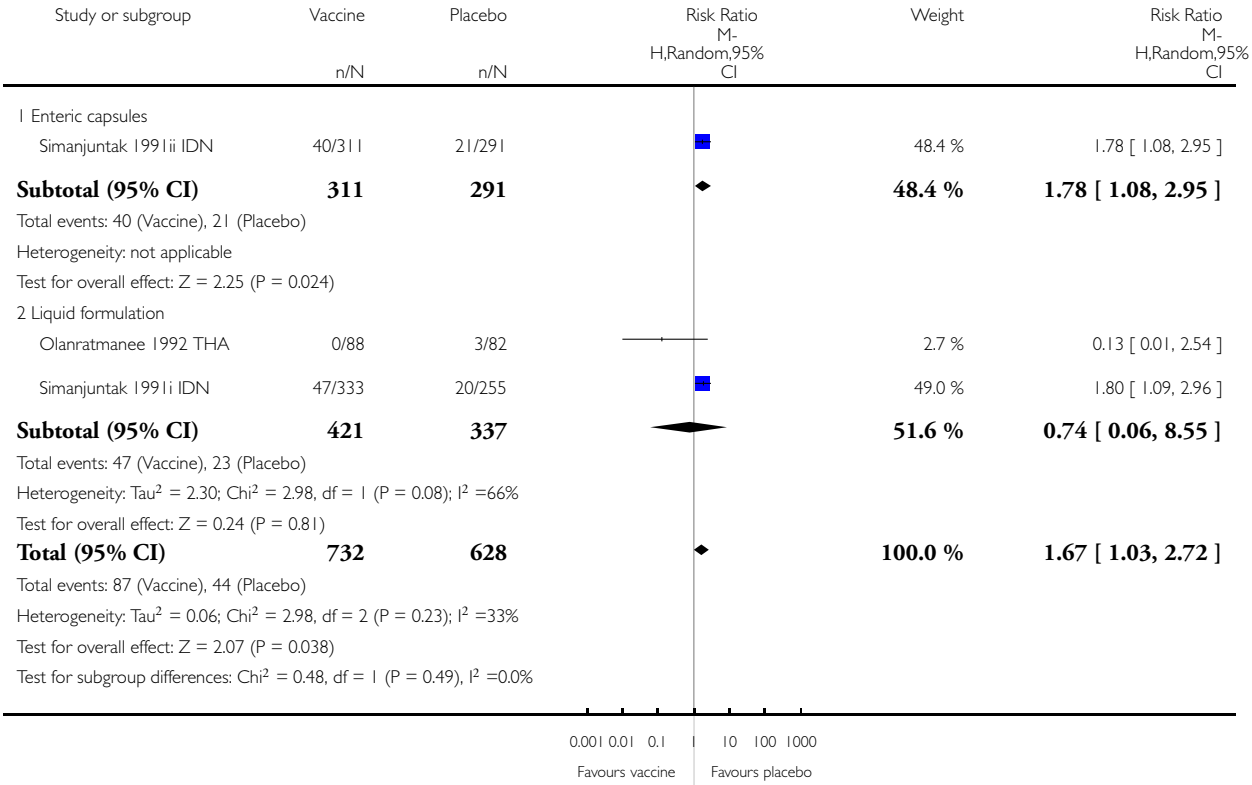


Analysis 3.7. Comparison 3 Ty21a vaccine vs control; adverse events, Outcome 7 Any mild adverse event.

Review: Vaccines for preventing typhoid fever

Comparison: 3 Ty21a vaccine vs control; adverse events

Outcome: 7 Any mild adverse event



Analysis 3.8. Comparison 3 Ty21a vaccine vs control; adverse events, Outcome 8 Serious adverse events.

Review: Vaccines for preventing typhoid fever

Comparison: 3 Ty21a vaccine vs control; adverse events

Outcome: 8 Serious adverse events

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Enteric capsules					
Levine 1986i CHL	0/172	0/367			Not estimable
Simanjuntak 1991ii IDN	0/311	0/291			Not estimable
Subtotal (95% CI)	**483**	**658**			**Not estimable**
Total events: 0 (Vaccine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Liquid formulation					
Olanratmanee 1992 THA	0/88	0/82			Not estimable
Simanjuntak 1991i IDN	0/333	0/255			Not estimable
Subtotal (95% CI)	**421**	**337**			**Not estimable**
Total events: 0 (Vaccine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 In milk with sodium bicarbonate					
Levine 1986ii CHL	0/165	0/172			Not estimable
Subtotal (95% CI)	**165**	**172**			**Not estimable**
Total events: 0 (Vaccine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**1069**	**1167**			**Not estimable**
Total events: 0 (Vaccine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%					

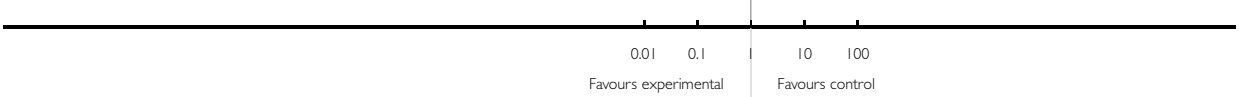
Analysis 4.1. Comparison 4 Vi polysaccharide vaccine (one dose) vs control; efficacy, Outcome 1 Incidence of typhoid fever.

Review: Vaccines for preventing typhoid fever

Comparison: 4 Vi polysaccharide vaccine (one dose) vs control; efficacy

Outcome: 1 Incidence of typhoid fever

Study or subgroup	Vaccine N	Control N	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Year 1						
Acharya 1987 NPL	3457	3450	-1.273 (0.1174)		41.7 %	0.28 [0.22, 0.35]
Klugman 1987 ZAF	5692	5692	-0.942 (0.1684)		24.8 %	0.39 [0.28, 0.54]
Wang 1997a CHN	41118	40388	-1.238 (0.1378)		33.5 %	0.29 [0.22, 0.38]
Subtotal (95% CI)	**50267**	**49530**			**100.0 %**	**0.31 [0.26, 0.37]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.79$, df = 2 (P = 0.25); $I^2 = 28\%$						
Test for overall effect: Z = 12.47 (P < 0.00001)						
2 Year 2						
Khan 2012 PAK	13238	13993	-0.411 (0.2273)		19.3 %	0.66 [0.42, 1.04]
Klugman 1987 ZAF	5692	5692	-0.734 (0.1811)		23.2 %	0.48 [0.34, 0.68]
Sur 2009 IND	12206	12877	-1.079 (0.0921)		31.4 %	0.34 [0.28, 0.41]
Yang 2001 CHN	65287	65984	-1.171 (0.1505)		26.1 %	0.31 [0.23, 0.42]
Subtotal (95% CI)	**96423**	**98546**			**100.0 %**	**0.41 [0.31, 0.55]**
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 10.87$, df = 3 (P = 0.01); $I^2 = 72\%$						
Test for overall effect: Z = 6.09 (P < 0.00001)						
3 Year 3						
Klugman 1987 ZAF	5692	5692	-0.693 (0.227)		100.0 %	0.50 [0.32, 0.78]
Subtotal (95% CI)	**5692**	**5692**			**100.0 %**	**0.50 [0.32, 0.78]**
Heterogeneity: not applicable						
Test for overall effect: Z = 3.05 (P = 0.0023)						
Test for subgroup differences: $Chi^2 = 5.47$, df = 2 (P = 0.07), $I^2 = 63\%$						



Analysis 4.2. Comparison 4 Vi polysaccharide vaccine (one dose) vs control; efficacy, Outcome 2 Cumulative incidence of typhoid fever at 2.5 to 3 years.

Review: Vaccines for preventing typhoid fever

Comparison: 4 Vi polysaccharide vaccine (one dose) vs control; efficacy

Outcome: 2 Cumulative incidence of typhoid fever at 2.5 to 3 years

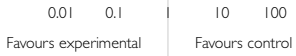
Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Klugman 1987 ZAF	30/5692	66/5692		100.0 %	0.45 [0.30, 0.70]
Total (95% CI)	**5692**	**5692**		**100.0 %**	**0.45 [0.30, 0.70]**

Total events: 30 (Vaccine), 66 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 3.59 (P = 0.00033)

Test for subgroup differences: Not applicable



Analysis 5.1. Comparison 5 Vi polysaccharide vaccine vs control; adverse events, Outcome 1 Fever.

Review: Vaccines for preventing typhoid fever

Comparison: 5 Vi polysaccharide vaccine vs control; adverse events

Outcome: 1 Fever

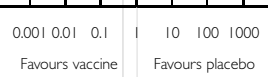
Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Keitel 1994 USA	3/237	1/86		0.4 %	1.09 [0.11, 10.33]
Wang 1997a CHN	4/384	0/393		0.3 %	9.21 [0.50, 170.49]
Yang 2001 CHN	325/65287	336/65984		95.9 %	0.98 [0.84, 1.14]
Zhou 2007 CHN	11/334	12/333		3.4 %	0.91 [0.41, 2.04]
Total (95% CI)	**66242**	**66796**		**100.0 %**	**0.98 [0.85, 1.14]**

Total events: 343 (Vaccine), 349 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.31$, df = 3 (P = 0.51); $I^2 = 0.0\%$

Test for overall effect: Z = 0.25 (P = 0.81)

Test for subgroup differences: Not applicable

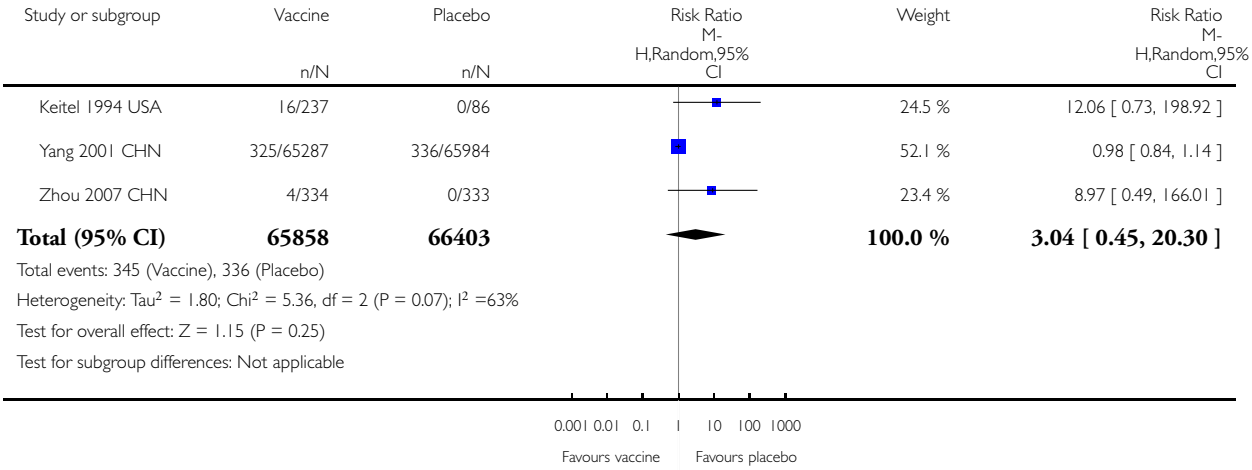


Analysis 5.2. Comparison 5 Vi polysaccharide vaccine vs control; adverse events, Outcome 2 Erythema.

Review: Vaccines for preventing typhoid fever

Comparison: 5 Vi polysaccharide vaccine vs control; adverse events

Outcome: 2 Erythema



Analysis 5.3. Comparison 5 Vi polysaccharide vaccine vs control; adverse events, Outcome 3 Swelling at injection site.

Review: Vaccines for preventing typhoid fever

Comparison: 5 Vi polysaccharide vaccine vs control; adverse events

Outcome: 3 Swelling at injection site

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Keitel 1994 USA	16/237	0/86		38.1 %	12.06 [0.73, 198.92]
Wang 1997a CHN	2/384	0/393		32.6 %	5.12 [0.25, 106.24]
Zhou 2007 CHN	1/334	0/333		29.3 %	2.99 [0.12, 73.16]
Total (95% CI)	**955**	**812**		**100.0 %**	**6.06 [1.07, 34.22]**

Total events: 19 (Vaccine), 0 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.49$, df = 2 (P = 0.78); $I^2 = 0.0\%$

Test for overall effect: Z = 2.04 (P = 0.041)

Test for subgroup differences: Not applicable

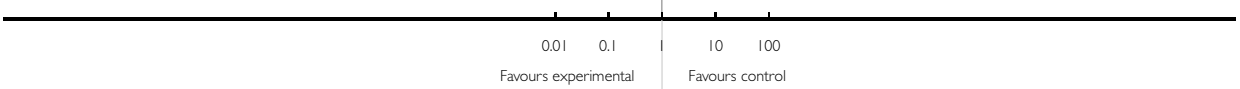
Analysis 5.4. Comparison 5 Vi polysaccharide vaccine vs control; adverse events, Outcome 4 Pain at injection site.

Review: Vaccines for preventing typhoid fever

Comparison: 5 Vi polysaccharide vaccine vs control; adverse events

Outcome: 4 Pain at injection site

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Zhou 2007 CHN	56/334	7/333		100.0 %	7.98 [3.69, 17.24]
Total (95% CI)	**334**	**333**		**100.0 %**	**7.98 [3.69, 17.24]**
Total events: 56 (Vaccine), 7 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.28 (P < 0.00001)					
Test for subgroup differences: Not applicable					



Analysis 5.5. Comparison 5 Vi polysaccharide vaccine vs control; adverse events, Outcome 5 Serious adverse events.

Review: Vaccines for preventing typhoid fever

Comparison: 5 Vi polysaccharide vaccine vs control; adverse events

Outcome: 5 Serious adverse events

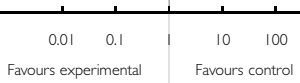
Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Keitel 1994 USA	0/237	0/86			Not estimable
Wang 1997a CHN	0/384	0/393			Not estimable
Yang 2001 CHN	0/65287	0/65984			Not estimable
Zhou 2007 CHN	0/334	0/333			Not estimable
Total (95% CI)	**66242**	**66796**			**Not estimable**

Total events: 0 (Vaccine), 0 (Placebo)

Heterogeneity: not applicable

Test for overall effect: not applicable

Test for subgroup differences: Not applicable

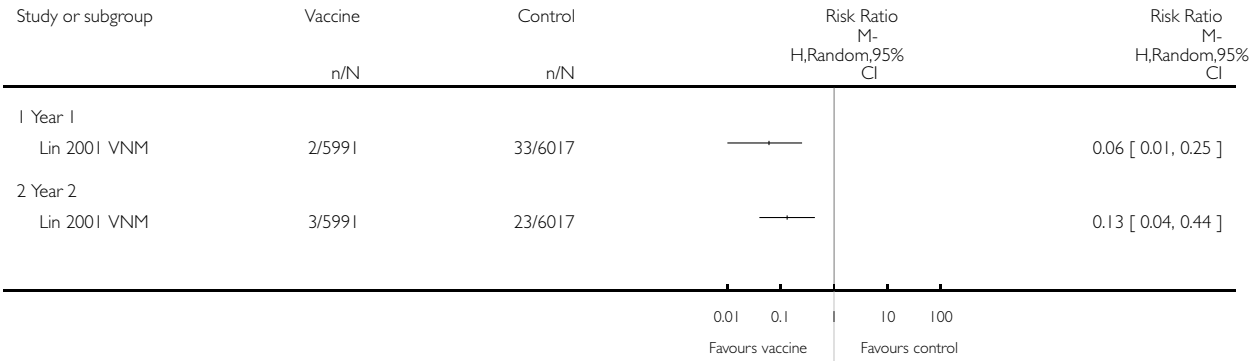


Analysis 6.1. Comparison 6 Vi-rEPA vaccine (two doses) vs control; efficacy, Outcome 1 Incidence of typhoid fever.

Review: Vaccines for preventing typhoid fever

Comparison: 6 Vi-rEPA vaccine (two doses) vs control; efficacy

Outcome: 1 Incidence of typhoid fever

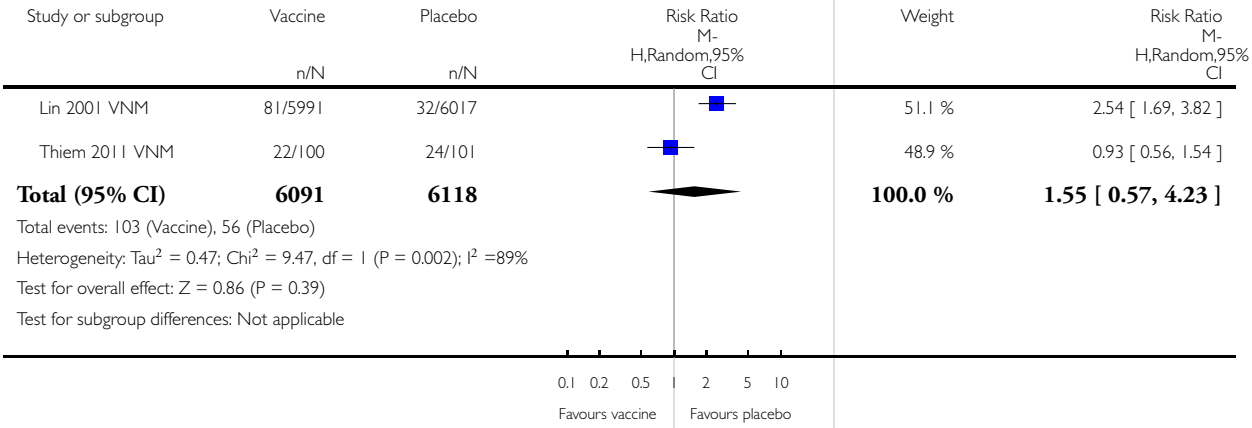


Analysis 7.1. Comparison 7 Vi-rEPA vaccine vs control; adverse events, Outcome 1 Fever after Vi-rEPA (dose1).

Review: Vaccines for preventing typhoid fever

Comparison: 7 Vi-rEPA vaccine vs control; adverse events

Outcome: 1 Fever after Vi-rEPA (dose1)

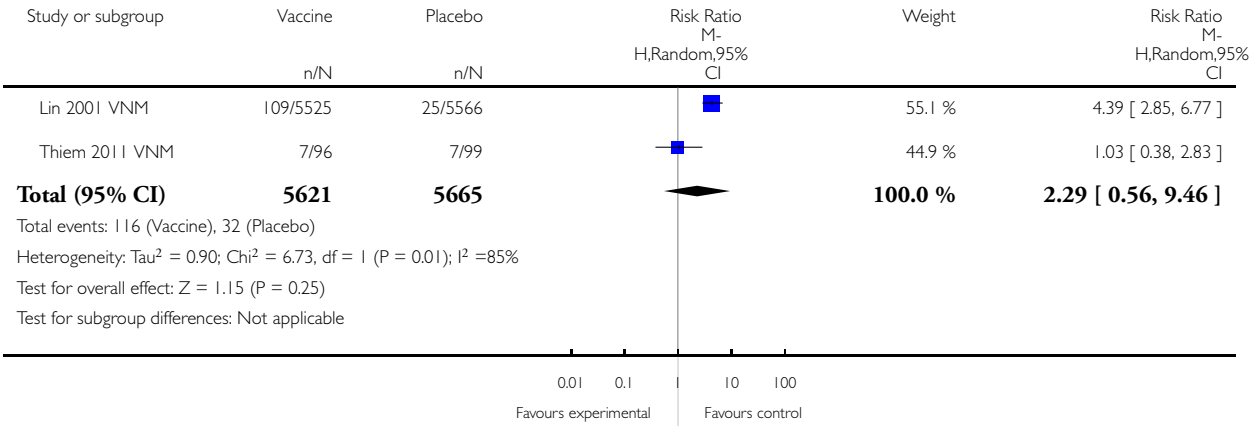


Analysis 7.2. Comparison 7 Vi-rEPA vaccine vs control; adverse events, Outcome 2 Fever after Vi-rEPA (dose 2).

Review: Vaccines for preventing typhoid fever

Comparison: 7 Vi-rEPA vaccine vs control; adverse events

Outcome: 2 Fever after Vi-rEPA (dose 2)



Analysis 7.3. Comparison 7 Vi-rEPA vaccine vs control; adverse events, Outcome 3 Erythema after Vi-rEPA (dose 1).

Review: Vaccines for preventing typhoid fever

Comparison: 7 Vi-rEPA vaccine vs control; adverse events

Outcome: 3 Erythema after Vi-rEPA (dose 1)

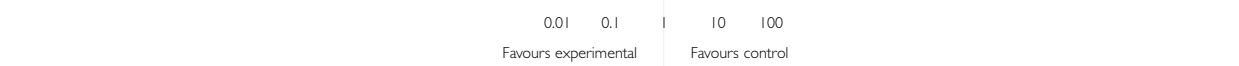
Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lin 2001 VNM	0/5991	0/6017			Not estimable
Thiem 2011 VNM	3/100	1/101		100.0 %	3.03 [0.32, 28.64]
Total (95% CI)	**6091**	**6118**		**100.0 %**	**3.03 [0.32, 28.64]**

Total events: 3 (Vaccine), 1 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.97 (P = 0.33)

Test for subgroup differences: Not applicable

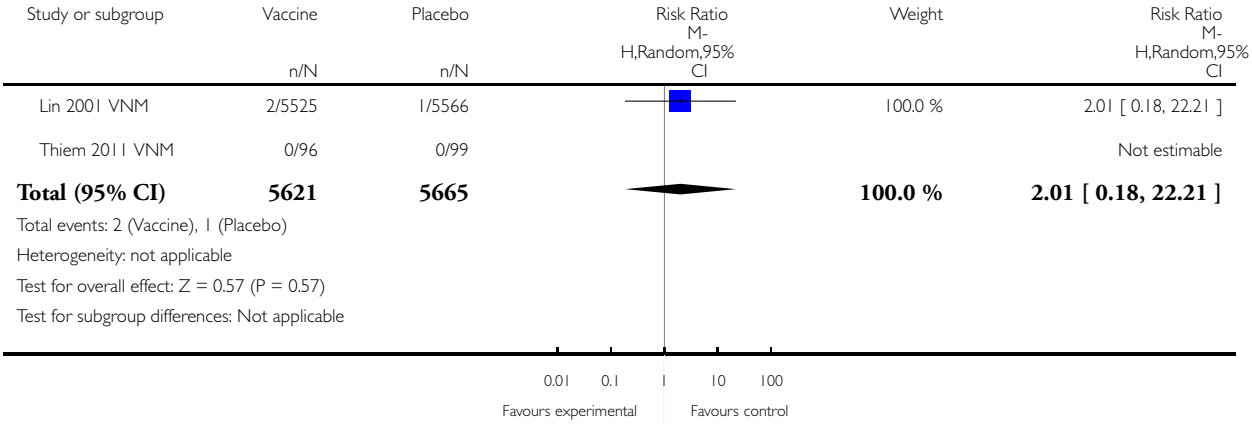


Analysis 7.4. Comparison 7 Vi-rEPA vaccine vs control; adverse events, Outcome 4 Erythema after Vi-rEPA (dose 2).

Review: Vaccines for preventing typhoid fever

Comparison: 7 Vi-rEPA vaccine vs control; adverse events

Outcome: 4 Erythema after Vi-rEPA (dose 2)



Analysis 7.5. Comparison 7 Vi-rEPA vaccine vs control; adverse events, Outcome 5 Swelling at injection site after Vi-rEPA (dose 1).

Review: Vaccines for preventing typhoid fever

Comparison: 7 Vi-rEPA vaccine vs control; adverse events

Outcome: 5 Swelling at injection site after Vi-rEPA (dose 1)

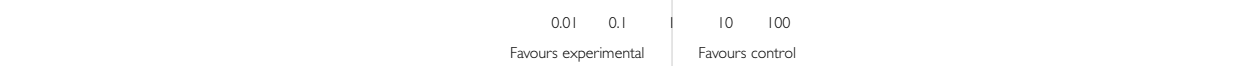
Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lin 2001 VNM	0/5991	0/6017			Not estimable
Thiem 2011 VNM	2/100	2/101		100.0 %	1.01 [0.15, 7.03]
Total (95% CI)	**6091**	**6118**		**100.0 %**	**1.01 [0.15, 7.03]**

Total events: 2 (Vaccine), 2 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.01 (P = 0.99)

Test for subgroup differences: Not applicable



Analysis 7.6. Comparison 7 Vi-rEPA vaccine vs control; adverse events, Outcome 6 Swelling at injection site after Vi-rEPA (dose 2).

Review: Vaccines for preventing typhoid fever

Comparison: 7 Vi-rEPA vaccine vs control; adverse events

Outcome: 6 Swelling at injection site after Vi-rEPA (dose 2)

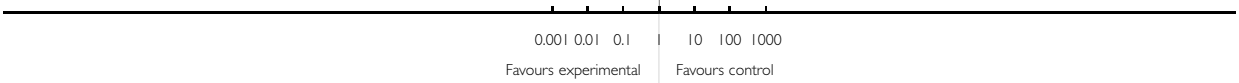
Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lin 2001 VNM	20/5525	1/5566		54.9 %	20.15 [2.71, 150.08]
Thiem 2011 VNM	1/96	1/99		45.1 %	1.03 [0.07, 16.25]
Total (95% CI)	**5621**	**5665**		**100.0 %**	**5.27 [0.26, 106.74]**

Total events: 21 (Vaccine), 2 (Placebo)

Heterogeneity: $Tau^2 = 3.24$; $Chi^2 = 3.14$, df = 1 (P = 0.08); I^2 =68%

Test for overall effect: Z = 1.08 (P = 0.28)

Test for subgroup differences: Not applicable



Analysis 7.7. Comparison 7 Vi-rEPA vaccine vs control; adverse events, Outcome 7 Serious adverse events.

Review: Vaccines for preventing typhoid fever

Comparison: 7 Vi-rEPA vaccine vs control; adverse events

Outcome: 7 Serious adverse events

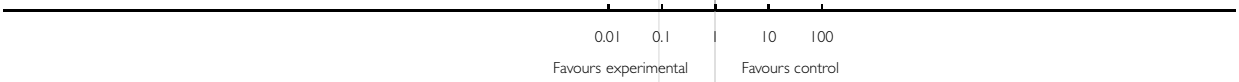
Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lin 2001 VNM	0/5991	0/6017			Not estimable
Thiem 2011 VNM	0/100	0/101			Not estimable
Total (95% CI)	**6091**	**6118**			**Not estimable**

Total events: 0 (Vaccine), 0 (Placebo)

Heterogeneity: not applicable

Test for overall effect: not applicable

Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Efficacy of Ty21a vaccine: unadjusted cluster-trial results[a]

Trial	Year	Preparation	No. doses	RR (95% CI)[b]	Efficacy
Black 1990ii CHL	1	Enteric capsules	1	0.75 (0.51 to 1.09)	25% (-9% to 49%)
	2			0.65 (0.39 to 1.08)	35% (-8% to 61%)
	3			0.99 (0.52 to 1.87)	1% (-87% to 48%)
	4			1.06 (0.63 to 1.77)	-6% (-77% to 37%)
	5			1.10 (0.57 to 2.13)	-10% (-113% to 43%)
Black 1990ii CHL	1	Enteric capsules	2	0.48 (0.31 to 0.74)	52% (24% to 69%)
	2			0.29 (0.15 to 0.56)	71% (44% to 85%)
	3			0.78 (0.40 to 1.54)	22% (-54% to 60%)
	4			0.81 (0.47 to 1.41)	19% (-41% to 53%)
	5			0.93 (0.47 to 1.84)	7% (-84% to 53%)
Levine 1987ii CHL	1	Enteric capsules	3	0.29 (0.12 to 0.67)	71% (33% to 88%)
	2			0.40 (0.17 to 0.90)	60% (10% to 83%)
	3			0.33 (0.15 to 0.73)	67% (27% to 85%)
	4			0.22 (0.07 to 0.65)	78% (35% to 93%)
	5			0.53 (0.22 to 1.24)	47% (124% to 78%)
Wahdan 1980a EGY	1	Liquid formulation	3	0.06 (0.00 to 1.13)	94% (-13% to 100%)
	2			0.06 (0.00 to 0.98)	94% (2% to 100%)
	3			0.14 (0.02 to 1.12)	86% (-12% to 98%)
Levine 1987i CHL	Cumulative incidence 2.5 to 3 years	Enteric capsules	3	0.41 (0.28 to 0.91)	59% (9% to 72%)
Levine 1987ii CHL	Cumulative incidence 2.5 to 3 years	Enteric capsules	3	0.33 (0.18 to 0.63)	67% (82% to 37%)

Table 1. Efficacy of Ty21a vaccine: unadjusted cluster-trial results[a] *(Continued)*

Levine 1990ii CHL	Cumulative incidence 2.5 to 3 years	Enteric capsules	3	0.63 (0.35 to 1.12)	37% (-12% to 65%)
Wahdan 1980a EGY	Cumulative incidence 2.5 to 3 years	Liquid formulation	3	0.04 (0.01 to 0.33)	96% (67% to 99%)
Levine 1990i CHL	Cumulative incidence 2.5 to 3 years	Liquid formulation	3	0.24 (0.13 to 0.47)	76% (53% to 87%)
Levine 1987iii CHL	Cumulative incidence 2.5 to 3 years	Gelatin capsules	3	0.69 (0.39 to 1.20)	31% (-20% to 61%)
Levine 1987iv CHL	Cumulative incidence 2.5 to 3 years	Gelatin capsules	3	0.81 (0.47 to 1.39)	19% (-39% to 53%)
Levine 1990i CHL	Cumulative incidence 2.5 to 3 years	Liquid preparation vs enteric capsules	3	0.35 (0.21, 0.56)	65% (44% to 79%)

[a] Failure to adjust for the potential effect of a cluster design is likely to lead to overestimation of the treatment effect.
[b] Risk ratio with 95% confidence intervals.

Table 2. Cumulative efficacy of Ty21a vaccine at > 3 years: vaccine vs control

Trial	Vaccine/ formulation	Length of follow-up	Vaccine: incidence	Control: incidence	Efficacy (95% CI)[a]
Black 1990i CHL	Ty21a: enteric capsules, 2 doses	5 years	95/27,620	164/27,305	43% (26% to 55%)
Black 1990ii CHL	Ty21a: enteric capsules, 1 dose	5 years	200/27,618	164/27,305	-21% (-48% to 2%)
Levine 1987ii CHL	Ty21a: enteric capsules, 3 doses	7 years	50/22,170	131/21,906	62% (48% to 73%)
Levine 1990i CHL	Ty21a: liquid formulation, 3 doses	5 years	34/36,623	43/10,302	79% (65% to 87%)

[a] Confidence intervals.

Table 3. Efficacy of Vi polysaccharide vaccine: unadjusted cluster-trial results by age[a]

Trial	Year	Age at baseline	Typhoid episodes: Vi vaccine	Typhoid episodes: control	Efficacy (95% CI): not adjusted
Khan 2012 PAK	Cumulative incidence at 2 years	2 to < 5 years	16/3154	13/3324	-30% (-183% to 40%)
		5 to 16 years	14/10,084	36/10,669	59% (9% to 81%)
Sur 2009 IND	Cumulative incidence at 2 years	2 to < 5 years	5/1097	27/1095	82% (58% to 92%)
		5 to < 15 years	21/4282	54/4584	59% (18% to 79%
		≥ 15 years	8/13,490	15/13,125	48% (-44% to 81%)

[a] Failure to adjust for the potential effect of a cluster design is likely to lead to overestimation of the treatment effect.

Table 4. Adverse events following ViPS vaccine delivery: unadjusted results from cluster-randomized trials[a]

Trial	Adverse event	Number of events: ViPS vaccine	Number of events: control group	Statistical significance
Khan 2012 PAK	Fever	5/125	1/117	Not significant
Khan 2012 PAK	Pain at injection site	4/125	1/117	Not significant
Sur 2009 IND	Erythema	24/110	5/92	P < 0.001
Sur 2009 IND	Pain at injection site	61/110	17/92	P < 0.001
Sur 2009 IND	Fever	8/110	1/92	P = 0.04

[a] Failure to adjust for the potential effect of a cluster design is likely to lead to overestimation of the treatment effect.

APPENDICES

Appendix 1. Search methods: detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	typhoid fever	typhoid*	typhoid*	typhoid$	typhoid fever
2	vaccine*	typhoid-fever*	typhoid fever	TYPHOID FEVER	vaccine*
3	1 and 2	salmonell*	TYPHOID FEVER	typhoid fever	1 and 2
4	-	1 or 2 or 3	salmonell*	salmonell$	typhoid vaccine
5	-	vaccine*	1 or 2 or 3 or 4	1 or 2 or 3 or 4	paratyphoid vaccine
6	-	4 and 5	vaccine*	vaccine$	3 or 4 or 5
7	-	-	5 and 6	5 and 6	-
8	-	-	TYPHOID-PARATYPHOID VACCINES	TYPHOID VACCINE	-
9	-	-	TY21 TYPHOID VACCINE	TYPHOID-PARATYPHOID VACCINE	-
10	-	-	VI POLYSACCHARIDE VACCINE, TYPHOID	7 or 8 or 9	-
11	-	-	7 or 8 or 9 or 10	Limit 10 to human	-
12	-	-	Limit 11 to human	-	-

[a] Cochrane Infectious Diseases Group Specialized Register.
[b] Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2006); upper case: MeSH or EMTREE heading; lower case: free text term.

WHAT'S NEW

Last assessed as up-to-date: 17 June 2013.

Date	Event	Description
17 June 2013	New search has been performed	This is an update of the review prepared by Fraser et al (Fraser 2007a). This review update includes four new trials, three evaluating the Vi polysaccharide vaccine (two reporting on efficacy and adverse events, one reporting

(*Continued*)

		on adverse events only) and one evaluating the Vi-rEPA vaccine (reporting adverse events)
17 June 2013	New citation required but conclusions have not changed	Four new trials added.

HISTORY

Protocol first published: Issue 4, 1998

Review first published: Issue 4, 1998

Date	Event	Description
22 August 2008	Amended	Converted to new review format with minor editing.
26 April 2007	New citation required and conclusions have changed	2007, Issue 3: This review is an update of the original version prepared by EA Engels and J Lau (Engels 1998a). This review evaluates the evidence available for a new vaccine (Vi-rEPA) and includes 3 new efficacy trials that were not included in Engels 1998a (1 evaluating the Vi-rEPA and 2 evaluating the Vi polysaccharide vaccine). It would also have included head-on comparisons of the different types of vaccines (not included in Engels 1998a) had these direct comparisons been conducted. Since Engels 1998a was published, killed whole-cell vaccines are no longer in use and therefore are not included in this review

CONTRIBUTIONS OF AUTHORS

E Anwar: data collection and management, analysis, interpretation of results and review writing. E Goldberg: data collection. M Paul: data extraction and review writing. A Fraser: review writing, CJ Acosta: review writing. L Leibovici: review writing.

DECLARATIONS OF INTEREST

For all review authors, none known.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.
- University of Liverpool, UK.

External sources

- Department for International Development (DFID), UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Randomized Controlled Trials as Topic; Salmonella typhi [immunology]; Typhoid Fever [immunology; *prevention & control]; Typhoid-Paratyphoid Vaccines [administration & dosage; * therapeutic use]; Vaccines, Attenuated [administration & dosage; therapeutic use]

MeSH check words

Adolescent; Adult; Child; Child, Preschool; Humans