Cochrane Library

**Cochrane** Database of Systematic Reviews

# Vaccines for preventing typhoid fever (Review)

Milligan R, Paul M, Richardson M, Neuberger A

Milligan R, Paul M, Richardson M, Neuberger A.
Vaccines for preventing typhoid fever.
*Cochrane Database of Systematic Reviews* 2018, Issue 5. Art. No.: CD001261.
DOI: 10.1002/14651858.CD001261.pub4.

**www.cochranelibrary.com**

# TABLE OF CONTENTS

[Intervention Review]

# Vaccines for preventing typhoid fever

Rachael Milligan[1], Mical Paul[2], Marty Richardson[1], Ami Neuberger[3]

[1]Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, UK. [2]Division of Infectious Diseases, Rambam Health Care Campus, Haifa, Israel. [3]Division of Infectious Diseases, Rambam Health Care Campus and The Ruth and Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Tel Aviv, Israel

**Contact address:** Rachael Milligan, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, L3 5QA, UK. Rachael.Milligan@lstmed.ac.uk.

**Editorial group:** Cochrane Infectious Diseases Group.
**Publication status and date:** Unchanged, published in Issue 5, 2018.

**Citation:** Milligan R, Paul M, Richardson M, Neuberger A. Vaccines for preventing typhoid fever. *Cochrane Database of Systematic Reviews* 2018, Issue 5. Art. No.: CD001261. DOI: 10.1002/14651858.CD001261.pub4.



## 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 widely available, Ty21a (oral) and Vi polysaccharide (parenteral). Newer typhoid conjugate vaccines are at varying stages of development and use. The World Health Organization has recently recommended a Vi tetanus toxoid (Vi-TT) conjugate vaccine, Typbar-TCV, as the preferred vaccine for all ages.

### Objectives

To assess the effects of vaccines for preventing typhoid fever.

### Search methods

In February 2018, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL, MEDLINE, Embase, LILACS, and *m*RCT. We also searched 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) in adults and children. Human challenge studies were not eligible.

### Data collection and analysis

Two review authors independently applied inclusion criteria and extracted data, and assessed the certainty of the evidence using the GRADE approach. 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 enterica* serovar 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 contributed to the quantitative analysis in this review: 13 evaluated efficacy (Ty21a: 5 trials; Vi polysaccharide: 6 trials; Vi-rEPA: 1 trial; Vi-TT: 1 trial), and 9 reported on adverse events. All trials but one took place in typhoid-endemic countries. There was no information on vaccination in adults aged over 55 years of age, pregnant women, or travellers. Only one trial included data on children under two years of age.

**Ty21a vaccine (oral vaccine, three doses)**

A three-dose schedule of Ty21a vaccine probably prevents around half of typhoid cases during the first three years after vaccination (cumulative efficacy 2.5 to 3 years: 50%, 95% CI 35% to 61%, 4 trials, 235,239 participants, moderate-certainty evidence). These data include patients aged 3 to 44 years.

Compared with placebo, this vaccine probably does not cause more vomiting, diarrhoea, nausea or abdominal pain (2 trials, 2066 participants; moderate-certainty evidence), headache, or rash (1 trial, 1190 participants; moderate-certainty evidence); however, fever (2 trials, 2066 participants; moderate-certainty evidence) is probably more common following vaccination.

**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%; 3 trials, 99,979 participants; high-certainty 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-certainty evidence). These data included participants aged 2 to 55 years of age.The three-year cumulative efficacy of the vaccine may be around 55% (95% CI 30% to 70%; 11,384 participants, 1 trial; low-certainty evidence). These data came from a single trial conducted in South Africa in the 1980s in participants aged 5 to 15 years.

Compared with placebo, this vaccine probably did not increase the incidence of fever (3 trials, 132,261 participants; moderate-certainty evidence) or erythema (3 trials, 132,261 participants; low-certainty evidence); however, swelling (3 trials, 1767 participants; moderate-certainty evidence) and pain at the injection site (1 trial, 667 participants; moderate-certainty 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%, 1 trial, 12,008 participants; moderate-certainty evidence). These data came from a single trial with children two to five years of age conducted in Vietnam.

Compared with placebo, both the first and the second dose of this vaccine increased the risk of fever (1 trial, 12,008 and 11,091 participants, low-certainty evidence) and the second dose increase the incidence of swelling at the injection site (one trial, 11,091 participants, moderate-certainty evidence).

**Vi-TT vaccine (two doses)**

We are uncertain of the efficacy of administration of two doses of Vi-TT (PedaTyph) in typhoid cases in children during the first year after vaccination (year 1: 94%, 95% CI −1% to 100%, 1 trial, 1625 participants; very low-certainty evidence). These data come from a single cluster-randomized trial in children aged six months to 12 years and conducted in India. For single dose Vi-TT (Typbar-TCV), we found no efficacy trials evaluating the vaccine with natural exposure.

There were no reported serious adverse effects in RCTs of any of the vaccines studied.

**Authors' conclusions**

The licensed Ty21a and Vi polysaccharide vaccines are efficacious in adults and children older than two years in endemic countries. The Vi-rEPA vaccine is just as efficacious, although data is only available for children. The new Vi-TT vaccine (PedaTyph) requires further evaluation to determine if it provides protection against typhoid fever. At the time of writing, there were only efficacy data from a human challenge setting in adults on the Vi-TT vaccine (Tybar), which clearly justify the ongoing field trials to evaluate vaccine efficacy.

26 March 2019

Up to date

All studies incorporated from most recent search

Updated review: all eligible published studies found in the last search (14 Feb, 2018) were included and three ongoing studies have been identified (see 'Characteristics of ongoing studies' section)

## PLAIN LANGUAGE SUMMARY

**Vaccines for preventing typhoid fever**

**What was studied in this review?**

Typhoid fever is a bacterial infection found mainly among children and adolescents in southern and eastern Asia, Africa, Latin America, and the Caribbean. Typhoid fever spreads through contaminated food, drink, or water. It is usually characterized initially by fever, headache, and abdominal symptoms, although other non-specific symptoms may be present. The infection also sometimes causes confusion or psychosis. In late stages of the infection, intestinal perforation or massive intestinal haemorrhage may occur. Treatment normally consists of antibiotics, but problems with drug-resistant bacteria 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.

**What are the main results?**

We found 18 relevant trials that evaluated four vaccines: 9 reported on vaccine effectiveness only, 4 reported on effectiveness and side effects, and 5 reported on side effects only (we could not analyse one additional trial on adverse events that met the inclusion criteria as it did not provide enough information). The two main vaccines currently licensed for use, Ty21a and Vi polysaccharide, were effective in reducing typhoid fever in adults and children over two years in endemic countries; adverse events such as nausea, vomiting, and fever were rare. Other vaccines, such as new, modified, conjugated Vi vaccines called Vi-rEPA and Vi-TT, are in development. These could be given to infants, which would be helpful as they are probably at higher risk for infection, although further evidence for these vaccines is still needed.

**How up-to-date is this review?**

We searched for studies published up to 14 February 2018.

## SUMMARY OF FINDINGS

### Summary of findings for the main comparison. Ty21a vaccine (three doses) versus control for preventing typhoid fever

**Ty21a vaccination (three doses) versus placebo for typhoid fever**

**Patient or population**: adults and children aged 5 years of age and older

**Settings**: any

**Intervention**: oral Ty21a (3 doses) - liquid, enteric capsule, or gelatin capsule

**Comparison**: placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | Number of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo | Ty21a (3 doses) | | | | |
| **Cases of typhoid fever, Year 1** | **Medium-risk population** | | **RR 0.55** (0.35 to 0.86) | 76,296 (3 studies) | ⊕⊕⊕⊖ **Moderate**[a,b,c,d] Due to imprecision | Cases of typhoid fever are probably reduced with vaccination |
| | **4 per 10,000** | **2 per 10,000** (1 to 3) | | | | |
| | **High-risk population** | | | | | |
| | **59 per 10,000** | **32 per 10,000** (21 to 51) | | | | |
| **Cases of typhoid fever, Year 2** | **Medium-risk population** | | **RR 0.41** (0.29 to 0.57) | 76,296 (3 studies) | ⊕⊕⊕⊖ **Moderate**[a,b,d,e] Due to imprecision | Cases of typhoid fever are probably reduced with vaccination |
| | **4 per 10,000** | **2 per 10,000** (1 to 2) | | | | |
| | **High-risk population** | | | | | |
| | **59 per 10,000** | **24 per 10,000** (17 to 34) | | | | |
| **Cases of typhoid fever, Year 3** | **Medium-risk population** | | **RR 0.44** (0.25 to 0.76) | 76,296 (3 studies) | ⊕⊕⊕⊖ **Moderate**[a,b,d,e] Due to imprecision | Cases of typhoid fever are probably reduced with vaccination |
| | **4 per 10,000** | **2 per 10,000** (1 to 3) | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | **High-risk population** | | | | | |
| | **59 per 10,000** | **26 per 10,000** (15 to 45) | | | | |
| **Cumulative cases of typhoid fever at 2.5 to 3 years** | **Medium-risk population** | | **RR 0.50** (0.39 to 0.65) | 235,239 (4 studies) | ⊕⊕⊕⊖ **Moderate**[a,b,d,f] Due to imprecision | Cases of typhoid fever are probably reduced with vaccination |
| | **4 per 10,000** | **2 per 10,000** (2 to 3) | | | | |
| | **High- risk population** | | | | | |
| | **59 per 10,000** | **30 per 10,000** (23 to 38) | | | | |

*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).
**Abbreviations: CI**: confidence interval; **RR**: risk ratio.

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

[a]No serious risk of bias detected.
[b]No serious indirectness detected: studies based in Chile, Indonesia, and Egypt.
[c]No serious inconsistency $I^2$ = 33%.
[d]Downgraded for imprecision: cluster-adjusted trials added, estimated ICC = 0.0015 (from Sur 2009 IND).
[e]No serious inconsistency, no heterogeneity $I^2$ = 0%.
[f]There is moderate heterogeneity ($I^2$ = 50%), which is not explained by stratifying into type of preparation. However, the CIs fall within a clinically important threshold, meaning the heterogeneity is unlikely be clinically significant, so we have not downgraded for this.

### Summary of findings 2. Vi polysaccharide vaccine (1 dose) versus control for preventing typhoid fever

**Vi polysaccharide vaccine (1 dose) versus control 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) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Control; efficacy | Vi polysaccharide vaccine (1 dose) | | | | |
| **Incidence of typhoid fever – year 1**<br>Blood culture | **Moderate**[a] | | **RR 0.31**<br>(0.26 to 0.37) | 99,797<br>(3 studies) | ⊕⊕⊕⊕<br>**High**[b,c,d,e] | Reduces incidence of typhoid fever |
| | **4 per 10,000** | **1.2 per 10,000**<br>(1.0 to 1.5) | | | | |
| | **High**[a] | | | | | |
| | **59 per 10,000** | **18.29 per 10,000**<br>(15.34 to 21.83) | | | | |
| **Incidence of typhoid fever – year 2** | **Moderate**[a] | | **RR 0.41**<br>(0.31 to 0.55) | 194,969<br>(4 studies) | ⊕⊕⊕⊖<br>**Moderate**[b,f,g,e]<br>Due to inconsistency | Probably reduces incidence of typhoid fever |
| | **4 per 10,000** | **1.6 per 10,000**<br>(1.2 to 2.2) | | | | |
| | **High**[a] | | | | | |
| | **59 per 10,000** | **24.19 per 10,000**<br>(18.29 to 32.45) | | | | |
| **Incidence of typhoid fever –year 3** | **Moderate**[a] | | **RR 0.5**<br>(0.32 to 0.78) | 11,384<br>(1 study) | ⊕⊕⊖⊖<br>**Low**[h,i]<br>Due to imprecision and indirectness | May reduce incidence of typhoid fever |
| | **4 per 10,000** | **2 per 10,000**<br>(1.28 to 3.12) | | | | |
| | **High**[a] | | | | | |
| | **59 per 10,000** | **29.5 per 10,000**<br>(18.88 to 46.02) | | | | |
| **Cumulative cases of typhoid fever at 2.5 to 3 years** | **Moderate**[a] | | **RR 0.45** (0.30 to 0.70) | 11,384<br>(1 study) | ⊕⊕⊖⊖<br>**Low**[h,i]<br>Due to imprecision and indirectness | May reduce incidence of typhoid fever |
| | **4 per 10,000** | **1.8 per 10,000**<br>(1.2 to 2.8) | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | **High**[a] | | | | | |
| | **59 per 10,000** | **26.55 per 10,000** (17.7 to 41.3) | | | | |
| **Serious adverse events** | No serious adverse events reported | | | | | |
| **Fever** | **5 per 1000** | **5 per 1000**<br>(4.2 to 5.7) | **RR 0.98**<br>(0.84 to 1.13) | 132,261<br>(3 studies) | ⊕⊕⊕⊖<br>**Moderate**[b,c,k,l]<br>Due to imprecision | Probably little or no association with fever |
| **Erythema** | **5 per 1000** | **6 per 1000**<br>(2 to 22) | **RR 1.15**<br>(0.33 to 4.03) | 132,261<br>(3 studies) | ⊕⊕⊕⊖<br>**Low**[b,j,l]<br>Due to imprecision and inconsistency | May have little or no association with erythema |

*The basis for the **assumed risk** (for example, 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).
**Abbreviations: CI**: confidence interval; **RR**: risk ratio.

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

[a]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).
[b]No serious risk of bias detected.
[c]No serious inconsistency: The result was consistent across all 3 trials ($I^2$ = 0%).
[d]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.
[e]No serious imprecision: the result is statistically significant with a narrow 95% CI. The meta-analysis is adequately powered to detect this effect.
[f]Downgraded by 1 level 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 Khan 2012 PAK suggesting lower protective effect in children < 5 years of age.
[g]No serious indirectness: the vaccine has been evaluated in trials from endemic settings (India, Pakistan, China and South Africa).
[h]Downgraded by 1 level for imprecision: wide CIs.
[i]Downgraded by 1 level for indirectness - only assessed in one trial in South Africa in children aged 5 to 15 years.
[k]No serious indirectness: the vaccine has been evaluated in trials from endemic settings (China) and in one trial conducted in a non-endemic setting (USA).
[l]Downgraded by 1 level for serious imprecision: The result is not statistically significant.
[j]Downgraded by 1 level for inconsistency ($I^2$ = 63%).

## Summary of findings 3. Vi-rEPA vaccine (2 doses) versus control for preventing typhoid fever

**Vi-rEPA vaccine (2 doses) versus control 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) | Number of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Control; efficacy | Vi-rEPA vaccine (2 doses) | | | | |
| **Incidence of typhoid fever – year 1**<br>Follow-up: 1 year | **Moderate**[a] | | **RR 0.06**<br>(0.01 to 0.25) | 12,008<br>(1 study) | ⊕⊕⊕⊖<br>**Moderate**[b,c]<br>Due to indirectness | Probably reduces incidence of typhoid fever |
| | **4 per 10,000** | **0.24 per 10,000**<br>(0.04 to 1) | | | | |
| | **High**[a] | | | | | |
| | **59 per 10,000** | **3.5 per 10,000**<br>(0.6 to 14.8) | | | | |
| **Incidence of typhoid fever – year 2** | **Moderate**[a] | | **RR 0.13**<br>(0.04 to 0.44) | 12,008<br>(1 study) | ⊕⊕⊕⊖<br>**Moderate**[c]<br>Due to indirectness | Probably reduces incidence of typhoid fever |
| | **4 per 10,000** | **0.52 per 10,000**<br>(0.16 to 1.8) | | | | |
| | **High**[a] | | | | | |
| | **59 per 10,000** | **7.7 per 10,000**<br>(2.4 to 26.0) | | | | |
| **Cumulative cases of typhoid fever at 2 years** | **Moderate**[a] | | **RR 0.09** (0.04 to 0.22) | 12,008<br>(1 study) | ⊕⊕⊕⊖<br>**Moderate**[c]<br>Due to indirectness | Probably reduces incidence of typhoid fever |
| | **4 per 10,000** | **0.36 per 10,000** (0.16 to 0.88) | | | | |
| | **High**[b] | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | **59 per 10,000** | **5.31 per 10,000** (2.36 to 12.98) | | | | |
| **Cumulative cases of typhoid fever at 3.8 years** | **Moderate**[a] | | **RR 0.11** (0.05 to 0.23) | 12,008 (1 study) | ⊕⊕⊕⊖ **Moderate**[c] Due to indirectness | Probably reduces incidence of typhoid fever |
| | **4 per 10,000** | **0.44 per 10,000** (0.2 to 0.92) | | | | |
| | **High**[b] | | | | | |
| | **59 per 10,000** | **6.49 per 10,000** (2.95 to 13.57) | | | | |
| **Serious adverse events** | See comment | See comment | Not estimable | 12,008 (1 study) | See comment | No serious adverse events were reported |
| **Fever after Vi-rEPA (dose1)** | **5 per 1000** | **13 per 1000** (8 to 18) | **RR 2.54** (1.69 to 3.62) | 12,008 (1 study) | ⊕⊕⊕⊖ **Moderate**[d] Due to imprecision | Probably associated with fever following vaccination |
| **Fever after Vi-rEPA (dose2)** | **4 per 1000** | **18 per 1000** (11 to 27) | **RR 4.39** (2.85 to 6.77) | 11,091 (1 study) | ⊕⊕⊕⊖ **Moderate**[d] Due to imprecision | Probably associated with fever following vaccination |
| **Erythema after Vi-rEPA (dose 2)** | **0.2 per 1000** | **0.4 per 1000** (0.04 to 4.4) | **RR 2.01** (0.19 to 22.21) | 11,091 (1 study) | ⊕⊕⊖⊖ **Low**[d,e] Due to serious imprecision | May have little or no association with erythema |
| **Swelling at injection site after Vi-rEPA (dose 2)** | **0.2 per 1000** | **4 per 1000** (0.5 to 30) | **RR 20.15** (2.71 to 150.08) | 11,091 (1 study) | ⊕⊕⊕⊖ **Moderate**[d] Due to imprecision | Probably associated with swelling at injection site |

*The basis for the **assumed risk** (for example, 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).
**Abbreviations: CI**: confidence interval; **RR**: risk ratio.

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

[a]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).
[b]No serious risk of bias detected.
[c]Downgraded by 1 level 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).
[d]Downgraded by 1 level for imprecision: wide 95% CIs.
[e]Downgraded by 1 level for serious imprecision: the result is not statistically significant.

### Summary of findings 4. Vi-TT conjugate vaccine (PedaTyph) (2 doses) versus control for preventing typhoid fever

**Vi-TT conjugate vaccine versus control for preventing typhoid fever**

**Patient or population**: children aged 6 months to 12 years

**Settings**: India
**Intervention**: Vi-TT (PedaTyph) vaccine (2 doses)

**Comparison**: control; efficacy

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | Number of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk[a] | Corresponding risk | | | | |
| | Control; efficacy | Vi-TT conjugate; (2 doses) | | | | |
| Incidence of typhoid fever – year 1<br><br>Follow-up: 1 year | 13 per 1000 | 0.8 per 1000<br><br>(0 to 13) | RR 0.06[b]<br><br>(0.00 to 1.01) | 1625<br>(1 study) | ⊕⊝⊝⊝<br>Very low[c,d,e]<br><br>Due to risk of bias, serious imprecision and indirectness | We do not know if this vaccine prevents typhoid fever |

*The basis for the **assumed risk** (for example, 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).
**Abbreviations: CI**: confidence interval; **RR**: risk ratio.

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

[a]The basis for the assumed risk is taken from the disease incidence in the control group in the trial (Mitra 2016 IND).

[b]Primary trial is not cluster-adjusted. This estimate uses a small assumed intracluster correlation coefficient of 0.0015 calculated from cluster-randomized ViPs vaccine trial Sur 2009 IND, which did adjust for clustering.
[c]Downgraded by 1 level for risk of bias.
[d]Downgraded by 1 level for imprecision. Wide CIs that include appreciable harm and few (11 events) in the trial.
[e]Downgraded by 1 level for indirectness. Only one trial in one setting and in children under 12 years.

# BACKGROUND

## Description of the condition

### Epidemiology

Typhoid fever is a systemic infection caused by the Gram-negative bacterium *Salmonella enterica* serovar Typhi (*S.* Typhi). *S.* Typhi spreads by food, drink, or water contaminated by faecal or urinary carriers excreting the bacteria. Typhoid fever, also called enteric fever, remains an important global public health problem. Estimating disease burden is difficult for a number of reasons, including the poor sensitivity of diagnostic tests and lack of surveillance in countries with suspected high prevalence (Andrews 2015). In 2010 there were an estimated 20.6 million cases of typhoid fever in low- and middle-income countries, with 223,000 deaths (although after adjusting for risk factors and corrected diagnostic testing, the estimate dropped to 11.9 million cases and 129,000 deaths; Mogasale 2014). This lack of robust data makes decision-making on priorities and resource allocation difficult and may negatively impact investment in typhoid fever (Crump 2015).

The highest burden of typhoid fever is thought to be in South Asia (Wain 2015). Typhoid fever incidence in sub-Saharan Africa has historically been poorly described; but the recent Typhoid Surveillance in Africa programme, funded by the Gates Foundation, has shown that incidence in many African countries may be as high as that in Asia (Steele 2016). Typhoid fever is rare in industrialized nations, although travellers to endemic countries are at risk of acquiring the disease, with a recent survey naming it the second most common potentially life threatening infectious disease in travellers (Jensenius 2013).

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

### Clinical features

After ingestion of *S.* Typhi or *S.* Paratyphi, the bacteria spread from the intestine via the blood, where they multiply to the intestinal lymph nodes, liver, and spleen. Typhoid fever is usually characterized initially by fever, headache, and abdominal symptoms, although other nonspecific symptoms may occur. Neuropsychiatric manifestations, including psychosis and confusion, may occur. Other signs include relative bradycardia, rose spots, hepatomegaly, and splenomegaly, although these signs are not pathognomonic (Mandell 2005).

Complications occur in 10% to 15% of untreated patients, usually in the third and fourth weeks of infection. The most important complications are gastrointestinal bleeding, occurring in up to 10% of patients (Parry 2002), followed by intestinal perforation and typhoid encephalopathy. 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).

Both *S.* Typhi and *S.* Paratyphi can cause enteric fever, and the clinical manifestations of these two infections are similar. In some areas enteric fever caused by *S.* Paratyphi is more common (MacLennan 2014).

### Diagnosis and treatment

Confirmation of typhoid fever requires isolating *S.* Typhi from blood, bone marrow, stool, or duodenal fluid by culture. The Widal test, which identifies antibodies against *S.* Typhi antigens in blood, has poor sensitivity overall and poor specificity in endemic areas (Bhan 2005; Qamar 2015). New-generation, rapid, serologic tests have been developed, including a dot enzyme-linked immunosorbent assay test that detects IgM and IgG antibodies against an outer membrane protein of Salmonella Typhi (Typhidot) and an anti-O9 IgM antibody specific for group D Salmonellae (Tubex) (Keddy 2011). However, a recent systemic review found inadequate sensitivity and specificity for these as well (Thriemer 2013).

Effective and early treatment with antibiotics shortens disease course and reduces the risk of complications (Kariuki 2015). A multi-drug resistant (MDR) strain of *S.* Typhi to chloramphenicol, ampicillin and co-trimoxazole emerged in the late 1980s in Asia, and later in Africa. This has declined with widespread use of fluoroquinolones. Unfortunatley, *S.* Typhi strains with reduced sensitivity and resistance to fluoroquinolones developed in the 1990s, mainly in the Indian subcontinent (Wain 2015). Third generation cephalosporins (such as ceftriaxone and cefotaxime) are often used, particularly in patients admitted to hospital. Sporadic reports of emerging resistance to these antibiotics is of serious concern (Kariuki 2015). Azithromicyn is being used increasingly as a first-line oral treatment option.

### Potential control measures

Given the route of transmission and the fact that humans are the only source of infection, improved sanitation and food hygiene are important control measures. However, these measures are associated with socioeconomic progress, which 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

Vaccination against typhoid fever is a key control measure; however, despite their evaluation in populations in endemic low- and middle- income countries, travellers from high-income countries are the primary users of typhoid fever vaccines. This situation is changing, thanks to the availability of high-quality burden of disease data from endemic countries (Ochiai 2008); to the experience of typhoid vaccination programmes in Thailand, China, Vietnam, and India (DeRoeck 2008); and to 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). Up until recently, there were no typhoid vaccines effective for children younger than two

years, who carry a large disease burden in developing countries. More recently, newer typhoid conjugate vaccines (TCV) have entered use, with evidence of immunogenicity in children from six months old. These show a potential for inclusion in the infant expanded programme on immunization (Date 2015).

The following typhoid vaccines have been developed.

#### Inactivated whole-cell typhoid vaccine

Although 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 (CI) 65% to 80%) (Engels 1998a). Different methods of inactivating *S.* Typhi cells 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

Ty21a is a live oral vaccine derived from an attenuated strain of *S.* Typhi, approved for use in children aged six years or older. It is available as an enteric-coated capsule and is given in three doses (four doses in North America) every other day. The liquid formulation, which was approved in children over two years old, is not currently available (WHO 2018b). It elicits protection that starts 10 to 14 days after the third dose. Travellers should be revaccinated every three to five years with continued or repeat exposure 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, none of the multiple large field trials conducted have documented such hypothetical effects, which are considered exceptionally unlikely given the degree of attenuation (WHO 2008).

#### M01ZH09 vaccine

A human challenge trial has assessed a new live attenuated oral typhoid vaccine, M01ZH09 (Darton 2016). M01ZH09 is constructed from a parent Ty2 strain. Following vaccination with M01ZH09 or placebo in a double-blind randomized trial, participants were artificially infected with *S.* Typhi. A single dose was not found to be effective in preventing infection (RR 1.81, 95% CI 0.66 to 5). However, as this was a human challenge, its clinical effects remain unknown.

#### Vi polysaccharide vaccine

Vi polysaccharide is based on a purified capsular polysaccharide of *S.* Typhi Vi antigen (Date 2015). Given in a single parenteral dose, protection begins seven days after injection, with maximum protection achieved at 28 days, when the highest antibody concentration is attained (Garmory 2002). This vaccine is approved for people aged two years and older. It is not immunogenic in younger children, Revaccination every three years is recommended.

#### Typhoid conjugate vaccines

Typhoid conjugate vaccines (TCV) are injectable subunit vaccines where Vi capsular polysaccharide antigen is linked to a protein carrier (Date 2015).

**Vi-rEPA**, a modified Vi vaccine conjugated to a nontoxic recombinant *Pseudomonas aeruginosa* exotoxin A (rEPA), is given as two parenteral doses. Although theoretically immunogenic from six months old, it has only been used in children over two years (Lin 2001 VNM). This vaccine has not been commercialized.

**Vi-TT**, a new conjugated Vi-polysaccharide linked to tetanus toxoid carrier protein, has been licensed in India in two preparations: **Peda Typh** (two doses, children six months and above; Mitra 2016 IND) and **Typbar-TCV** (one dose, children six months and above; Jin 2017; Mohan 2015). WHO has approved Typbar-TCV for infants and children over six months of age in endemic areas (WHO 2018a).

### Why it is important to do this review

This update of the 2014 Cochrane Review, Anwar 2014, provides an updated assessment of the efficacy and safety of vaccines to prevent typhoid fever by incorporating data from new trials and vaccines and incorporating cluster-randomized controlled trials in the meta-analyses.

## OBJECTIVES

To assess the effects of vaccines for preventing 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*

Vaccines against *S.* Typhi include the following.

- Live oral vaccine Ty2la or genetic modifications of this strain.
- Vi polysaccharide vaccine.
- Conjugate vaccines.

##### *Control*

- No vaccine, placebo or typhoid-inactive agents (vaccine for a different disease)
- Other typhoid vaccines

For the secondary outcome of adverse events, we included only placebo-controlled trials.

##### *Excluded interventions*

We excluded studies focusing on the following types of interventions.

- Trials that evaluated killed whole-cell vaccines, because these vaccines are no longer in use.
- Trials that reported only on immunogenicity.
- Trials that assessed only adverse events but not clinical efficacy of vaccines that have not yet been evaluated for clinical efficacy.
- Human challenge studies where participants were artificially infected with*S.* Typhi at a certain time point following vaccination, since the bacterial inoculum in challenge trials is constant and the timing of infection relative to vaccination is highly controlled compared to the real life situation. We therefore believe these trials to be less relevant for clinicians and policy-making.

### Types of outcome measures

#### *Primary outcomes*

##### Typhoid fever

Typhoid fever defined by isolation of *S.* Typhi from blood cultures.

#### *Secondary outcomes*

##### Adverse events

- Serious adverse events, defined as leading to death, requiring inpatient hospitalization or prolonged existing hospitalization, life threatening, or resulting in persistent or significant disability or incapacity.
- Other adverse events, including fever, erythema at injection site, vomiting, and diarrhoea.

When the occurrence of adverse events was reported after each of several doses, we extracted the occurrence following each dose separately. 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.

## 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 (searched 14 February 2018); Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library (2018, Issue 2 of 12); MEDLINE (1966 to 14 February 2018); Embase (1974 to 14 February 2018); and LILACS (1982 to 14 February 2018). We also searched the *meta*Register of Controlled Trials (*m*RCT) using ‘typhoid' and ‘vaccine' as search terms (searched 14 February 2018). We searched the Internet for new drug application (NDA) documents of the US Food and Drug Administration, which may include unpublished studies (last accessed 14 February 2018).

### Conference proceedings

We searched the following conference proceedings for relevant abstracts: International Conference on Typhoid and other Invasive Salmonelloses (2013 to 2017); Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC/ASM Microbe; 1995 to 2017); European Congress of Clinical Microbiology and Infectious Diseases (ECCMID; 2001 to 2017); and the Annual Meeting of the Infectious Diseases Society of America (IDSA; 2001 to 2017).

### Reference lists

We examined the reference lists of the included trials.

## Data collection and analysis

### Selection of studies

Two review authors independently inspected titles and abstracts identified by the literature search to identify potentially relevant publications, retrieving the full text of any record that at least one review author judged as potentially relevant. We applied the inclusion criteria for the final decision regarding eligibility. We also ascertained 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. If a single included reference included more than one trial, we labelled the trials separately using a letter (for example, Wahdan 1980a EGY and Wahdan 1980b EGY). We resolved disagreements by discussion and consensus, documenting reasons for excluding studies from the review. 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

Two review authors independently extracted data into a standard form; a third review author extracted the data in cases of disagreement. One review author entered data into RevMan 5 (RevMan 2014).

### Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias in included trials; in cases of disagreement, we consulted a third review author. 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 they reported results for all randomized participants.

### Measures of treatment effect

We recorded the number of participants experiencing the event and the number analysed in each treatment group. We aimed to extract data according to an intention-to-treat analysis and reported any discrepancies in the number randomly assigned and the numbers analysed in each treatment group. We calculated risk ratios with 95% CIs, and in cluster-RCTs that reported cluster adjusted effect estimates, we extracted the reported effects as risk ratios or hazard ratios.

### Unit of analysis issues

For trials randomly assigning clusters, we extracted cluster-adjusted effect estimates when available. We also recorded the number of clusters in the trial, the average size of clusters, the unit of randomization (for example, household or institution) and the statistical methods used to analyse the trial results. For cluster-

RCTs reporting individual patient results without adjustment for clustering, we calculated an intracluster correlation coefficient (ICC) using trial data from Sur 2009 IND (that allowed calculation of unadjusted risk ratios from crude number of individuals and reported cluster-adjusted hazard ratios) as 0.0015. We calculated the design effect of cluster-RCTs that did not adjust for clustering taking into account average cluster size. We used this design effect to calculate the effective number of events per control and intervention and the effective number of participants per control and intervention to be used in the meta-analysis. We present cluster-unadjusted results in a separate table but do not use them in the meta-analysis.

If a single included trial compared several vaccine arms with a control arm, we labelled the arms separately using a Roman numeral (for example, 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.

### Dealing with missing data

When necessary, we contacted the trial authors for clarification or additional details regarding trial methodology or results. In cluster-RCTs, we asked authors for distribution of outcomes in the different clusters.

### Assessment of heterogeneity

We assessed heterogeneity by inspecting the forest plots to detect overlapping CIs and the $I^2$ statistic used to denote levels of heterogeneity as defined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

- 0% to 40% heterogeneity: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

### Assessment of reporting biases

We planned to inspect funnel plots to assess small study effects and explore the possibility of reporting bias. However, all analyses included too few trials to analyse the funnel plot.

### Data synthesis

We conducted separate meta-analyses for each vaccine type. We combined dichotomous data from trials that randomly assigned individuals or corrected numbers from cluster-RCTs that did not adjust by using risk ratios (RRs) with 95% CIs. In analyses including cluster-RCTs that reported adjusted risk ratios, we pooled risk ratios from all the trials using inverse variance meta-analysis. We interpreted the results as efficacy, defined as 1 − RR and expressed as a percentage. We analysed 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 up to three years and longer if available, regardless of whether changes over time occurred within this period. We rounded to the nearest year when trials included follow-up for only part of a year. 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.

### Subgroup analysis and investigation of heterogeneity

We had planned to explore the following potential sources of heterogeneity in subgroup analyses: number of doses; length of follow-up; type of oral formulation in the Ty21a vaccine (capsules and type of capsule, liquid formulation) and age. However, data were sparse, so we present only the subgroup by type of oral formulation in the meta-analyses.

### Sensitivity analysis

We conducted sensitivity analyses by limiting the meta-analysis to trials at low of risk of bias due to randomization methods for the primary outcome and assessing whether vaccine efficacy changed. We considered that blinding would not affect bias for our primary outcome of typhoid fever cases, as this measure is objective (Savović 2012).

### *'Summary of findings' table*

We assessed the certainty of the evidence across each outcome measure using the GRADE approach. The certainty rating across studies has one of four levels: high, moderate, low or very low. GRADE initially classifies randomized trials as high certainty, downgrading may be warranted after assessment of five criteria: risk of bias, consistency, directness, imprecision, and publication bias (Guyatt 2008). The 'Summary of findings' tables present the main results of the review and the certainty assessments.

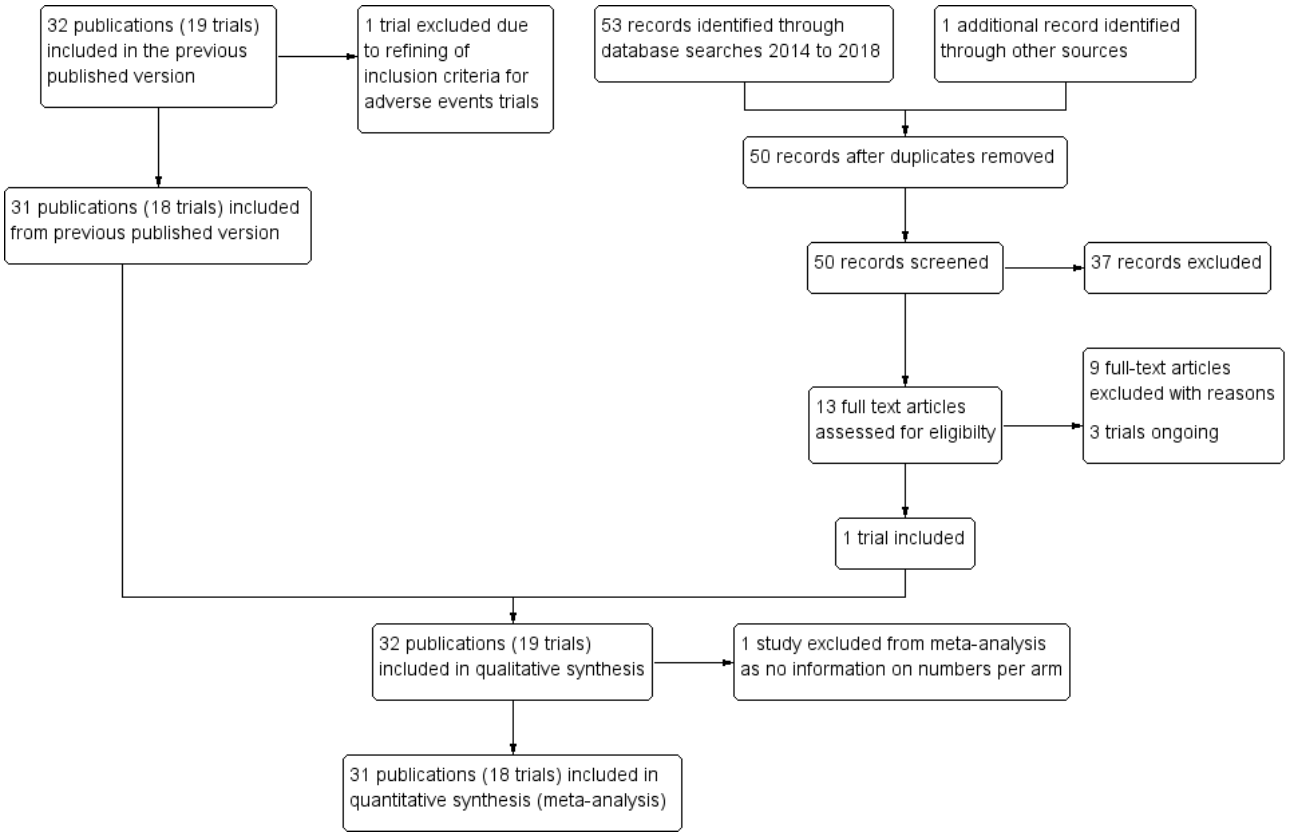
## RESULTS

## Description of studies

### Results of the search

We present the search results in a PRISMA study flow diagram in Figure 1. In the previous version of this review, Anwar 2014, we included 32 publications of 19 trials (the previous version misreported this number, but we have corrected it in the update). We excluded one study that was in the previous review, Thiem 2011, due to the refining of the inclusion criteria for adverse events trials. We updated the literature search to 14 February 2018 and identified 50 new unique records. We assessed 13 full-text articles for eligibility after abstract screening. One new trial met the inclusion criteria (Mitra 2016 IND), while three trials were ongoing (see the Characteristics of ongoing studies section).

**Figure 1. Study flow diagram.**




### Included studies

In total, 32 records reporting on 19 trials (12 RCTs randomizing individuals and 7 cluster-RCTs) met the inclusion criteria: see details in Characteristics of included studies table. The 2018 review update includes one new trial evaluating the efficacy of Vi polysaccharide conjugated to tetanus toxoid vaccine (Vi-TT), PedaTyph (Mitra 2016 IND).

All of the trials except Keitel 1994 USA took place in countries where typhoid fever is endemic: Chile (four trials), China (three trials), Vietnam (one trial), Thailand (two trials), Pakistan (one trial), Egypt (one trial), India (two trials), Indonesia (one trial), Nepal (one trial), and South Africa (one trial). None of the trials evaluated vaccine efficacy in travellers from developed countries or compared the efficacy of different types of typhoid vaccines.

Participants ranged in age across the trials. Three trials included children aged under 12 years only (Lin 2001 VNM; Mitra 2016 IND; Wahdan 1980a EGY), and one trial reported on adults only (Levine 1986i CHL). Only three efficacy trials included data on adults over 25 years of age (Acharya 1987 NPL; Simanjuntak 1991i IDN; Wang 1997 CHN). None of the trials reported on use of typhoid vaccination in adults aged over 55 years. Only one trial included children under two years of age (Mitra 2016 IND). All trials either excluded pregnant participants or included no details on their inclusion.

#### *Outcomes*

Data on the primary outcome, cases of typhoid fever, were derived from 13 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 1997 CHN; Yang 2001 CHN).
- One Vi-rEPA trial (Lin 2001 VNM).
- One Vi-TT (PedaTyph) trial (Mitra 2016 IND).

Data on the secondary outcome, adverse events, came from nine trials.

- Five trials of Ty21a (Levine 1986i CHL; Levine 1986ii CHL; Olanratmanee 1992 THA; Wahdan 1980a EGY; Wahdan 1980b EGY; Simanjuntak 1991i IDN; Simanjuntak 1991ii IDN).
- Three trials of Vi polysaccharide (Keitel 1994 USA; Yang 2001 CHN; Zhou 2007 CHN).
- One trial of Vi-rEPA (Lin 2001 VNM).

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

### Excluded studies

In this 2018 update we excluded nine trials. Across all versions of this review, we excluded 60 publications (53 trials). For

details of excluded trials and reasons for their exclusion, see the Characteristics of excluded studies table.

### Risk of bias in included studies

See Figure 2 for a summary of the 'Risk of bias' 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.**

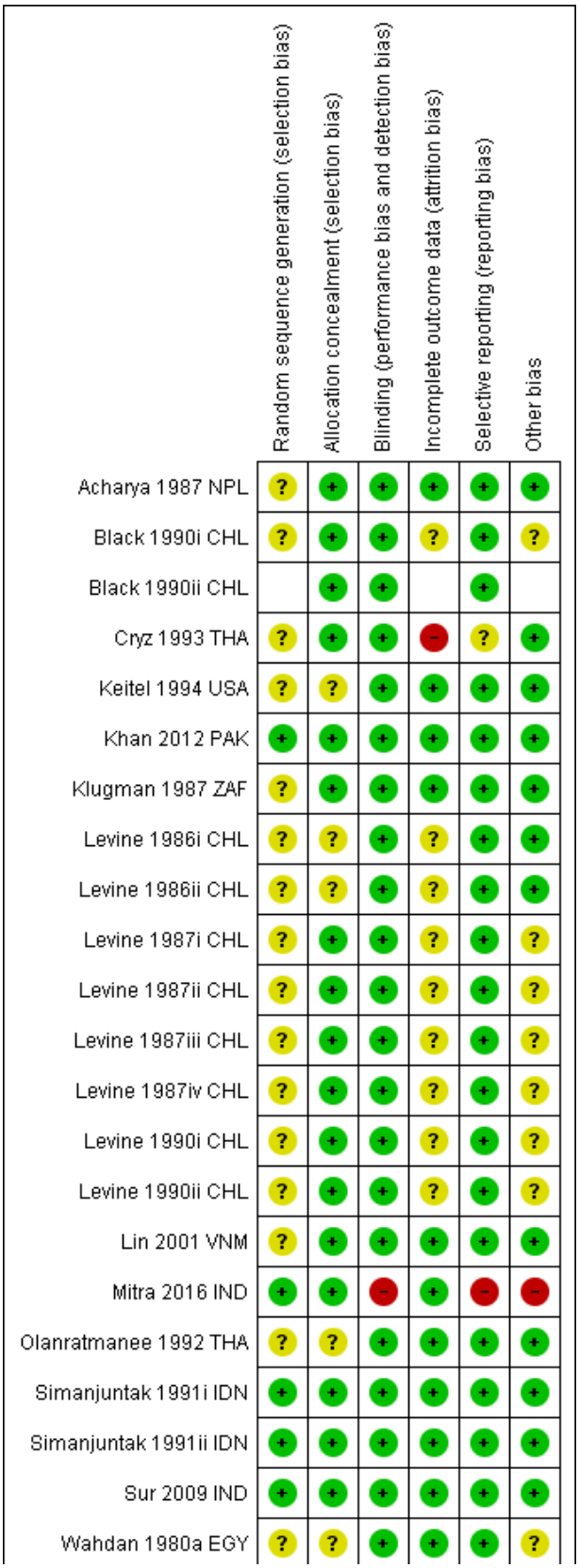
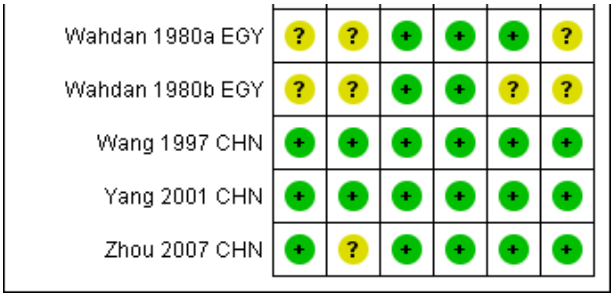


**Figure 2. (Continued)**




### Allocation

Six of the 13 trials reporting on efficacy reported low-risk randomization procedures (Khan 2012 PAK; Mitra 2016 IND; Simanjuntak 1991i IDN; Simanjuntak 1991ii IDN; Sur 2009 IND; Wang 1997 CHN; Yang 2001 CHN). The other seven trials did not provide enough information to permit judgement. All but one trial, Klugman 1987 ZAF, used low-risk methods to conceal allocation.

Three of the 10 trials reporting adverse events described low-risk randomization procedures (Simanjuntak 1991i IDN; Simanjuntak 1991ii IDN; Yang 2001 CHN; Zhou 2007 CHN). Likewise, three used low-risk methods to conceal allocation (Lin 2001 VNM; Simanjuntak 1991i IDN; Simanjuntak 1991ii IDN; Yang 2001 CHN). The other trials did not report enough information to permit judgement.

### Blinding

All but 3 of the 13 trials on clinical efficacy used double-blinding. Two cluster-randomized trials could not guarantee blinding of researchers or participants, as they used vaccines that were packaged differently and therefore did not look identical (Khan 2012 PAK; Sur 2009 IND). 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. One cluster-randomized trial, Mitra 2016 IND, was open label with no placebo arm, with the control group having vaccinations as per the normal schedule. There is no information as to whether researchers were blinded.

All of the trials that included adverse effects used double-blinding.

### Incomplete outcome data

Ten of 13 trials that investigated vaccine efficacy included all randomly assigned participants in the analysis, so we classified them at low risk of attrition bias. Three trials provided no reasons for missing data (Black 1990i CHL; Black 1990ii CHL; Levine 1987i CHL; Levine 1987ii CHL; Levine 1987iii CHL; Levine 1987iv CHL; Levine 1990i CHL; Levine 1990ii CHL).

We assessed 5 of 10 trials that included adverse events as being at low risk 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). We judged the trial that did not provide the number of participants per study arm as being at high risk of attrition bias (Cryz 1993 THA).

### Selective reporting

All but one of the 13 trials on vaccine efficacy reported on pre-planned outcomes, meriting a classification of low risk of bias. Mitra 2016 IND did not report on paratyphoid outcomes as the prospectively registered protocol had described, so we classified it as being at high risk of bias. The vaccine assessed would not have affected the incidence of *S.* Paratyphi infections but would have aided us to judge whether the decreased number of infections was due to the effect of the vaccine or consequences of better socioeconomic status of the immunized group (see other sources of bias described below).

All 10 trials included in the adverse events analysis reported on plausible outcomes, so we classified them as being at low risk of bias, even though protocols were not available.

### Other potential sources of bias

Four of the seven cluster-RCTs on vaccine efficacy provided data on the efficacy of the Ty21a vaccine (Black 1990i CHL; Levine 1987i CHL; Levine 1990i CHL; Wahdan 1980a EGY). These four cluster-RCTs, all of which randomly assigned by classroom, did not adjust for clustering in their results.

Two of the vaccine efficacy cluster-RCTs provided data on the efficacy of the Vi polysaccharide vaccine (Khan 2012 PAK; Sur 2009 IND). Both of these trials randomly assigned geographic clusters. Study authors provided unpublished cluster-adjusted data for the meta-analysis.

The remaining vaccine efficacy cluster-RCT provided data on the efficacy of the Vi-TT conjugate vaccine PedaTyph (Mitra 2016 IND). The trial cluster-randomized children by school and did not adjust for clustering in the sample size calculations or in results. The intervention and control groups were different in terms of socioeconomic data, despite randomization, with lower status in the control group. As typhoid fever is associated with poor sanitation and hygiene, it is plausible that the vaccine would prevent more cases in lower socioeconomic groups. Although the authors did not mention it in the published paper, according to the prospectively registered protocol the company who manufactures Peda Typh funded the study. We classified this trial as being at high risk of other sources of bias.

## Effects of interventions

See: **Summary of findings for the main comparison** Ty21a vaccine (three doses) versus control for preventing typhoid fever; **Summary of findings 2** Vi polysaccharide vaccine (1 dose) versus control for preventing typhoid fever; **Summary of findings 3** Vi-

rEPA vaccine (2 doses) versus control for preventing typhoid fever; **Summary of findings 4** Vi-TT conjugate vaccine (PedaTyph) (2 doses) versus control for preventing typhoid fever

### TY21a vaccine

#### *Efficacy*

Investigators assessed the TY21a vaccine in one four-arm individual RCT, Simanjuntak 1991i IDN, and four cluster-RCTs, reported in Black 1990ii CHL Levine 1987i CHL Levine 1987ii CHL Levine 1987iii CHL Levine 1987iv CHL Levine 1990i CHL Levine 1990ii CHL and Wahdan 1980a EGY. The cluster-RCTs did not adjust analyses for the effect of clustering, so they may have overestimated any protective effect. We adjusted results from these trials using an estimated ICC of 0.0015 and average cluster size to calculate the design effect so we could include them in the meta-analysis. Table 1 displays adjusted results, and we refer to these findings unless otherwise specified. Table 2 shows unadjusted results.

A three-dose schedule of Ty21a vaccine provided vaccine efficacy of 45% at year 1 (95% CI 14% to 65%; 76,296 participants; Analysis 1.1), 59% at year 2 (95% CI 43% to 71%; 76,296 participants; Analysis 1.2) and 56% at year 3 (95% CI 24% to 75%; 76,296 participants; Analysis 1.3). The cumulative efficacy of the Ty21a vaccine over 2.5 to 3 years was 50% (95% CI 35% to 61%; 235,239 participants; Analysis 1.4).

Cumulative efficacy of the three-dose schedule of Ty21a vaccine for over three years is available from two of the adjusted cluster-RCTs (Levine 1987ii CHL; Levine 1990i CHL). Cumulative efficacy was 77% at five years (95% CI 60% to 86%; Table 1) and 63% at seven years (95% CI 42% to 76%; Table 1).

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

In the cumulative analysis there is moderate heterogeneity that is not explained by stratifying results by type of preparation. In direct randomized comparisons between liquid and enteric capsules (Analysis 2.1) and between enteric and gelatin capsules (Analysis 3.1), the heterogeneity was too high to pool the results, so we were unable to conduct a meta-analysis.

#### *Adverse events*

None of the individual- or cluster-randomized trials reported any serious adverse events (5 trials, 235,239 participants: Levine 1986i CHL; Levine 1986ii CHL; Olanratmanee 1992 THA; Wahdan 1980a EGY; Wahdan 1980b EGY; Simanjuntak 1991i IDN; Simanjuntak 1991ii IDN; Appendix 2).

Compared with placebo, the Ty21a vaccine (both preparations) did not increase the incidence of vomiting (2 trials, 2066 participants; Analysis 4.2), diarrhoea (2 trials, 2066 participants; Analysis 4.3), nausea or abdominal pain (2 trials, 2066 participants; Analysis 4.4), headache (1 trial, 1190 participants; Analysis 4.5), or rash (1 trial, 1190 participants; Analysis 4.6) compared with control. However, fever was more common after vaccine delivery (RR 1.84, 95% CI 1.02 to 3.05; 2 trials, 2066 participants). 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; 2 trials, 1360 participants; Analysis 4.7).

The cluster-randomized studies Wahdan 1980a EGY and Wahdan 1980b EGY reported adverse events per dose of vaccine rather than per patient, so we could use these data in the meta-analysis. There appeared to be more episodes of vomiting and nausea/abdominal pain per dose with the vaccine, but the overall incidence was low (0.1% vomiting with Ty21a versus 0.05% with placebo; 0.03% nausea/abdominal pain with Ty21a versus 0.004% with placebo, Appendix 2).

Cryz 1993 THA did not supply the number of participants in the vaccine and placebo groups, so results could not be analysed. Authors noted that all reactions were mild.

See Summary of findings for the main comparison.

### Vi polysaccharide vaccine

#### *Efficacy*

Four individually randomized RCTs assessed the efficacy of this vaccine (Acharya 1987 NPL; Klugman 1987 ZAF; Wang 1997 CHN; Yang 2001 CHN), as did two cluster-RCTs (Khan 2012 PAK; Sur 2009 IND). We obtained cluster-adjusted results for efficacy at year 2 following vaccination from the study authors, so we were 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%; 3 trials, 99,797 participants; Analysis 5.1) and 59% at year 2 (95% CI 45% to 69%; 4 trials, 194,969 participants; Analysis 5.1) There was high heterogeneity in year 2 ($I^2$ = 72%), which we were unable to explain with subgroup analysis. Ty21a efficacy was 50% at year 3 based on a single trial (95% CI 22% to 68%; 11,384 participants; Analysis 5.1). 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 5.2).

Two of the trials used the Widal test (as well as a positive culture) to detect cases of typhoid fever (Wang 1997 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 culture-based results demonstrated that protection was significant in each of the first two years but not in years 3 or 6. 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 RCTs conducted subgroup analysis by age: Yang 2001 CHN used individual randomization, while Khan 2012 PAK and Sur 2009 IND were cluster trials. However, the individually based RCT included very small numbers in each age group (Yang 2001 CHN); the two cluster-RCTs 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% (Khan 2012 PAK; Sur 2009 IND). We were therefore unable to conduct subgroup analysis by age. Table 3 presents unadjusted results by age from the two cluster-RCTs. The cluster-randomized trial conducted in India, Sur 2009 IND, found that two years after vaccination, the Vi polysaccharide vaccine provided significantly more protection than the control condition for children two to five years of age (efficacy 82%, 95% CI 58% to 92%). 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 on serious adverse events.

Overall, we did not find a significant difference between vaccine and placebo in the incidence of fever (3 trials, 132,261 participants; Analysis 6.1) or erythema (3 trials, 132,261 participants; Analysis 6.2). However, swelling (RR 6.06, 95% CI 1.07 to 34.22; 3 trials, 1767 participants; Analysis 6.3) and pain at the injection site (RR 7.98, 95% CI 3.69 to 17.24; 1 trial, 667 participants; Analysis 6.4) were more common after delivery of the Vi polysaccharide vaccine.

See Summary of findings 2.

### Vi-rEPA vaccine

#### *Efficacy*

One trial in children aged two to five years, conducted in Vietnam, evaluated the efficacy of this vaccine (Lin 2001 VNM), reporting that it was 94% at year 1 (95% CI 75% to 99%; 12,008 participants; Analysis 7.1) and 87% in year 2 (95% CI 56% to 96%; 12,008 participants; Analysis 7.1), with a two-year cumulative efficacy of 91% (95% CI 78% to 96%; 12,008 participants; Analysis 7.1). The cumulative efficacy of the Vi-rEPA vaccine after 3.8 years was 89% (95% CI 77% to 95%; 12,008 participants, Analysis 7.1). The planned vaccine schedule was two doses of vaccine approximately six weeks apart. Although 388 children in the vaccine group received only one dose of vaccine instead of two, authors still analysed them along with those who had received two doses. The cumulative two-year efficacy for two doses of vaccine was the same as for one or two doses of vaccine, so this did not seem to undermine the validity of the results.

No trials assessed the efficacy of this vaccine in children older than five or in adults.

#### *Adverse events*

One trial evaluated adverse events associated with this vaccine, reporting no serious events (Lin 2001 VNM). Fever was more common following delivery of both the first and second vaccinations with Vi-rEPA compared with placebo (dose 1: RR 2.54, 95% CI 1.69 to 3.82, 12,008 participants, 1 trial, Analysis 8.1; dose 2: RR 4.39, 95% CI 2.85 to 6.77, 11,091 participants, 1 trial, Analysis 8.2). After the first dose of Vi-rEPA, no participants in either the test or placebo group reported erythema or swelling at the injection site (Analysis 8.3; Analysis 8.5). After the second dose, there was no significant difference between the vaccine and placebo for erythema (Analysis 8.4), but swelling at the injection site was more common in the Vi-rEPA group (RR 20.15, 95% CI 2.71 to 150.8; 11,091 participants, 1 trial; Analysis 8.6).

See Summary of findings 3.

### Vi-tetanus toxoid conjugated typhoid vaccine (Pedatyph)

#### *Efficacy*

One cluster-randomized trial in children aged six months to 12 years of age assessed the efficacy of this vaccine in India (Mitra 2016 IND). The authors did not adjust for cluster randomization. Using an estimated ICC of 0.0015 (from Sur 2009 IND) and an average cluster size of 135, we calculated the design effect as 1.201 and adjusted results accordingly. Table 4 shows unadjusted results.

The adjusted efficacy of Vi-TT (PedaTyph, 2 doses) at one-year follow-up was 94% (95% CI −1% to 100%; 1625 participants; Analysis 9.1).

#### *Adverse effects*

The trial did not report any serious adverse effects.

See Summary of findings 4.

### Heterogeneity

Other than where already stated, in most comparisons that included several trials, the degree of heterogeneity was not substantial (that is, $I^2$ statistic < 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 identify the reason for the greater degree of heterogeneity in some comparisons.

### Sensitivity analyses

We performed sensitivity analyses for trials with a split control arm in the main analyses and found that the results did not change (analyses not shown). As most comparisons included few trials, we could not perform sensitivity analyses according to risk of bias. We did not notice any difference in adverse event results from trials that did and did not evaluate efficacy, although we did not undertake formal testing.

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

#### *Ty21a vaccine*

The liquid formulation of the Ty21a vaccine had a three-year cumulative protective efficacy of 71% (95% CI 34% to 88%; Levine 1990i CHL; Simanjuntak 1991i IDN; Wahdan 1980a EGY; Analysis 1.4). The incidence rate in the control group was 544/100,000 with a corresponding NNTB of 259 (95% CI 209 to 541). The enteric capsule formulation of the Ty21a vaccine had three-year cumulative protective efficacy of 46% (95% CI 32% to 58%; Levine 1987i CHL; Levine 1987ii CHL; Levine 1990ii CHL; Simanjuntak 1991ii IDN; Analysis 1.4). The incidence in the control group was 734/100,000, and the corresponding NNTB was 296 (95% CI 235 to 426).

#### *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 4.2), with an incidence rate of 1160/100,000. From these data, we estimated the NNTB to be 157 (95% CI 1234 to 287).

## DISCUSSION

### Summary of main results

### Ty21a vaccine (three doses)

A three-dose schedule of Ty21a vaccine probably prevents around half of typhoid cases during the first three years after vaccination (moderate-certainty evidence). These data include patients aged 3 to 44 years.

Compared with placebo, this vaccine probably does not cause more vomiting, diarrhoea, nausea, or abdominal pain, (moderate-certainty evidence) headache, or rash (moderate-certainty evidence); however, fever is probably more common following vaccination (moderate-certainty evidence).

See Summary of findings for the main comparison.

**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 (high-certainty evidence). In year 2, trial results were more variable, with the vaccine probably preventing between 45% and 69% of typhoid cases (moderate-certainty evidence). These data included participants aged 2 to 55 years of age. The three-year cumulative efficacy of the vaccine may be around 55% (low-certainty evidence). These data were taken from a single trial conducted in South Africa in the 1980s in participants aged 5 to 15 years.

Compared with placebo, this vaccine probably did not increase the incidence of fever (moderate-certainty evidence) or erythema (low-certainty evidence); however, swelling (moderate-certainty evidence) and pain at the injection site (moderate-certainty evidence) were more common in the vaccine group.

See Summary of findings 2.

**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 (moderate-certainty evidence). These data were taken from a single trial with children two to five years of age conducted in Vietnam.

Compared with placebo, both the first and the second dose of this vaccine increased the risk of fever (low-certainty evidence) and the second dose increased the incidence of swelling at the injection site (moderate-certainty evidence).

See Summary of findings 3.

**Vi-TT vaccine (two doses)**

We are uncertain of the efficacy of administering two doses of Vi-TT (PedaTyph) in typhoid cases in children during the first year after vaccination (very low-certainty evidence). These data are taken from a single cluster-randomized trial in children aged six months to 12 years conducted in India.

See Summary of findings 4.

WIth all vaccines, there were no reported serious adverse effects in RCTs.

## 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 (three doses) and the Vi polysaccharide vaccine was 50% (95% CI 35% to 61%) and 55% (95% CI 30% to 70%), respectively. Both of these vaccines are widely used but are not immunogenic in children under two years old, which is a limitation. A recent systematic review into burden of enteric fever in children found contradictory evidence on the prevalence of typhoid fever in children under the age of five, with a suspected hidden burden, which may be multi-factorial but includes diagnostic difficulties in this age group (Britto 2017). The newer typhoid conjugate vaccines address this gap, as they are suitable to use in children under two years of age. 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 and has not been used commercially. Adverse events were mild in nature and, for the most part, were not significantly different between vaccine and placebo groups.

There is information on efficacy in Asia for each of the vaccines. There is limited data on efficacy of typhoid fever vaccination in Africa, with one trial in Egypt for Ty21a, Wahdan 1980a EGY, and one ViPs trial in South Africa, Klugman 1987 ZAF. There is no information on efficacy of typhoid vaccination in sub-Saharan Africa. There is evidence on efficacy for Ty21a in South America (Levine 1987i CHL), but not for any of the other vaccines.

The newer typhoid conjugate vaccines Vi-TT (PedaTyph and Typbar-TCV) show promise in immunogenicity studies but as of yet efficacy data are only available for PedaTyph (two doses intramuscularly; Mitra 2016 IND). In October 2017, the WHO's strategic advisory group of experts (SAGE) recommended Typbar-TCV (1 dose intramuscularly; Mohan 2015) for children over six months in typhoid endemic countries (WHO SAGE 2017), and in 2018 the WHO recommended this vaccine as the preferred choice for adults and children from six months to 44 years of age (WHO 2018a). In a human challenge setting Typbar-TCV demonstrated similar levels of efficacy in healthy adults to ViPS (Jin 2017), with higher rates of seroconversion and higher antibody GMTs in the conjugate vaccine group. At the time of writing, there were no efficacy data on Typbar-TCV from field trials. Although promising, it is important to remember that human challenge studies are inherently small. In addition, the bacterial load and the timing of vaccination in relation to the challenge are highly controlled. These studies cannot replace large-scale real-life RCTs as sole evidence for approval of new vaccines but could be incorporated into a more efficient approval process. An RCT assessed Typbar-TCV versus ViPS for immunogenicity and safety in people aged 2 to 45 years old (Mohan 2015). Infants and children aged 6 to 23 months were observed in a non-controlled parallel trial. As there was no placebo control group, the trial could not assess adverse events from Typbar-TCV, but these were reported as similar with TCV and ViPs, fever being the most common, with a single serious adverse event deemed unrelated to the vaccine. In an observational group of children under two years in the same study, authors again described adverse events as uncommon, with fever being the most usual (Mohan 2015).

From the evidence available we cannot comment on vaccine herd protection. As typhoid fever is spread faeco-orally through contaminated food and water, it is plausible that if endemic populations began to routinely use the vaccines, intensity of transmission would be reduced due to a subsection of the population who were protected against infection (Clemens 2011). However, we did not find any studies describing the effect of vaccination on disease burden in the rest of the community.

## Quality of the evidence

We assessed the certainty of evidence provided by the randomized studies using the GRADE approach, presenting our assessments

in Summary of findings for the main comparison, Summary of findings 2, Summary of findings 3, and Summary of findings 4.

For the most widely used vaccines, oral Ty21a and ViPS, the evidence of benefit is of moderate certainty. A main limitation for us with Ty21a was the lack of cluster adjustment in trials using this method. For our meta-analysis we estimated the effect of clustering, extrapolating from a ViPs trial where clustering was taken into account. For this reason we downgraded certainty to moderate. Although there is moderate unexplained heterogeneity in the 2.5 to 3 year cumulative efficacy of Ty21a, the CIs fall within a clinically important threshold, meaning the heterogeneity is unlikely be clinically significant.

For ViPs the certainty of evidence for efficacy in year 1 was high, but we downgraded it to moderate in the second year due to unexplained heterogeneity. Efficacy in year 3 and the 2.5-year cumulative efficacy was low, but only one trial assessed longer follow-up in South Africa in children aged 5 to 15. There was also imprecision as CIs were wide for both of these results.

The certainty of evidence for Vi-rEPA was moderate, as there was a single trial, in one location (Vietnam) and only in children aged two to five.

Certainty of evidence for the new Vi-TT vaccine is too limited to clearly make a recommendation for its adoption. The certainty of evidence for Vi-TT (PedaTyph) is very low. There was lack of adjustment for cluster-randomization and a risk of bias (funding by vaccine manufacturer, differing socioeconomic status between vaccine and control group, and selective outcome reporting). As the efficacy data is limited to one trial in children aged six months to 12 years in one location in India, we also downgraded the certainty of evidence for indirectness. The longer-term protection for PedaTyph is still unknown, as only one-year follow-up data are available.

There were no serious adverse events reported for any of the vaccines, so we could not assess certainty of evidence.

### Potential biases in the review process

We estimated an ICC for unadjusted cluster-randomized trials that might not be precise. We did not conduct sensitivity analyses for the ICC, but we took a conservative approach and believe that the estimates are reasonable.

Diagnosis of typhoid fever remains a challenge, which may have affected the trial results for all of the vaccines. Our analysis for vaccine efficacy relies on blood-culture positive typhoid fever; typhoid fever cases that are blood culture negative were missed. In one study the sensitivity of blood cultures compared to bone marrow cultures was only 66% (Mogasale 2014). However, all of the trials that we included used positive blood culture for diagnosis of typhoid fever, and we did not exclude any trials on this basis of the efficacy outcome definition alone. Thus, we have presented the evidence as completely as possible.

None of the vaccines identified protect against *S.* Paratyphi A, the other 'typhoidal' serovar of *Salmonella,* and most vaccine trials did not include outcomes for incidence of paratyphoid fever. Thus results reflect efficacy against typhoid fever caused by*S.* Typhi alone and do not reflect the overall efficacy against the disease in locations where *S.* Paratyphi*A* causes a significant number of cases.

We excluded human challenge studies as the bacterial inoculum in challenge trials is much higher and the timing of infection relative to vaccination is highly controlled compared to the real life situation, meaning the effect in real life is more difficult to extrapolate.This could have introduced bias against this vaccine because we had fewer data available for some of the newer vaccines, as human challenge studies provide results in a more time- and cost-efficient manner compared to large scale implementation in RCTs. We are examining the methodological aspects of this approach of evaluating vaccines and how best to assess and present human challenge studies.

### Agreements and disagreements with other studies or reviews

No other systematic reviews were identified since the last publication of this review in 2014.

WHO recommends ViPS in people over two years old and oral Ty21a enteric capsules in people over six in areas with endemic typhoid fever and for outbreak control. This review provides evidence in support of this recommendation. The WHO recommends Vi-TT Typbar-TCV for infants and children over six months old in typhoid endemic with catch-up vaccination where feasible (WHO 2018a). This review does not provide evidence for this recommendation, but it is likely that updates will when the ongoing studies investigating Vi-TT Tybar-TCV are completed (ISRCTN11643110; ISRCTN43385161; NCT03299426).

## AUTHORS' CONCLUSIONS

### Implications for practice

Based on the available evidence from natural exposure, the currently licensed Ty21a and Vi polysaccharide vaccines are efficacious for preventing typhoid fever in children aged two years or older and in young adults living in typhoid-endemic regions. Factors such as costs, availability and convenience of administration may determine which vaccine is chosen for use.

We are uncertain of the effects of Vi-TT on typhoid fever, and further data are needed to assess PedaTyph and Typbar-TCV efficacy in adults and children evaluated through natural exposure. The recent approval of conjugate typhoid vaccine Typbar-TCV for use in endemic countries by the WHO and SAGE; together with the formation of the Typhoid Vaccine Acceleration Consortium (TyVAC); results of some seroefficacy studies (Voysey 2018); and the pending results of Typbar-TCV RCTs currently being conducted in Malawi (NCT03299426), Nepal (ISRCTN43385161), and Bangladesh (ISRCTN11643110), will help establish the firm knowledge base required for the introduction of typhoid conjugate vaccines to endemic countries (Meiring 2017).

### Implications for research

An effective typhoid vaccine is still needed for children under two years of age. The new Vi-TT vaccines are promising; however, at present there was only one trial available, which we judged to have very low certainty-evidence. Further efficacy data are pending and are likely to change this certainty when available. Neither the Vi polysaccharide vaccine nor the Ty21a vaccine is licensed for children younger than two years of age. Future trials should be sufficiently powered to present results stratified by age group. This would mean that vaccine efficacy in different groups could be

analysed and would ensure that vaccine delivery can be targeted appropriately (for example, via a school-based programme or through the expanded programme of immunization (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

Dr Michael Eisenhut was the Academic Editor of this review update.

We thank the author team of the previous version of this review (Elspeth Anwar, Elad Goldberg, Abigail Fraser, Camilo Acosta, and Leonard Leibovici).

We thank Paul Garner and the Cochrane Infectious Diseases Group (CIDG) for support and assistance provided. We thank Vittoria Lutje, CIDG Information Specialist, for writing and performing the search strategy. The CIDG editorial base is funded by the UK Department for International Development (DFID) for the benefit of low- and middle-income countries (Grant: 5242).

The World Health Organization (WHO) and the SAGE Working Group on Typhoid Vaccines in reviewing and advising on a provisional report of the results.

The WHO provided funds through a grant to Cochrane Response for author salary to complete this update.

# 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}*

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.

**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. Development of Vaccines and Drugs Against Diarrhea. 11th Noble Conference; 1985; Stockholm. Lund, Sweden: Studentlitteratur, 1986:90-101.

**Levine 1986ii 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; 1985; Stockholm. Lund, Sweden: Studentlitteratur, 1986:90-101.

**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}*

Levine MM, Taylor DN, Ferreccio C. Typhoid vaccines come of age. *Pediatric Infectious Disease Journal* 1989;**8**(6):374-81.

**Levine 1987iii CHL** *{published data only}*

Levine MM, Taylor DN, Ferreccio C. Typhoid vaccines come of age. *Pediatric Infectious Disease Journal* 1989;**8**(6):374-81.

**Levine 1987iv CHL** *{published data only}*

Levine MM, Taylor DN, Ferreccio C. Typhoid vaccines come of age. *Pediatric Infectious Disease Journal* 1989;**8**(6):374-81.

**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}*

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.

**Lin 2001 VNM** *{published data only}*

Lanh MN, Van Bay P, Ho VA, Thanh TC, 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.

* 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.

**Mitra 2016 IND** *{published data only}*

Mitra M, Shah N, Ghosh A, Chatterjee S, Kaur I, Bhattacharya N, et al. Efficacy and safety of vi-tetanus toxoid conjugated typhoid vaccine (PedaTyph™) in Indian children: School based cluster randomized study. *Human Vaccines & Immunotherapeutics* 2016;**12**(4):939-45.

**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}*

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.

**Sur 2009 IND** *{published and unpublished data}*

Sur D, Ochiai RL, Bhattacharya SK, Ganguly NK, Ali M, Manna B, et al. A cluster-randomized effectiveness trial of Vi typhoid vaccine in India. *New England Journal of Medicine* 2009;**361**(4):335-44.

**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 1997 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.

**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, Zhang J, Park JK, Zhu F, et al. Revaccination with locally-produced Vi typhoid polysaccharide vaccine among Chinese school-aged children: safety and immunogenicity findings. *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**(2):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**(5):631-4.

**Bhutta 2014** *{published data only}*

Bhutta ZA, Capeding MR, Bavdekar A, Marchetti E, Ariff S, Soofi SB, et al. Immunogenicity and safety of the Vi-CRM197 conjugate vaccine against typhoid fever in adults, children, and infants in south and southeast Asia: results from two randomised, observer-blind, age de-escalation, phase 2 trials. *Lancet Infectious Diseases* 2014;**14**(2):119-29.

**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.

**Blomke 2017** *{published data only}*

Blohmke CJ, Hill J, Darton TC, Carvalho-Burger M, Eustace A, Jones C, et al. Induction of cell cycle and NK cell responses by live-attenuated oral vaccines against typhoid fever. *Frontiers in Immunology* 2017;**8**:1276.

**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, issue 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.

**Darton 2016** *{published data only}*

Darton TC, Jones C, Blohmke CJ, Waddington CS, Zhou L, Peters A, et al. Using a Human Challenge Model of Infection to Measure Vaccine Efficacy: A Randomised, Controlled Trial Comparing the Typhoid Vaccines M01ZH09 with Placebo and Ty21a. *PLOS Neglected Tropical Diseases* 2016;**10**(8):e0004926.

**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):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**(3):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):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.

**House 2011** *{unpublished data only}*

EUCTR 2011-003653-26-GB. Understanding immunity after typhoid vaccination [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.]. clinicaltrialsregister.eu/ctr-search/trial/2011-003653-26/GB EUCTR Identifier: (first received 12 December 2011).

**Jin 2017** *{published data only}*

Jin C, Gibani MM, Moore M, Juel HB, Jones E, Meiring J, et al. Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomised controlled, phase 2b trial. *Lancet* 2017;**390**(10111):2472-80.

**Juel 2018** *{published data only}*

Juel HB, Thomaides-Brears HB, Darton T, Jones C, Jones E, Shrestha S, et al. Salmonella Typhi bactericidal antibodies reduce disease severity but do not protect against typhoid fever in a controlled human infection model. *Frontiers in Immunology* 2017;**8**:1916.

**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.

**Meiring 2017** *{published data only}*

Meiring JE, Gibani M. The Typhoid Vaccine Acceleration Consortium (TyVAC): Vaccine effectiveness study designs: Accelerating the introduction of typhoid conjugate vaccines and reducing the global burden of enteric fever. Report from a meeting held on 26-27 October 2016, Oxford, UK. *Vaccine* 2017;**35**(38):5081-8.

**Mohan 2015** *{published data only}*

Mohan VK, Varanasi V, Singh A, Pasetti MF, Levine MM, Venkatesan R, Ella KM. Safety and immunogenicity of a Vi polysaccharide–tetanus toxoid conjugate vaccine (Typbar-TCV) in healthy infants, children, and adults in typhoid endemic areas: a multicenter, 2-cohort, open-label, double-blind, randomized controlled phase 3 study. *Clinical Infectious Diseases* 2015;**61**(3):393-402.

**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.

**Ochiai 2014** *{published data only}*

Ochiai RL, Khan MI, Soofi SB, Sur D, Kanungo S, You YA, et al. Immune responses to Vi capsular polysaccharide typhoid vaccine in children 2 to 16 years old in Karachi, Pakistan, and Kolkata, India. *Clinical and Vaccine Immunology* 2014;**21**(5):661-6.

**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. *Southeast Asian Journal of Tropical Medicine and Public Health* 2006;**37**(3):515-22.

**Thiem 2011** *{published data only}*

Thiem VD, Lin FY, Son NH, Anh DD, Mao ND, Chu C. 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.

**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.

**Voysey 2018** *{published data only}*

Voysey M, Pollard AJ. Sero-efficacy of Vi-polysaccharide tetanus-toxoid typhoid conjugate vaccine (Typbar-TCV). Clinical Infectious Diseases 2018 Jan 17 [Epub ahead of print]. [DOI: 10.1093/cid/cix1145]

**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;**22**(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**(3):357-69.

Yugoslav Typhoid Commission. Field and laboratory studies with typhoid vaccines. A preliminary report. *Bulletin of the World Health Organization* 1957;**16**(5):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**(5):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

**ISRCTN11643110** *{unpublished data only}*

ISRCTN11643110. TyVAC Bangladesh: Typhoid Vaccine Trial [Assessing the impact of a Vi-Polysaccharide Conjugate Vaccine in preventing typhoid infection among Bangladeshi children – a Phase IV trial]. isrctn.com/ISRCTN11643110 (first received 5 February 2018).

**ISRCTN43385161** *{unpublished data only}*

ISRCTN43385161. TyVAC Nepal: typhoid vaccine study [Assessing the impact of a Vi-Polysaccharide Conjugate Vaccine in preventing typhoid infection among Nepalese children – a Phase III trial]. isrctn.com/ISRCTN43385161 (first received 20 June 2017).

**NCT03299426** *{unpublished data only}*

NCT03299426. Clinical efficacy of typhoid conjugate vaccine (Vi-TCV) among children age 9 months through 12 years in Blantyre, Malawi [A Phase III Randomized, Double-Blind, Controlled Trial of the Clinical Efficacy of Typhoid Conjugate Vaccine (Vi-TCV) Among Children Age 9 Months Through 12 Years in Blantyre, Malawi]. clinicaltrials.gov/show/NCT03299426 (first received 3 October 2017).

## Additional references

**Andrews 2015**

Andrews JR, Ryan ET. Diagnostics for invasive Salmonella infections: current challenges and future directions. *Vaccine* 2015;**33**(3):C8-15.

**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.

**Britto 2017**

Britto C, Pollard AJ, Voysey M, Blohmke CJ. An appraisal of the clinical features of pediatric enteric fever: systematic review and meta-analysis of the age-stratified disease occurrence. *Clinical Infectious Diseases* 2017;**64**(11):1604-11.

**Clemens 2011**

Clemens J, Shin S, Ali M. New approaches to the assessment of vaccine herd protection in clinical trials. *Lancet Infectious Diseases* 2011;**11**(6):482-7.

**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 2015**

Crump JA. Building the case for wider use of typhoid vaccines. *Vaccine* 2015;**33**(3):C1-2.

**Date 2015**

Date KA, Bentsi-Enchill A, Marks F, Fox K. Typhoid fever vaccination strategies. *Vaccine* 2015;**33**(3):C55-61.

**DeRoeck 2008**

Deroeck D, Ochiai L, Yang J, Anh D, Alag V, Clemens J. Typhoid vaccination: the Asian experience. *Expert Review of 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 2011**

Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org. The Cochrane Collaboration.

**Jensenius 2013**

Jensenius M, Han PV, Schlagenhauf P, Schwartz E, Parola P, Castelli F, et al. Acute and potentially life-threatening tropical diseases in western travelers—a GeoSentinel multicenter study, 1996–2011. *American Journal of Tropical Medicine and Hygiene* 2013;**88**(2):397-404.

**Jüni 2001**

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

**Kariuki 2015**

Kariuki S, Gordon MA, Feasey N, Parry CM. Antimicrobial resistance and management of invasive Salmonella disease. *Vaccine* 2015;**33**(3):C21-9.

**Keddy 2011**

Keddy KH, Sooka A, Letsoalo ME, Hoyland G, Chaignat CL, Morrissey AB, Crump JA. Sensitivity and specificity of typhoid fever rapid antibody tests for laboratory diagnosis at two sub-

Saharan African sites. *Bulletin of the World Health Organization* 2011;**89**(9):640-7.

**MacLennan 2014**

MacLennan CA, Martin LB, Micoli F. Vaccines against invasive Salmonella disease: current status and future directions. *Human Vaccines & Immunotherapeutics* 2014;**10**(6):1478-93.

**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. *Lancet* 2012;**379**(9817):699-700.

**Mogasale 2014**

Mogasale V, Maskery B, Ochiai RL, Lee JS, Mogasale VV, Ramani E, et al. Burden of typhoid fever in low-income and middle-income countries: a systematic, literature-based update with risk-factor adjustment. *Lancet Global Health* 2014;**2**(10):e570-80.

**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.

**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 Organization* 2008;**86**(4):260-8.

**Parry 2002**

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

**Qamar 2015**

Qamar FN, Azmatullah A, Bhutta ZA. Challenges in measuring complications and death due to invasive Salmonella infections. *Vaccine* 2015;**33**(3):C16-20.

**RevMan 2014 [Computer program]**

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

**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.

**Savović 2012**

Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. *Annals of Internal Medicine* 2012;**157**(6):429-38.

**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.

**Steele 2016**

Steele AD, Burgess DC, Diaz Z, Carey ME, Zaidi AK. Challenges and opportunities for typhoid fever control: a call for coordinated action. *Clinical Infectious Diseases* 2016;**62**(1):S4-8.

**Thriemer 2013**

Thriemer K, Ley B, Menten J, Jacobs J, van den Ende J. Review and meta-analysis of the performance of two point of care typhoid fever tests, Tubex TF and Typhidot, in endemic countries. *PLOS ONE* 2013;**8**(12):e81263.

**Wain 2015**

Wain J, Hendriksen RS, Mikoleit ML, Keddy KH, Ochiai RL. Typhoid Fever. *Lancet* 2015;**385**(9973):1136-45.

**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. Diarrhoeal diseases. State of the Art of Vaccine Research and Development. Geneva: World Health Organization, 2005.

**WHO 2008**

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

**WHO 2018a**

World Health Organization. Tyhoid vaccines: WHO position paper - March 2018. Weekly Epidemiological Record 2018; Vol. 93, issue 13:154-72, Available from: apps.who.int/iris/bitstream/handle/10665/272272/WER9313.pdf?ua=1 (last accessed 23 April 2018).

**WHO 2018b**

World Health Organization. Table 1: Summary of WHO position papers - recommendations for routine immunization. cdrwww.who.int/immunization/policy/Immunization_routine_table1.pdf Updated April 2018 (accessed 30 April 2018).

**WHO SAGE 2017**

WHO Strategic Advisory Group of Experts (SAGE) on Immunization. Summary of the October 2017 meeting of the Strategic Advisory Group of Experts on Immunization. October 2017. www.who.int/immunization/policy/sage/SAGE_oct_2017_meeting_summary.pdf?ua=1 (accessed prior to 31 October 2017).

## References to other published versions of this review

**Anwar 2014**

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. [DOI: 10.1002/14651858.CD001261.pub3]

**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<br><br>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 postvaccination) |
| Participants | Number: 6907<br><br>Inclusion criteria: age 5 to 44 years<br><br>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<br>2. Pneumococcal vaccine: 25 µg; 3450 participants<br><br>Route and schedule: intramuscular injection; 1 dose<br><br>Concomitant medication: not specified |
| Outcomes | 1. Typhoid fever cases (*S.* Typhi bacteraemia)<br>2. Adverse events |
| Notes | Location: 5 villages near Kathmandu, Nepal<br><br>Socioeconomic description: rural, low income<br><br>Setting: home<br><br>Date: 1986 to 1988<br><br>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 |

**Acharya 1987 NPL** *(Continued)*

| | | |
|---|---|---|
| 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 |
| Other bias | Low risk | None |

**Black 1990i CHL**

| | |
|---|---|
| Methods | Design: cluster-RCT (classroom)<br>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<br>Number of classrooms: 3655<br>Inclusion criteria: age 5 to 22 years<br>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<br>2. Placebo: in enteric-coated capsule; 27,305 participants<br>Route and schedule: oral; 2 doses, 1 week apart<br>Concomitant medication: not specified |
| Outcomes | Typhoid fever cases (*S.* Typhi bacteraemia or in bone marrow) |
| Notes | Location: northern area of Santiago, Chile<br>Socioeconomic description: no details<br>Setting: school<br>Date: 1982 to 1987<br>No demographic information |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Generation of allocation sequence: unclear |

**Black 1990i CHL** *(Continued)*

| | | |
|---|---|---|
| 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 |
| Other bias | Unclear risk | Unclear whether data were adjusted for clustering |

**Black 1990ii CHL**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | 1. Lyophilized attenuated *S.* Typhi strain Ty21a: enteric-coated capsule containing 2-5 × $10^9$ viable Ty21a; 27,618 participants<br>2. Placebo: in enteric-coated capsule; 27,305 participants<br>Route and schedule: oral; 1 dose (2nd dose contained placebo in all participants)<br>Concomitant medication: not specified |
| Outcomes | |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | |
| Blinding (performance bias and detection bias) All outcomes | Low risk | |
| Selective reporting (reporting bias) | Low risk | |

**Cryz 1993 THA**

| | |
|---|---|
| Methods | Design: individual-RCT |
| Participants | Number: 634 |

**Cryz 1993 THA** *(Continued)*

| | |
|---|---|
| | Inclusion criteria: children 2 to 6 years old with no history of typhoid fever<br>Exclusion criteria: no details |
| Interventions | 1. Ty21a liquid formulation<br>2. Placebo<br>Route and schedule: oral solution; 3 doses |
| Outcomes | 1. Adverse events<br>2. Immunogenicity |
| Notes | Location: Thailand<br>Socioeconomic description: no details<br>Date: no details<br>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)<br>All outcomes | Low risk | Double-blind |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Number of participants per study arm not specified |
| Selective reporting (reporting bias) | Unclear risk | Insufficient information to permit judgement |
| Other bias | Low risk | None |

**Keitel 1994 USA**

| | |
|---|---|
| Methods | Design: individually based RCT<br>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<br>Inclusion criteria: age 8 to 40 years; healthy; no previous typhoid vaccination<br>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 |

**Keitel 1994 USA** *(Continued)*

| | |
|---|---|
| | 2. Placebo: 86 participants<br>Route and schedule: intramuscular injection; 1 dose<br>Concomitant medication: not specified |
| Outcomes | 1. Adverse events<br>2. Immunogenicity |
| Notes | Location: Houston, Texas, USA<br>Socioeconomic description: urban, high income<br>Setting: clinic<br>Date: no information<br>No demographic information<br>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)<br>All outcomes | Low risk | Double-blind |
| Incomplete outcome data (attrition bias)<br>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-RCT (geographic clusters)<br>Intermediate surveillance for efficacy: participants were identified through 3 study health centres during study period (2 years)<br>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<br>120 geographic clusters using the geographic information system (GIS) imagery (60 clusters in each study arm) |

**Khan 2012 PAK** *(Continued)*

| | |
|---|---|
| | Inclusion criteria: children between the ages of 2 and 16 years<br><br>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 |
| Interventions | 1. Single-dose capsular polysaccharide of *S.* Typhi, Vi vaccine (dose 25 mcg)<br>2. Hepatitis A vaccine (dose 720 IU)<br><br>Route and schedule: single intramuscular injection, Vi vaccine or hepatitis A vaccine |
| Outcomes | 1. Typhoid fever cases (*S.* Typhi bacteraemia)<br>2. Indirect protection from typhoid fever<br>3. Adverse events |
| Notes | Location: Karachi, Pakistan<br><br>Socioeconomic description: low-socioeconomic urban squatter settlements<br><br>Date: 2002 and 2007<br><br>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)<br>All outcomes | Low risk | Participants and investigators blinded – vaccines identified only by code. One vaccine administered per cluster |
| Incomplete outcome data (attrition bias)<br>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: individually based RCT<br><br>Active surveillance for efficacy: blood cultures if febrile with no obvious clinical cause |
| Participants | Number: 11,384<br><br>Inclusion criteria: 5 to 15 years<br><br>Exclusion criteria: no details |

**Klugman 1987 ZAF** *(Continued)*

| | |
|---|---|
| Interventions | 1. Capsular polysaccharide of *S.* Typhi, Vi vaccine: 25 µg Vi; 5692 participants<br>2. Meningococcal vaccine: 25 µg Vi; 5692 participants<br>Route and schedule: intramuscular injection; 1 dose<br>Concomitant medication: not specified |
| Outcomes | 1. Typhoid fever cases (*S.* Typhi bacteraemia)<br>2. Immunogenicity |
| Notes | Location: eastern Transvaal area of South Africa<br>Socioeconomic description: no details<br>Setting: school<br>Date: 1985 to 1988<br>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)<br>All outcomes | Low risk | Double-blind. Vaccines identical in appearance |
| Incomplete outcome data (attrition bias)<br>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: individually based RCT<br>Active surveillance for adverse events: no further details |
| Participants | Number: 539<br>Inclusion criteria: adults, no details<br>Exclusion criteria: no details |
| Interventions | 1. Enteric-coated capsules *S.* Typhi Ty21a vaccine: 172 participants<br>2. Placebo: 367 participants |

**Levine 1986i CHL** *(Continued)*

| | |
|---|---|
| | Route and schedule: oral capsules; 3 doses<br>Concomitant medication: not specified |
| Outcomes | Adverse events |
| Notes | Location: Chile<br>Socioeconomic description: no details<br>Setting: no details<br>Date: no details<br>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)<br>All outcomes | Low risk | Blinding: double-blind (no details) |
| Incomplete outcome data (attrition bias)<br>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<br>Inclusion criteria: children, no details<br>Exclusion criteria: no details |
| Interventions | 1. *S.* Typhi Ty21a vaccine in milk with NaHCO3S: 172 participants<br>2. Placebo: 172 participants<br>Route and schedule: oral capsules; 3 doses<br>Concomitant medication: not specified |
| Outcomes | Details as for Levine 1986i CHL |

**Levine 1986ii CHL** *(Continued)*

| | |
|---|---|
| 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-RCT (classroom)<br>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<br>Number of classrooms: 4312<br>Inclusion criteria: age 6 to 21 years; parental consent; no further details<br>Exclusion criteria: no details |
| Interventions | 1. Enteric capsules of *S.* Typhi, Ty21a vaccine: 21,598 participants<br>2. Placebo: 5476 participants (placebo group divided into 4 equal groups for the comparison)<br>Route and schedule: oral capsules; 3 doses given 21 days apart<br>Concomitant medication: not specified |
| Outcomes | Typhoid fever cases (*S.* Typhi bacteraemia, in bone marrow or in duodenal fluid) |
| Notes | Location: Chile socioeconomic description: no details<br>Setting: school<br>Date: 1983 to 1986<br>No demographic information |

**Levine 1987i CHL** *(Continued)*

***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)<br>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<br>2. Placebo: 5477 participants (placebo group divided into 4 equal groups for the comparison)<br>Route and schedule: oral capsules; 3 doses given 2 days apart<br>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 |

**Levine 1987ii 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 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:<br>1. Gelatin capsules of *S.* Typhi, Ty21a vaccine: 21,541<br>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 |
| 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)<br>Details as for Levine 1987i CHL, except blinding: placebo given in a similar regimen, but not mentioned whether identical to gelatin or enteric capsules |

**Levine 1987iv CHL** *(Continued)*

| | |
|---|---|
| Participants | Details as for Levine 1987i CHL, except number: 27,856 |
| Interventions | 1. Gelatin capsules of *S.* Typhi, Ty21a vaccine: 22,379 participants<br>2. Placebo: 5477 participants (placebo group divided into 4 equal groups for the comparison)<br>Route and schedule: oral capsules; 3 doses given 2 days apart<br>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)<br>All outcomes | Low risk | Details as for Levine 1987i CHL |
| Incomplete outcome data (attrition bias)<br>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-RCT (classroom)<br>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<br>Number of classes: 5423<br>Inclusion criteria: 5 to 19 years old; parental consent; no further details<br>Exclusion criteria: no details |
| Interventions | 1. Liquid formulation of *S.* Typhi, Ty21a vaccine: 36,623 participants<br>2. Placebo: 5450 participants<br>Route and schedule: oral solution; 3 doses given 2 days apart<br>Concomitant medication: not specified |

**Levine 1990i CHL** *(Continued)*

| | |
|---|---|
| Outcomes | Typhoid fever cases (*S.* Typhi bacteraemia, in bone marrow or in duodenal fluid) |
| Notes | Location: Chile<br>Socioeconomic description: no details<br>Setting: school<br>Date: 1986 to 1991<br>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)<br>All outcomes | Low risk | Double-blind. Identical packets and capsules |
| Incomplete outcome data (attrition bias)<br>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)<br>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:<br>1. Enteric capsules of *S.* Typhi, Ty21a vaccine: 34,696 participants<br>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 |
|---|---|---|

**Levine 1990ii CHL** *(Continued)*

| | | |
|---|---|---|
| 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)<br>All outcomes | Low risk | Details as for Levine 1990i CHL |
| Incomplete outcome data (attrition bias)<br>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: individually based RCT<br>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<br>Passive surveillance: 19 additional months |
| Participants | Number: 12,008<br>Inclusion criteria: age 2 to 5 years; no further details<br>Exclusion criteria: illnesses that required ongoing medical care; fever > 37.5°C at first injection |
| 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<br>2. Placebo: 6017 participants<br>Route and schedule: intramuscular injection; 2 doses, 6 weeks apart<br>Concomitant medication: not specified |
| Outcomes | 1. Typhoid fever cases (*S.* Typhi bacteraemia)<br>2. Adverse events<br>3. Immunogenicity<br>Subgroups for gender, age and study year |
| Notes | Location: Dong Thap Province, Mekong Delta, Vietnam<br>Socioeconomic description: rural; low income<br>Setting: home<br>Date: 1998 to 2000 |

**Lin 2001 VNM** *(Continued)*

| | |
|---|---|
| | 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)<br>All outcomes | Low risk | Double-blind. Vaccine and placebo vials indistinguishable |
| Incomplete outcome data (attrition bias)<br>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 |

**Mitra 2016 IND**

| | |
|---|---|
| Methods | Design: open label, cluster-RCT (school)<br><br>12 months active follow-up: weekly telephone follow-up, monthly social worker follow-up in school, school absenteeism record and subject diary kept by parent (collected after 12 months) |
| Participants | Number: 1765<br><br>Inclusion criteria: children 6 months to 12 years old. 12 schools in 2 municipal wards in Kolkata, India. Voluntary written informed consent from parent/guardian.<br><br>Siblings of school children aged 6 months to 3 years were also invited.<br><br>Exclusion criteria: fever > 38.5°C at time of enrolment or history of undiagnosed fever/infection of more than 3 days duration within 1 month prior to vaccination, established or clinically suspected immunosuppressive or immune compromised disorder/state (congenital or acquired drug induced, neoplastic, TB etc), anyone who had a typhoid vaccination in the last 3 years and with a known allergy to any of the components in PedaTyph |
| Interventions | 1. PedaTyph (test group): containing 5micrograms of Vi polysaccharide of S. Typhi conjugated to 5 µg of tetanus toxoid (Vi-TT): 905 participants<br>2. Normal vaccination course (control): 860 participants<br><br>Route and administration: 2 doses of PedaTyph vaccine 0.5 mL administered intramuscularly in the upper arm with a 6 week interval between doses<br><br>Concomitant medication: not specified |
| Outcomes | 1. Microbiologically proven (BACTEC positive) Typhoid fever<br>2. Immunogenicity |

**Mitra 2016 IND** *(Continued)*

| | |
|---|---|
| | 3. Adverse effects at 30 minutes, 1 month and clinical events up to 12 months (observational as no placebo comparison) |
| Notes | Location: Kolkata, India<br>Socioeconomic description: low income, urban<br>Setting: school<br>Date: no details |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Statistician used graph pad software to generate random numbers to assign clusters to vaccine and control group |
| Allocation concealment (selection bias) | Low risk | Allocation by a statistician who was blinded as to clusters |
| Blinding (performance bias and detection bias)<br>All outcomes | High risk | Open label – no placebo |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 6 lost to follow-up in test group due to moving out of area. Although 140 patients in the test group did not get the second dose of the vaccine they were all followed up |
| Selective reporting (reporting bias) | High risk | Paratyphoid cases were not reported (as was intended in the protocol registered prospectively). |
| Other bias | High risk | According to prospectively published protocol, funding was by the company who manufacturers the Peda Typh vaccine (no mention of this in the published trial)<br>The intervention and the control group were very different in terms of socioeconomic status, with lower status in the control group.<br>The trial results were unadjusted for cluster randomization. |

**Olanratmanee 1992 THA**

| | |
|---|---|
| Methods | Design: individually based RCT<br>Active surveillance for adverse events: 1.5 hours of observation and parental reporting via adverse event report sheet |
| Participants | Number: 170<br>Inclusion criteria: age 4 to 6 years; no further details<br>Exclusion criteria: no details |
| Interventions | 1. Liquid formulation of *S.* Typhi, TY21a: 88 participants<br>2. Placebo: 82 participants<br>Route and schedule: oral solution; 3 doses, alternate days |

**Olanratmanee 1992 THA** *(Continued)*

| | |
|---|---|
| | Concomitant medication: not specified |
| Outcomes | 1. Adverse events<br>2. Immunogenicity |
| Notes | Location: Thailand<br>Socioeconomic description: no details<br>Setting: clinic<br>Date: no details<br>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)<br>All outcomes | Low risk | Double-blind. Identical vaccine and placebo packages |
| Incomplete outcome data (attrition bias)<br>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: individually based RCT<br>Intermediate surveillance for efficacy: isolation of *S.* Typhi from blood during trial (2.5 years)<br>Surveillance for adverse events: questionnaires collected from 588 individuals |
| Participants | Number: 10,212<br>Inclusion criteria: age 3 to 44 years; no further details<br>Exclusion criteria: pregnant women; febrile illness |
| Interventions | 1. Liquid formulation of *S.* Typhi, Ty21a: 5066 participants<br>2. Placebo: 5146 participants<br>Route and schedule: oral solution; 3 doses, 1 week apart<br>Concomitant medication: not specified |

**Simanjuntak 1991i IDN** *(Continued)*

| | |
|---|---|
| | Note Simanjuntak 1991ii IDN is 2 different arms 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)<br>2. Adverse events<br><br>Subgroups for age and study year |
| Notes | Location: Plaju and Sungai Gerong, Sumatra, Indonesia<br><br>Socioeconomic description: no details<br><br>Setting: clinic<br><br>Date: 1986 to 1989<br><br>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)<br>All outcomes | Low risk | Double-blind. Identical vaccine and placebo |
| Incomplete outcome data (attrition bias)<br>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 |
| Other bias | Low risk | None |

**Simanjuntak 1991ii IDN**

| | |
|---|---|
| Methods | See Simanjuntak 1991i IDN (Simanjuntak 1991ii IDN is a different arm of the same trial)<br><br>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<br>2. Placebo: 5122 participants<br><br>Route and schedule: oral capsules; 3 doses, 1 week apart<br>Concomitant medication: not specified |

**Simanjuntak 1991ii IDN** *(Continued)*

| | |
|---|---|
| | Note Simanjuntak 1991i IDN is two different arms of the same trial (see above 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-RCT (geographic clusters)<br><br>Active surveillance for efficacy: 5 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)<br><br>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<br><br>80 contiguous geographic clusters (40 clusters in each study group)<br><br>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<br><br>Exclusion criteria: not stated |
| Interventions | 1. Single-dose capsular polysaccharide of *S.* Typhi, Vi vaccine (dose 25 mcg)<br>2. Inactivated hepatitis A vaccine (dose 720 IU for children 2 to 18, 1440 IU for adults)<br><br>Route and schedule: single intramuscular injection, Vi vaccine or inactivated hepatitis A vaccine |
| Outcomes | 1. Typhoid fever cases (*S.* Typhi bacteraemia) |

**Sur 2009 IND** *(Continued)*

| | |
|---|---|
| | 2. Indirect protection from typhoid fever<br>3. Adverse events |
| Notes | Location: Kolkata, India<br><br>Socioeconomic description: slum-dwelling residents<br><br>The clusters were stratified according to ward and the number of residents who were 18 years of age or younger (< 200 versus ≥ 200 people) and the number of residents who were older than 18 years (< 500 versus ≥ 500 people), resulting in 8 strata<br><br>Date: November 2004 to December 2006<br><br>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, 2 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)<br>All outcomes | Low risk | Participants and study personnel blind. Not stated whether outcome assessors were blinded |
| Incomplete outcome data (attrition bias)<br>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 |

**Wahdan 1980a EGY**

| | |
|---|---|
| Methods | Design: cluster-RCT (classroom)<br><br>Intermediate surveillance for efficacy: isolation of *S.* Typhi from blood in the hospital during the study (3 years)<br><br>Surveillance for adverse events: no details |
| Participants | Number: 32,388<br><br>Inclusion criteria: age 6 to 7 years; no further details<br><br>Exclusion criteria: no details |
| Interventions | 1. Liquid formulation of *S.* Typhi, Ty21a: 16,486 participants<br>2. Placebo: 15,902 participants |

**Wahdan 1980a EGY** *(Continued)*

| | |
|---|---|
| | Route and schedule: oral solution; 3 doses, alternate days<br>Concomitant medication: not specified |
| Outcomes | 1. Typhoid fever cases (*S.* Typhi bacteraemia)<br>2. Adverse events |
| Notes | Location: Alexandria, Egypt<br>Socioeconomic description: no details<br>Setting: school<br>Date: 1978 to 1981<br>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)<br>All outcomes | Low risk | Vaccine and placebo identical |
| Incomplete outcome data (attrition bias)<br>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-RCT (classroom)<br>Surveillance for adverse events: no details |
| Participants | Number: 884<br>Inclusion criteria: age 6 to 7 years; no further details<br>Exclusion criteria: no details<br>This trial was a pilot study done prior to Wahdan 1980a EGY (see above) to assess tolerability of the vaccines. Results were presented as part of the trial data for Wahdan 1980a EGY. |
| Interventions | 1. Liquid formulation of *S.* Typhi, Ty21a: 413 participants<br>2. Placebo: 471 participants |

**Wahdan 1980b EGY** *(Continued)*

| | |
|---|---|
| | Route and schedule: oral solution; 3 doses, alternate days<br>Concomitant medication: not specified |
| Outcomes | Adverse events |
| Notes | Location: Alexandria, Egypt<br>Socioeconomic description: no details<br>Setting: school<br>Date: 1978<br>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)<br>All outcomes | Low risk | Vaccine and placebo identical |
| Incomplete outcome data (attrition bias)<br>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 1997 CHN**

| | |
|---|---|
| Methods | Design: individually based RCT<br>Passive surveillance for efficacy: signs and symptoms of typhoid fever; blood cultures and serum Widal's test (1 year) |
| Participants | Number: 81,506<br>Inclusion criteria: age 5 to 55 years; healthy<br>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<br>2. Meningococcal vaccine: 40,388 participants<br>Route and schedule: intramuscular injection; 1 dose |

**Wang 1997 CHN** *(Continued)*

| | |
|---|---|
| | Concomitant medication: not specified |
| Outcomes | 1. Typhoid fever cases (*S.* Typhi bacteraemia)<br>2. Adverse reactions<br><br>Subgroups for age and gender |
| Notes | Location: Baoying County, Jiangsu Province, China<br><br>Socioeconomic description: no details<br><br>Setting: no details<br><br>Date: 1994 to 1995<br><br>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)<br>All outcomes | Low risk | Double-blind. Identical vaccine and placebo vials |
| Incomplete outcome data (attrition bias)<br>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 |

**Yang 2001 CHN**

| | |
|---|---|
| Methods | Design: individually based RCT<br><br>Passive surveillance for efficacy: clinical symptoms; positive blood cultures and serum Widal's test during trial (1.6 years)<br><br>Surveillance for adverse events: parental reporting of adverse effects in 3 schools |
| Participants | Number: 131,271<br><br>Inclusion criteria: healthy children aged 3 to 19 years and adults aged < 51 years<br><br>Exclusion criteria: chronic disease; under medication; pregnancy |
| Interventions | 1. Capsular polysaccharide of *S.* Typhi, Vi vaccine: 30 µg Vi; 65,287 participants<br>2. Placebo: 65,984 participants |

**Yang 2001 CHN** *(Continued)*

| | |
|---|---|
| | Route and schedule: hypodermically; 1 dose<br>Concomitant medication: not specified |
| Outcomes | 1. Typhoid fever cases (*S.* Typhi bacteraemia)<br>2. Adverse events<br>Subgroups for age, profession and sex |
| Notes | Location: county of Quan, north-eastern part of Guangxi Zhuang<br>Autonomous Region, southern China<br>Socioeconomic description: no details<br>Setting: clinic<br>Date: 1995 to 1996<br>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 |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Double-blind |
| Incomplete outcome data (attrition bias)<br>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: individually based RCT<br>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<br>Inclusion criteria: school children aged 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 |

**Zhou 2007 CHN** *(Continued)*

| | |
|---|---|
| | 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<br>2. Placebo (normal saline), 333 participants<br><br>Route and schedule: intramuscular injection, one dose |
| Outcomes | Adverse events |
| Notes | Location: Suzhou, Jiangsu, China<br><br>Socioecomic description: no details<br><br>Setting: school<br><br>Date: 2002 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | "Computer generated random numbers" |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to permit judgement |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Double-blind – blinding of participants and study personnel. Vaccine and placebo identical |
| Incomplete outcome data (attrition bias)<br>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 (for example, classrooms); **ELISA**: enzyme-linked immunosorbent assay; **individually-based 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 |

| Study | Reason for exclusion |
|---|---|
| Bhutta 2014 | No efficacy data yet for Vi-CRM197 so according to protocol cannot include for side effects/safety only |
| Black 1983 | No relevant outcome measures |
| Blomke 2017 | Additional info for Darton 2016 - human challenge study – already excluded |
| 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 |
| Darton 2016 | Human challenge study |
| Ferreccio 1989 | RCT compared different doses of the Ty21a vaccine |
| 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 |
| House 2011 | Vi-CRM197 human challenge study. Published protocol and note on register that ended prematurely |
| Jin 2017 | Vi-TT (Typbar-TCV) - human challenge study - excluded |
| Juel 2018 | Additional information on Darton 2016 – excluded as human challenge study |
| Kantele 2013 | No relevant outcome measures |
| Keddy 1999 | No relevant outcome measures |
| Khan 2007 | Non-randomized study |
| Khoo 1995 | Evaluated safety of Vi vaccine compared with meningococcal vaccine or combination |

| Study | Reason for exclusion |
|---|---|
| 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 |
| Meiring 2017 | Review article - no new trials referenced |
| Mohan 2015 | No efficacy data for Typbar TCV yet so excluded as per protocol as must have efficacy data available for vaccine for adverse effects to be included in review |
| Murphy 1991 | No random allocation to vaccine and placebo arms |
| Nisini 1993 | No random allocation |
| Ochiai 2014 | No efficacy or adverse effects/safety outcomes |
| 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 |
| 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 |
| Thiem 2011 | Adverse event only trial and placebo not used for comparison (Hibb vaccine used as comparison) |
| van Damme 2011 | Evaluated adverse events of new conjugate vaccine (Vi-CRM); no efficacy trials of this vaccine |
| Voysey 2018 | Additional data for Mohan 2015 - Vi-TT (Typbar-TCV) - no efficacy data, immunological data |
| 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]*

**ISRCTN11643110**

| | |
|---|---|
| Trial name or title | Assessing the impact of a Vi-polysaccharide conjugate vaccine in preventing typhoid infection among Bangladeshi children – a phase IV trial |
| Methods | Cluster-randomized controlled trial |
| Participants | Consenting children/guardians within the age range (9 months to < 16 years) residing in the area of Mirpur, Dhaka<br><br>Inclusion criteria:<br><br>1. Parent/guardian is willing and competent to provide informed consent. If the participant is 11 to < 16 years of age, informed assent will also be sought<br>2. Aged between 9 months (or eligible for measles vaccination according to local protocol) and <16 years (that is, up to 15 years 364 days) at time of vaccination<br>3. Apparently healthy (no complaints of febrile illness) on the day of vaccination<br>4. Parent/guardian confirms that their child will be willing and be able to comply with study requirements including follow-up contact, according to the schedule<br>5. Living within the study catchment area at the time of vaccination<br><br>Exclusion criteria:<br><br>1. Has knowingly received a typhoid or Japanese encephalitis vaccine in the last three years<br>2. Known allergy to any of the vaccine components<br>3. Medical or social reasons that will prevent the participant from conforming to the study requirements as judged by a medical professional<br>4. Planning to move away from the catchment area within the next month<br>5. Pregnant at the time of vaccination, as confirmed by a urine test (urine pregnancy test will be done in girls who are married)<br><br>Target number of participants: 43,350<br><br>150 Residential clusters of around 1250 people each are randomized in a 1:1 ratio to receive Vi-TCV or the control vaccine (SA 14-14-2). |
| Interventions | Intervention: Vi Typhoid conjugate vaccine (Vi-TCV), trade name: TyBar<br>Control: Japanese encephalitis vaccine: trade name: SA14-14-2, Japanese encephalitis vaccine, Live |
| Outcomes | Primary outcome: the efficacy and rate reduction of the Vi-TCV in preventing blood culture-confirmed symptomatic infection caused by *S.* Typhi, measured through the incidence of blood culture confirmed typhoid fever in vaccinees in intervention clusters compared to control clusters<br><br>Secondary outcomes: Vi-TCV safety, efficacy and rate reduction of typhoid fever in clusters, impact on fever presentation, impact on clinical diagnosis typhoid fever, paratyphoid fever infection rates |
| Starting date | 12 February 18 |
| Contact information | Prof Andrew Pollard,<br><br>Oxford Vaccine Group<br><br>Centre for Clinical Vaccinology and Tropical Medicine (CCVTM)<br><br>Churchill Hospital Old Road<br><br>Oxford |

**ISRCTN11643110** *(Continued)*

| | |
|---|---|
| | OX3 7LE<br><br>United Kingdom |
| Notes | A pilot phase, prior to the main study, individually randomises 200 children, in an area separate from the main trial site, in an age stratified manner to receive either Vi-TCV or the JE vaccine. Safety data is presented to the local DSMB (LDSMB), IRB and to the Directorate General of Drug Administration (DGDA), the National Regulatory Authority of Bangladesh prior to initiating the main cluster-randomized trial<br><br>Intention to publish date: 1 February 2021<br><br>Trial protocol available: www.isrctn.com/ISRCTN11643110 |

**ISRCTN43385161**

| | |
|---|---|
| Trial name or title | Assessing the impact of a Vi-polysaccharide conjugate vaccine in preventing typhoid infection among Nepalese children – a phase III trial |
| Methods | Randomized controlled trial |
| Participants | Inclusion criteria<br><br>1. Parent/legal guardian is willing and competent to provide informed consent. If the participant is 12 years of age or older, informed assent will also be sought<br>2. Aged between 9 months (or eligible for measles vaccination according to local protocol) and < 16 years (that is, up to 15 years 364 days) at time of vaccination<br>3. In good health on the day of vaccination<br>4. Parent/legal guardian confirms that their child will be wiling and be able to comply with study requirements including follow-up contact, according the trial schedule<br>5. Live within the study catchment area at the time of vaccination<br><br>Exclusion criteria<br><br>1. Parent/legal guardian is willing and competent to provide informed consent. If the participant is 12 years of age or older, informed assent will also be sought<br>2. Aged between 9 months (or eligible for measles vaccination according to local protocol) and < 16 years (that is, up to 15 years 364 days) at time of vaccination<br>3. In good health on the day of vaccination<br>4. Parent/legal guardian confirms that their child will be wiling and be able to comply with study requirements including follow-up contact, according the trial schedule<br>5. Live within the study catchment area at the time of vaccination<br><br>Target number of participants: 20,000 |
| Interventions | Intervention: Vi Typhoid conjugate vaccine (Vi-TCV), trade name: TyBar, single dose<br><br>Control: meningococcal group A vaccine (MenA), trade name: MenAfriVac, single dose |
| Outcomes | Primary outcome: efficacy and rate reduction of Vi-TCV in preventing blood culture confirmed *S.* Typhi infection<br><br>Secondary outcomes: safety of Vi-TCV, impact on admission rates for febrile illness days spent in hospital with febrile illness, incidence of clinically suspected typhoid fever, paratyphoid infection rates<br><br>Follow-up: 2 years |

**ISRCTN43385161** *(Continued)*

| | |
|---|---|
| Starting date | 1 November 2017 |
| Contact information | Prof Andrew Pollard<br>Oxford Vaccine Group<br>Centre for Clinical Vaccinology and Tropical Medicine (CCVTM)<br>Churchill Hospital Old Road<br>Oxford<br>OX3 7LE<br>United Kingdom |
| Notes | Intention to publish date: 1 August 2021<br>Trial protocol: www.isrctn.com/ISRCTN43385161 |

**NCT03299426**

| | |
|---|---|
| Trial name or title | A phase III randomized, double-blind, controlled trial of the clinical efficacy of typhoid conjugate vaccine (Vi-TCV) among children age 9 months through 12 years in Blantyre, Malawi |
| Methods | Randomized controlled trial<br>(Participant, investigator, outcomes assessor blinded) |
| Participants | Inclusion criteria<br>• Healthy male or female child between the ages of 9 months and 12 years/364 days at the time of study vaccination<br>• A child whose parent or guardian resides primarily within the Ndirande or Zingwangwa study areas at the time of study vaccinations and who intends to be present in the area for the duration of the trial<br>• A child whose parent or guardian has voluntarily given informed consent<br>Exclusion criteria<br>• History of documented hypersensitivity to any component of the vaccine<br>• Prior receipt of any typhoid vaccine in the past 3 years<br>• History of severe allergic reaction with generalized urticarial, angioedema, or anaphylaxis<br>• Any condition determined by the investigator to be likely to interfere with evaluation of the vaccine or to be a significant potential health risk to the child or make it unlikely that the child would complete the study<br>Target number of participants: 24,000 |
| Interventions | Intervention: Vi-typhoid conjugate vaccine (Vi-TCV); single 0.5-mL intramuscular injection<br>Control: meningococcal A conjugate vaccine (MCV-A); single intramuscular injection. Children 9-11 months will receive a 5 µg/0.5 mL dose. Children 12 months and older will receive a 10 µg/0.5 mL dose |
| Outcomes | Primary outcome: efficacy of Vi-TCV (blood culture confirmed; follow-up until 36 months) |

| | |
|---|---|
| **NCT03299426** *(Continued)* | Secondary outcomes: safety of Vi-TCV (follow-up until 6 months); immunogenicity of Vi-TCV (28 days); number of typhoid fever cases prevented by Vi-TCV (follow-up until 36 months) |
| Starting date | January 2018 |
| Contact information | Principal Investigator: Kathleen Neuzil, Professor, University of Maryland<br>Provided contact details: Kenneth Simiyu Ksimiyu@som.umaryland.edu; Ian Woods iwoods@som.umaryland.edu |
| Notes | Estimated study completion date: January 2021<br>Trial protocol: clinicaltrials.gov/show/NCT03299426 |

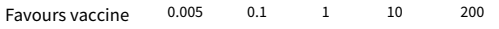
## DATA AND ANALYSES

### Comparison 1. Ty21a vaccine (3 doses) versus control: efficacy

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Incidence of typhoid fever, year 1 | 4 | 76296 | Risk Ratio (M-H, Random, 95% CI) | 0.55 [0.35, 0.86] |
| 2 Incidence of typhoid fever, year 2 | 4 | 76296 | Risk Ratio (M-H, Random, 95% CI) | 0.41 [0.29, 0.57] |
| 3 Incidence of typhoid fever, year 3 | 4 | 76296 | Risk Ratio (M-H, Random, 95% CI) | 0.44 [0.25, 0.76] |
| 4 Cumulative incidence of typhoid fever at 2.5 to 3 years | 9 | 235239 | Risk Ratio (M-H, Random, 95% CI) | 0.50 [0.39, 0.65] |

### Analysis 1.1. Comparison 1 Ty21a vaccine (3 doses) versus control: efficacy, Outcome 1 Incidence of typhoid fever, year 1.

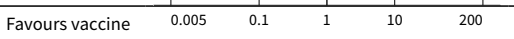
| Study or subgroup | Vaccine n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| Wahdan 1980a EGY | 0/13980 | 7/15087 | | 2.44% | 0.07[0,1.26] |
| Levine 1987ii CHL | 7/21400 | 6/5286 | | 14.24% | 0.29[0.1,0.86] |
| Simanjuntak 1991i IDN | 24/5066 | 42/5146 | | 40.41% | 0.58[0.35,0.96] |
| Simanjuntak 1991ii IDN | 30/5209 | 41/5122 | | 42.91% | 0.72[0.45,1.15] |
| **Total (95% CI)** | **45655** | **30641** | | **100%** | **0.55[0.35,0.86]** |
| Total events: 61 (Vaccine), 96 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0.07; $Chi^2$=4.45, df=3(P=0.22); $I^2$=32.61% | | | | | |
| Test for overall effect: Z=2.6(P=0.01) | | | | | |




Favours vaccine — Favours control

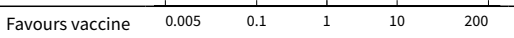
## Analysis 1.2. Comparison 1 Ty21a vaccine (3 doses) versus control: efficacy, Outcome 2 Incidence of typhoid fever, year 2.

| Study or subgroup | Vaccine n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| Levine 1987ii CHL | 8/21400 | 5/5286 | | 9.29% | 0.4[0.13,1.21] |
| Simanjuntak 1991i IDN | 17/5066 | 51/5146 | | 38.67% | 0.34[0.2,0.59] |
| Simanjuntak 1991ii IDN | 25/5209 | 50/5122 | | 50.62% | 0.49[0.3,0.79] |
| Wahdan 1980a EGY | 0/13980 | 8/15087 | | 1.43% | 0.06[0,1.1] |
| **Total (95% CI)** | **45655** | **30641** | | **100%** | **0.41[0.29,0.57]** |
| Total events: 50 (Vaccine), 114 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=2.72, df=3(P=0.44); $I^2$=0% | | | | | |
| Test for overall effect: Z=5.2(P<0.0001) | | | | | |



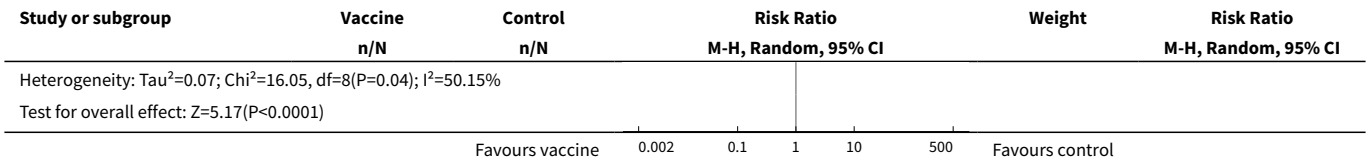

## Analysis 1.3. Comparison 1 Ty21a vaccine (3 doses) versus control: efficacy, Outcome 3 Incidence of typhoid fever, year 3.

| Study or subgroup | Vaccine n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| Levine 1987ii CHL | 8/21400 | 6/5286 | | 27.82% | 0.33[0.11,0.95] |
| Simanjuntak 1991i IDN | 7/5066 | 12/5146 | | 35.9% | 0.59[0.23,1.5] |
| Simanjuntak 1991ii IDN | 6/5209 | 12/5122 | | 32.48% | 0.49[0.18,1.31] |
| Wahdan 1980a EGY | 0/13980 | 7/15087 | | 3.8% | 0.07[0,1.26] |
| **Total (95% CI)** | **45655** | **30641** | | **100%** | **0.44[0.25,0.76]** |
| Total events: 21 (Vaccine), 37 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=2.32, df=3(P=0.51); $I^2$=0% | | | | | |
| Test for overall effect: Z=2.91(P=0) | | | | | |




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

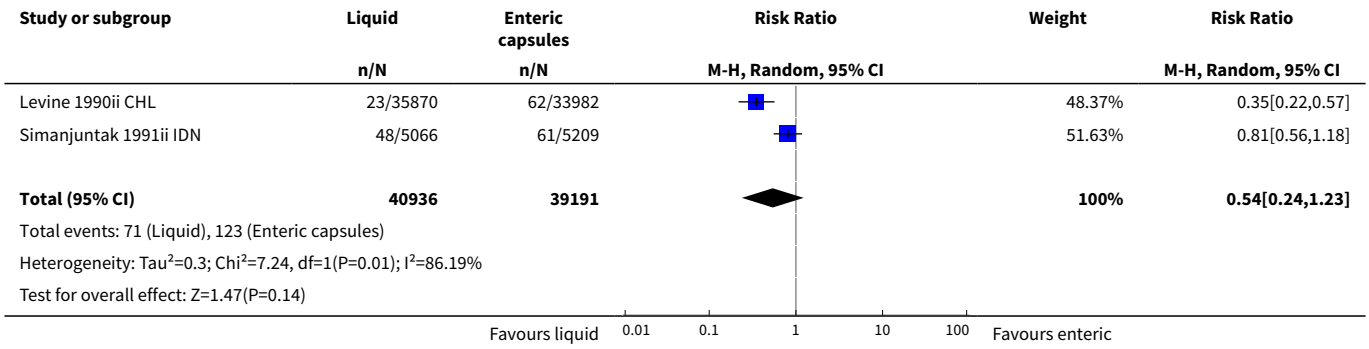
| Study or subgroup | Vaccine n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| Levine 1987i CHL | 33/20847 | 16/5286 | | 10.71% | 0.52[0.29,0.95] |
| Levine 1987ii CHL | 22/21340 | 16/5286 | | 9.8% | 0.34[0.18,0.65] |
| Levine 1987iii CHL | 44/20792 | 16/5287 | | 11.22% | 0.7[0.39,1.24] |
| Levine 1987iv CHL | 54/21570 | 16/5279 | | 11.54% | 0.83[0.47,1.44] |
| Levine 1990i CHL | 23/35870 | 14/5338 | | 9.43% | 0.24[0.13,0.47] |
| Levine 1990ii CHL | 62/33982 | 14/4752 | | 11.06% | 0.62[0.35,1.11] |
| Simanjuntak 1991i IDN | 48/5066 | 104/5146 | | 17.31% | 0.47[0.33,0.66] |
| Simanjuntak 1991ii IDN | 61/5209 | 104/5122 | | 18.1% | 0.58[0.42,0.79] |
| Wahdan 1980a EGY | 0/13980 | 21/15087 | | 0.83% | 0.03[0,0.41] |
| **Total (95% CI)** | **178656** | **56583** | | **100%** | **0.5[0.39,0.65]** |
| Total events: 347 (Vaccine), 321 (Control) | | | | | |




## Comparison 2. Ty21a vaccine: liquid formulation versus 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 | 2 | 80127 | Risk Ratio (M-H, Random, 95% CI) | 0.54 [0.24, 1.23] |

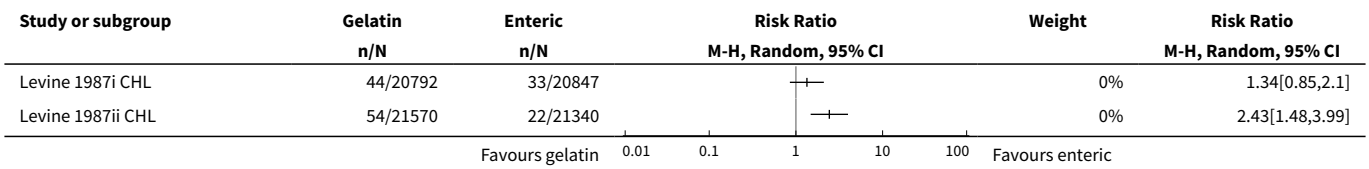
### Analysis 2.1. Comparison 2 Ty21a vaccine: liquid formulation versus enteric capsules (3 doses), Outcome 1 Cumulative incidence of typhoid fever at 2.5 to 3 years.




## Comparison 3. Ty21a vaccine: enteric versus gelatin formulation; cumulative efficacy at 2.5 to 3 years

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Incidence of typhoid fever | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |

### Analysis 3.1. Comparison 3 Ty21a vaccine: enteric versus gelatin formulation; cumulative efficacy at 2.5 to 3 years, Outcome 1 Incidence of typhoid fever.

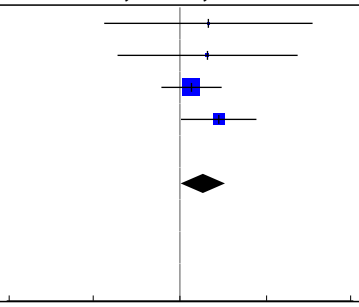


### Comparison 4. Ty21a vaccine versus control: adverse events

| 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] |
| 2 Vomiting | 4 | 2066 | Risk Ratio (M-H, Random, 95% CI) | 1.15 [0.43, 3.05] |
| 3 Diarrhoea | 4 | 2066 | Risk Ratio (M-H, Random, 95% CI) | 0.80 [0.52, 1.24] |
| 4 Nausea or abdominal pain | 4 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 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] |
| 6 Rash | 2 | 1190 | Risk Ratio (M-H, Random, 95% CI) | 2.94 [0.61, 14.12] |
| 7 Any mild adverse event | 3 | 1360 | Risk Ratio (M-H, Random, 95% CI) | 1.67 [1.03, 2.72] |

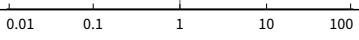
### Analysis 4.1. Comparison 4 Ty21a vaccine versus control: adverse events, Outcome 1 Fever.

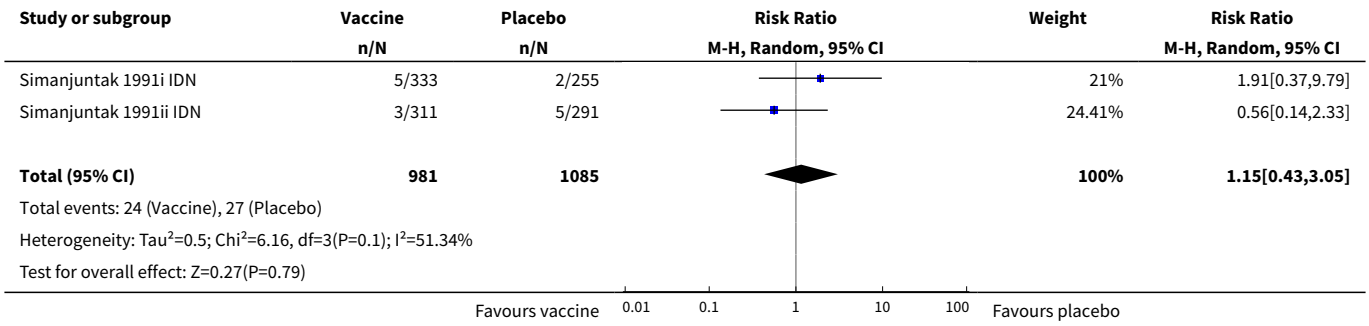
| Study or subgroup | Vaccine n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| Levine 1986i CHL | 1/172 | 1/367 | | 4.56% | 2.13[0.13,33.91] |
| Levine 1986ii CHL | 2/165 | 1/172 | | 6.1% | 2.08[0.19,22.77] |
| Simanjuntak 1991i IDN | 16/333 | 9/255 | | 54.44% | 1.36[0.61,3.03] |
| Simanjuntak 1991ii IDN | 15/311 | 5/291 | | 34.9% | 2.81[1.03,7.63] |
| **Total (95% CI)** | **981** | **1085** | | **100%** | **1.84[1.02,3.31]** |
| Total events: 34 (Vaccine), 16 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=1.26, df=3(P=0.74); $I^2$=0% | | | | | |
| Test for overall effect: Z=2.02(P=0.04) | | | | | |



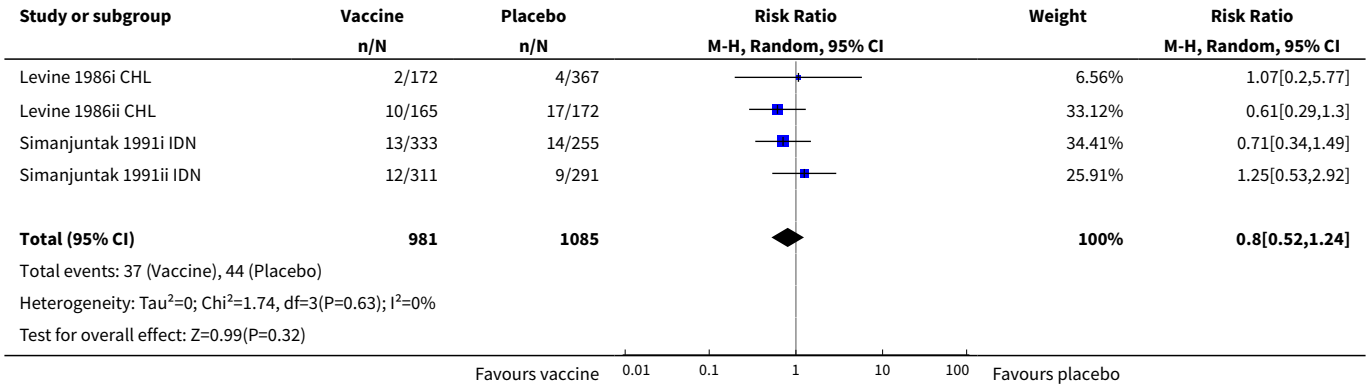

### Analysis 4.2. Comparison 4 Ty21a vaccine versus control: adverse events, Outcome 2 Vomiting.

| Study or subgroup | Vaccine n/N | Placebo n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| Levine 1986i CHL | 4/172 | 1/367 | | 14.37% | 8.53[0.96,75.79] |
| Levine 1986ii CHL | 12/165 | 19/172 | | 40.22% | 0.66[0.33,1.31] |

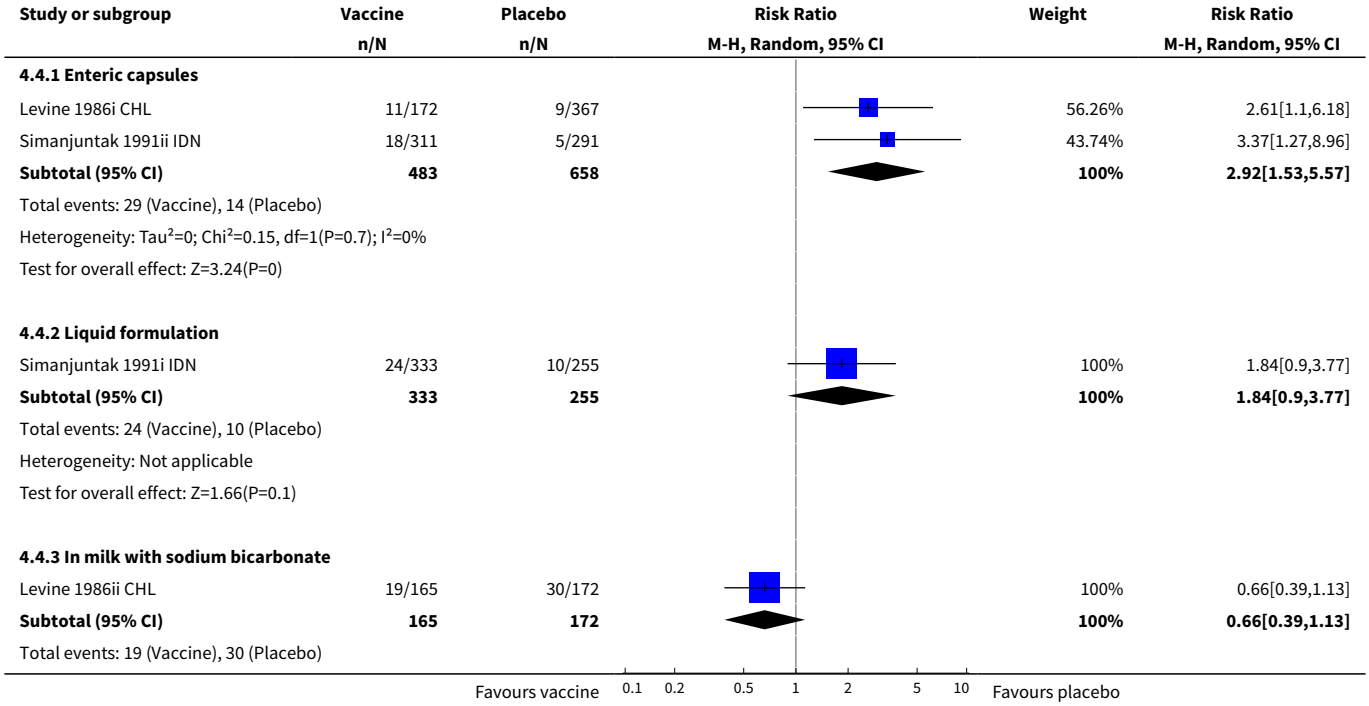


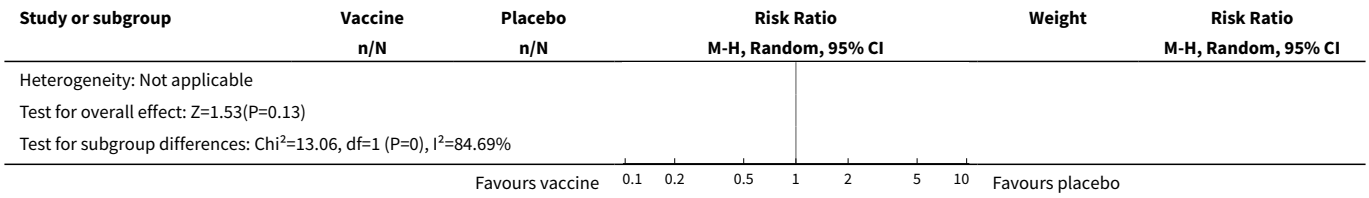



## Analysis 4.3. Comparison 4 Ty21a vaccine versus control: adverse events, Outcome 3 Diarrhoea.

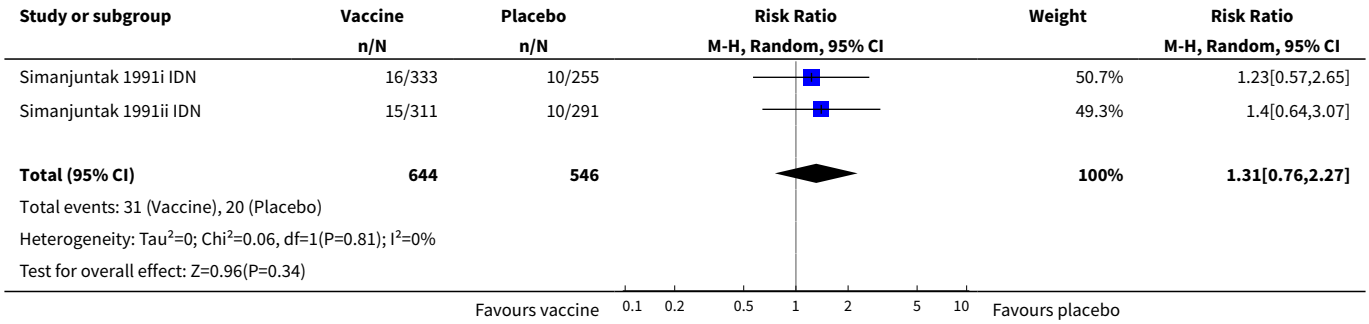



## Analysis 4.4. Comparison 4 Ty21a vaccine versus control: adverse events, Outcome 4 Nausea or abdominal pain.

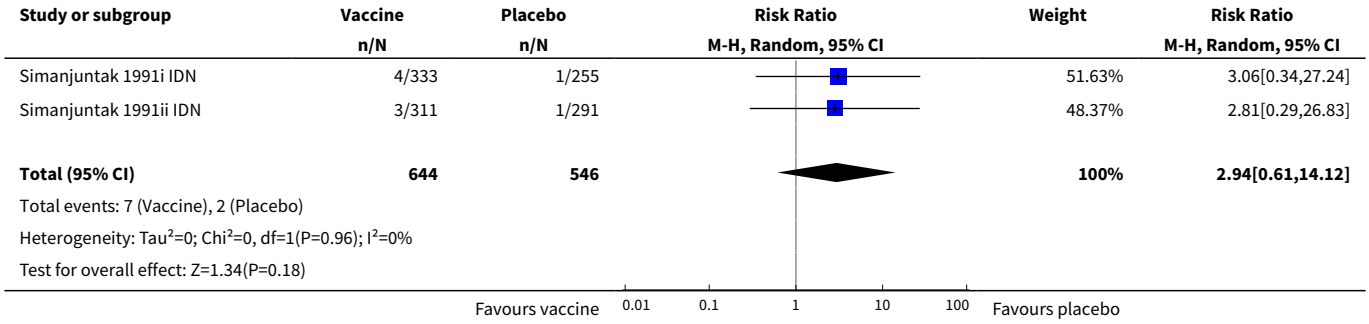




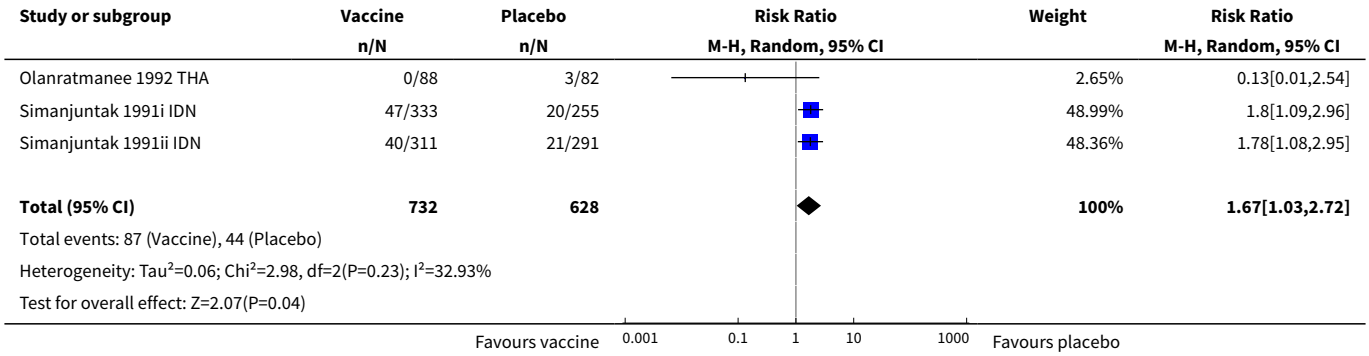

### Analysis 4.5. Comparison 4 Ty21a vaccine versus control: adverse events, Outcome 5 Headache.




### Analysis 4.6. Comparison 4 Ty21a vaccine versus control: adverse events, Outcome 6 Rash.




### Analysis 4.7. Comparison 4 Ty21a vaccine versus control: adverse events, Outcome 7 Any mild adverse event.

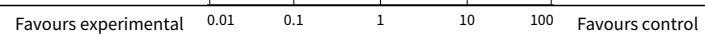


## Comparison 5. Vi polysaccharide vaccine (1 dose) versus control: efficacy

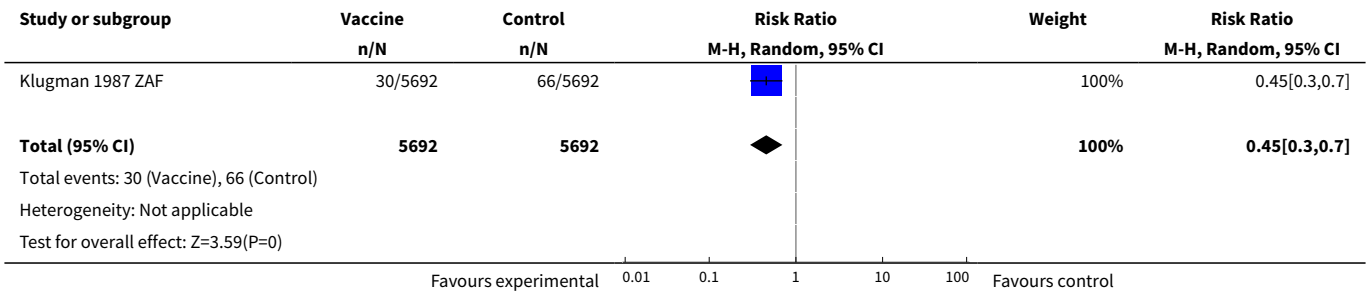
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Incidence of typhoid fever | 6 | | Risk Ratio (Random, 95% CI) | Subtotals only |
| 1.1 Year 1 | 3 | 99797 | Risk Ratio (Random, 95% CI) | 0.31 [0.26, 0.37] |
| 1.2 Year 2 | 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] |

### Analysis 5.1. Comparison 5 Vi polysaccharide vaccine (1 dose) versus 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 |
|---|---|---|---|---|---|---|
| **5.1.1 Year 1** | | | | | | |
| Acharya 1987 NPL | 3457 | 3450 | -1.3 (0.117) | | 41.66% | 0.28[0.22,0.35] |
| Klugman 1987 ZAF | 5692 | 5692 | -0.9 (0.168) | | 24.81% | 0.39[0.28,0.54] |
| Wang 1997 CHN | 41118 | 40388 | -1.2 (0.138) | | 33.53% | 0.29[0.22,0.38] |
| **Subtotal (95% CI)** | | | | | **100%** | **0.31[0.26,0.37]** |
| Heterogeneity: $Tau^2$=0.01; $Chi^2$=2.79, df=2(P=0.25); $I^2$=28.31% | | | | | | |
| Test for overall effect: Z=12.47(P<0.0001) | | | | | | |
| **5.1.2 Year 2** | | | | | | |
| Khan 2012 PAK | 13238 | 13993 | -0.4 (0.227) | | 19.29% | 0.66[0.42,1.04] |
| Klugman 1987 ZAF | 5692 | 5692 | -0.7 (0.181) | | 23.21% | 0.48[0.34,0.68] |
| Sur 2009 IND | 12206 | 12877 | -1.1 (0.092) | | 31.44% | 0.34[0.28,0.41] |
| Yang 2001 CHN | 65287 | 65984 | -1.2 (0.151) | | 26.06% | 0.31[0.23,0.42] |
| **Subtotal (95% CI)** | | | | | **100%** | **0.41[0.31,0.55]** |
| Heterogeneity: $Tau^2$=0.06; $Chi^2$=10.87, df=3(P=0.01); $I^2$=72.39% | | | | | | |
| Test for overall effect: Z=6.09(P<0.0001) | | | | | | |
| **5.1.3 Year 3** | | | | | | |
| Klugman 1987 ZAF | 5692 | 5692 | -0.7 (0.227) | | 100% | 0.5[0.32,0.78] |
| **Subtotal (95% CI)** | | | | | **100%** | **0.5[0.32,0.78]** |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z=3.05(P=0) | | | | | | |



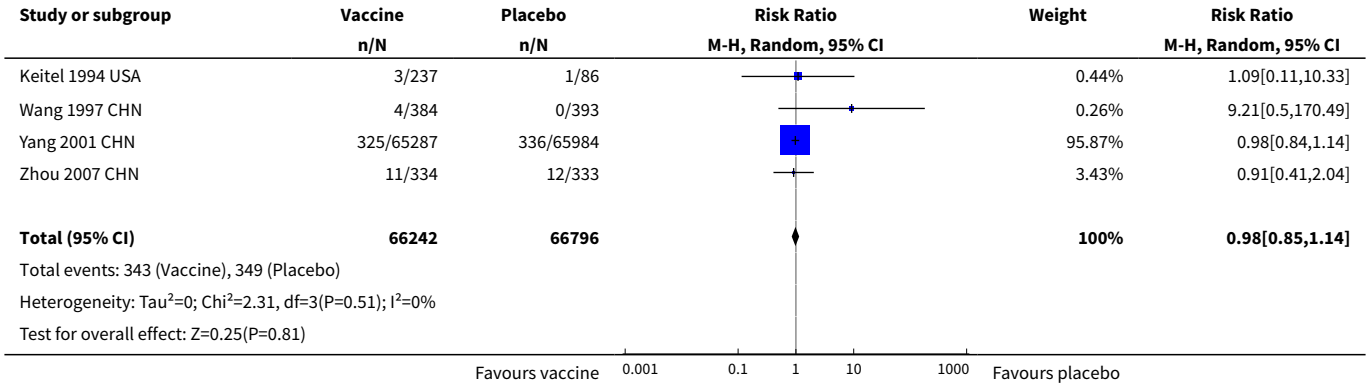
**Analysis 5.2. Comparison 5 Vi polysaccharide vaccine (1 dose) versus control: efficacy, Outcome 2 Cumulative incidence of typhoid fever at 2.5 to 3 years.**




## Comparison 6. Vi polysaccharide vaccine versus control: adverse events

| Outcome or subgroup title | No. of studies | No. of partici-pants | 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] |

**Analysis 6.1. Comparison 6 Vi polysaccharide vaccine versus control: adverse events, Outcome 1 Fever.**



## Analysis 6.2. Comparison 6 Vi polysaccharide vaccine versus control: adverse events, Outcome 2 Erythema.

| 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 | | 24.46% | 12.06[0.73,198.92] |
| Yang 2001 CHN | 325/65287 | 336/65984 | | 52.13% | 0.98[0.84,1.14] |
| Zhou 2007 CHN | 4/334 | 0/333 | | 23.41% | 8.97[0.49,166.01] |
| **Total (95% CI)** | **65858** | **66403** | | **100%** | **3.04[0.45,20.3]** |
| Total events: 345 (Vaccine), 336 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=1.8; $Chi^2$=5.36, df=2(P=0.07); $I^2$=62.71% | | | | | |
| Test for overall effect: Z=1.15(P=0.25) | | | | | |




## Analysis 6.3. Comparison 6 Vi polysaccharide vaccine versus 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 | | 38.13% | 12.06[0.73,198.92] |
| Wang 1997 CHN | 2/384 | 0/393 | | 32.56% | 5.12[0.25,106.24] |
| Zhou 2007 CHN | 1/334 | 0/333 | | 29.31% | 2.99[0.12,73.16] |
| **Total (95% CI)** | **955** | **812** | | **100%** | **6.06[1.07,34.22]** |
| Total events: 19 (Vaccine), 0 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.49, df=2(P=0.78); $I^2$=0% | | | | | |
| Test for overall effect: Z=2.04(P=0.04) | | | | | |

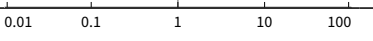



## Analysis 6.4. Comparison 6 Vi polysaccharide vaccine versus control: adverse events, Outcome 4 Pain at injection site.

| 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% | 7.98[3.69,17.24] |
| **Total (95% CI)** | **334** | **333** | | **100%** | **7.98[3.69,17.24]** |
| Total events: 56 (Vaccine), 7 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=5.28(P<0.0001) | | | | | |

### Analysis 6.5. Comparison 6 Vi polysaccharide vaccine versus 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 1997 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 | | | | | |

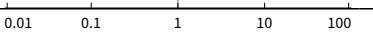


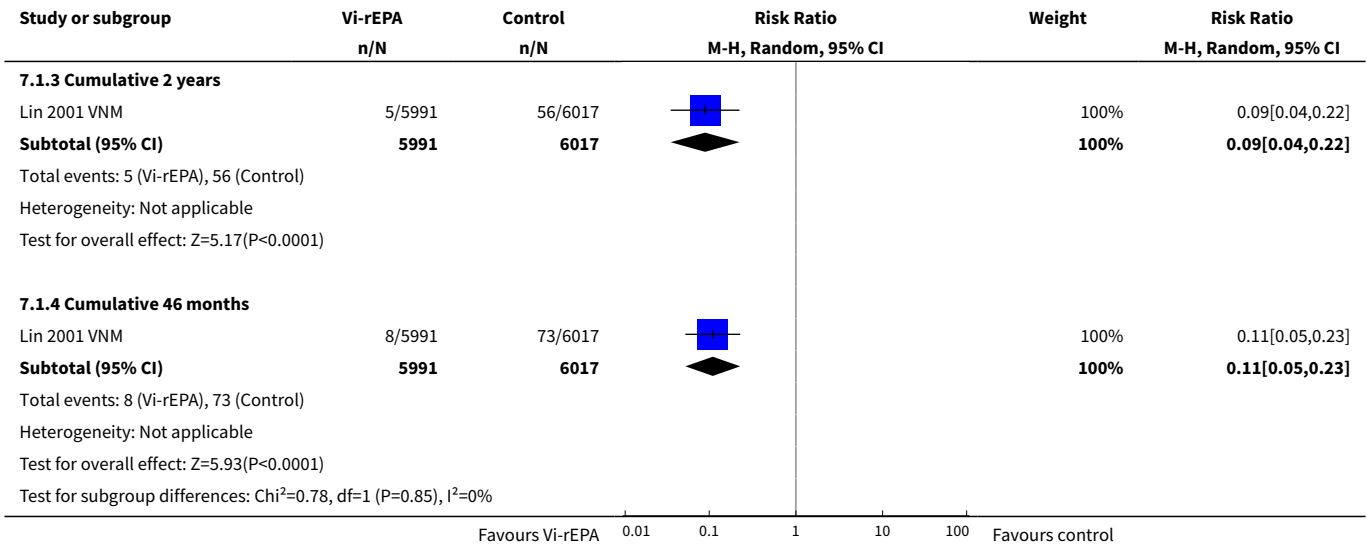

## Comparison 7. Vi-rEPA (2 doses) versus control: efficacy

| Outcome or subgroup title | No. of studies | No. of partici-pants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Incidence of typhoid fever | 1 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 1.1 Year 1 | 1 | 12008 | Risk Ratio (M-H, Random, 95% CI) | 0.06 [0.01, 0.25] |
| 1.2 Year 2 | 1 | 12008 | Risk Ratio (M-H, Random, 95% CI) | 0.13 [0.04, 0.44] |
| 1.3 Cumulative 2 years | 1 | 12008 | Risk Ratio (M-H, Random, 95% CI) | 0.09 [0.04, 0.22] |
| 1.4 Cumulative 46 months | 1 | 12008 | Risk Ratio (M-H, Random, 95% CI) | 0.11 [0.05, 0.23] |

### Analysis 7.1. Comparison 7 Vi-rEPA (2 doses) versus control: efficacy, Outcome 1 Incidence of typhoid fever.

| Study or subgroup | Vi-rEPA n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **7.1.1 Year 1** | | | | | |
| Lin 2001 VNM | 2/5991 | 33/6017 | | 100% | 0.06[0.01,0.25] |
| **Subtotal (95% CI)** | **5991** | **6017** | | **100%** | **0.06[0.01,0.25]** |
| Total events: 2 (Vi-rEPA), 33 (Control) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=3.84(P=0) | | | | | |
| **7.1.2 Year 2** | | | | | |
| Lin 2001 VNM | 3/5991 | 23/6017 | | 100% | 0.13[0.04,0.44] |
| **Subtotal (95% CI)** | **5991** | **6017** | | **100%** | **0.13[0.04,0.44]** |
| Total events: 3 (Vi-rEPA), 23 (Control) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=3.31(P=0) | | | | | |

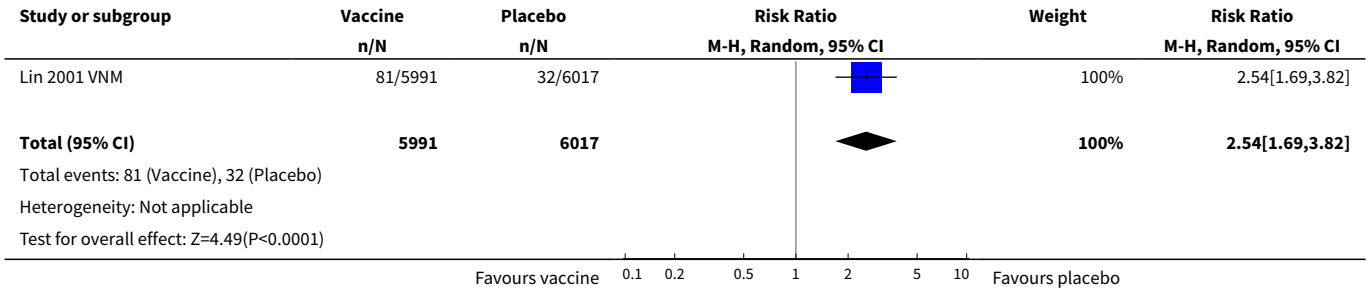




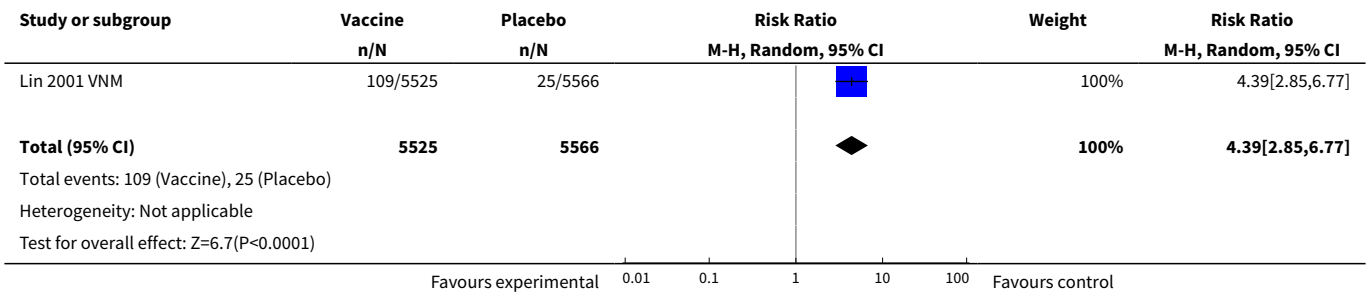

## Comparison 8. Vi-rEPA vaccine versus control: adverse events

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Fever after Vi-rEPA (dose1) | 1 | 12008 | Risk Ratio (M-H, Random, 95% CI) | 2.54 [1.69, 3.82] |
| 2 Fever after Vi-rEPA (dose 2) | 1 | 11091 | Risk Ratio (M-H, Random, 95% CI) | 4.39 [2.85, 6.77] |
| 3 Erythema after Vi-rEPA (dose 1) | 1 | 12008 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Erythema after Vi-rEPA (dose 2) | 1 | 11091 | Risk Ratio (M-H, Random, 95% CI) | 2.01 [0.18, 22.21] |
| 5 Swelling at injection site after Vi-rEPA (dose 1) | 1 | 12008 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |
| 6 Swelling at injection site after Vi-rEPA (dose 2) | 1 | 11091 | Risk Ratio (M-H, Random, 95% CI) | 20.15 [2.71, 150.08] |
| 7 Serious adverse events | 1 | 12008 | Risk Ratio (M-H, Random, 95% CI) | 0.0 [0.0, 0.0] |

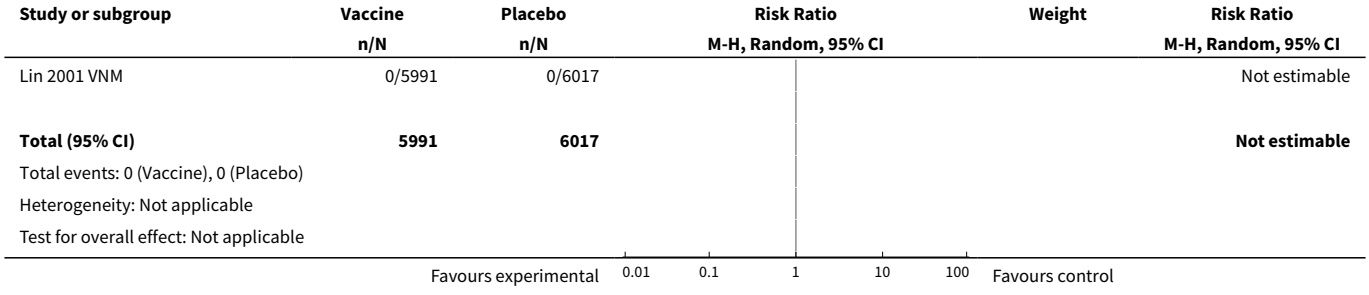
### Analysis 8.1. Comparison 8 Vi-rEPA vaccine versus control: adverse events, Outcome 1 Fever after Vi-rEPA (dose1).



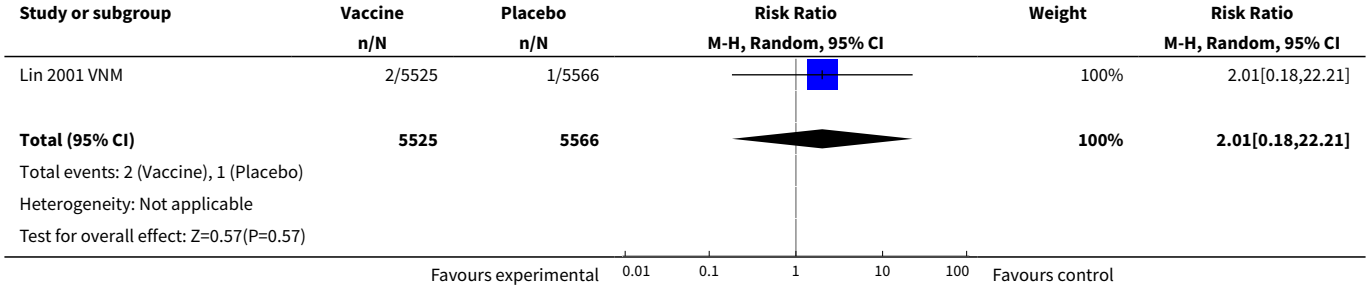
### Analysis 8.2. Comparison 8 Vi-rEPA vaccine versus control: adverse events, Outcome 2 Fever after Vi-rEPA (dose 2).



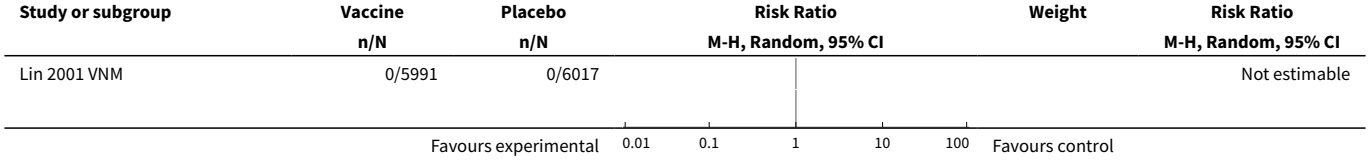

### Analysis 8.3. Comparison 8 Vi-rEPA vaccine versus control: adverse events, Outcome 3 Erythema after Vi-rEPA (dose 1).

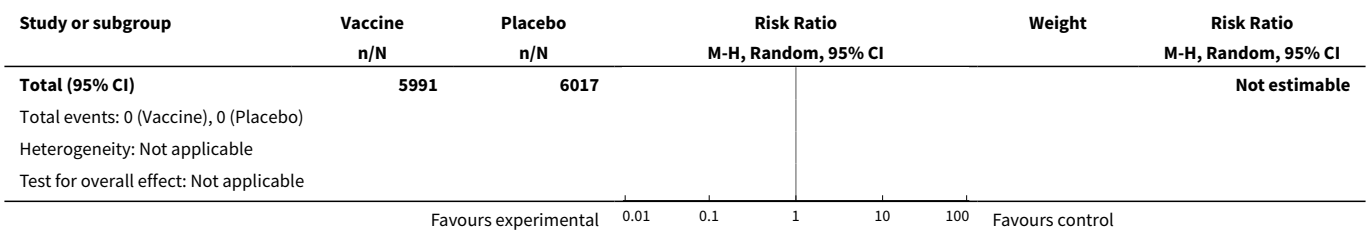



### Analysis 8.4. Comparison 8 Vi-rEPA vaccine versus control: adverse events, Outcome 4 Erythema after Vi-rEPA (dose 2).

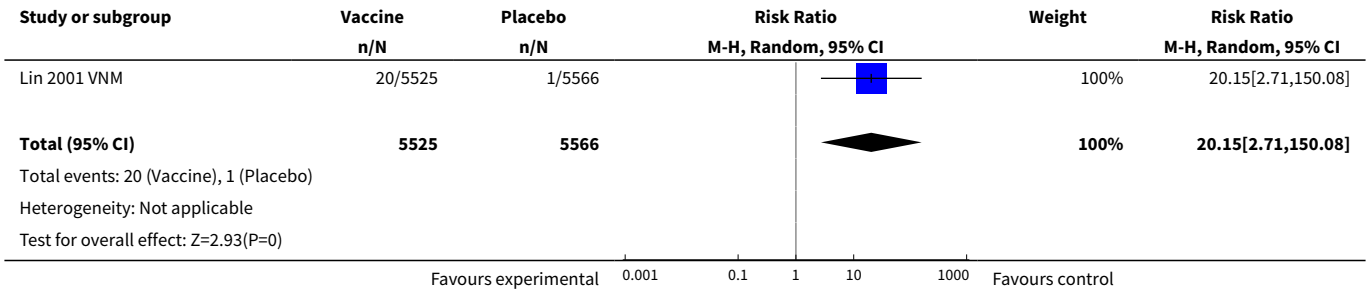



### Analysis 8.5. Comparison 8 Vi-rEPA vaccine versus control: adverse events, Outcome 5 Swelling at injection site after Vi-rEPA (dose 1).

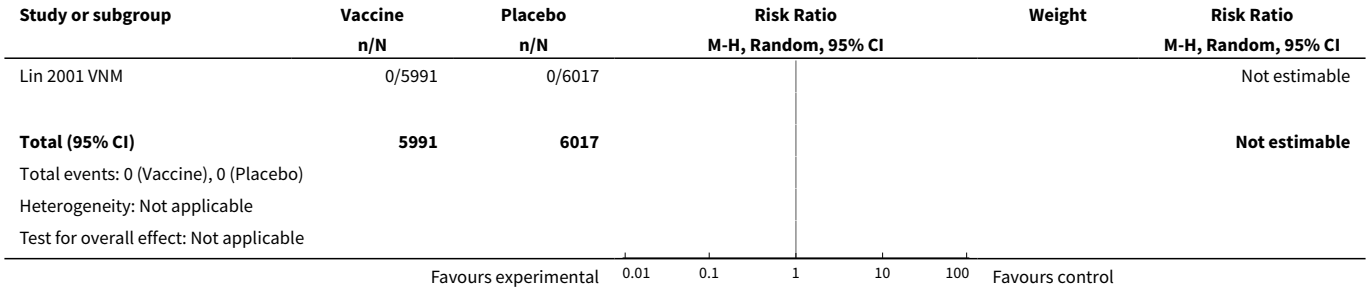





### Analysis 8.6. Comparison 8 Vi-rEPA vaccine versus control: adverse events, Outcome 6 Swelling at injection site after Vi-rEPA (dose 2).




### Analysis 8.7. Comparison 8 Vi-rEPA vaccine versus control: adverse events, Outcome 7 Serious adverse events.

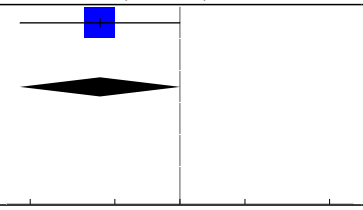



## Comparison 9. Vi-TT vaccine Peda Typh (2 doses) versus control: efficacy

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Incidence of typhoid fever, Year 1 | 1 | 1353 | Risk Ratio (M-H, Random, 95% CI) | 0.06 [0.00, 1.01] |

**Analysis 9.1. Comparison 9 Vi-TT vaccine Peda Typh (2 doses) versus control: efficacy, Outcome 1 Incidence of typhoid fever, Year 1.**

| Study or subgroup | Vi-TT (2 doses) n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| Mitra 2016 IND | 0/637 | 9/716 | | 100% | 0.06[0,1.01] |
| **Total (95% CI)** | **637** | **716** | | **100%** | **0.06[0,1.01]** |
| Total events: 0 (Vi-TT (2 doses)), 9 (Control) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=1.95(P=0.05) | | | | | |




## ADDITIONAL TABLES

**Table 1. Cluster-randomized trials: efficacy of oral Ty21a (3 doses) versus control; adjusted results**

| Trial | Year | Preparation (N doses) | ICC[a] | Average cluster size | Design effect | Typhoid episodes/participants in intervention group | Typhoid episodes/participants in control group | Risk ratio (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Levine 1987i CHL | 1 | Enteric capsules (3) | 0.0015 | 25 | 1.036 | 7/21,400 | 6/5286 | 0.29 (0.10 to 0.86) |
| | 2 | | | | 1.036 | 8/21,400 | 5/5286 | 0.40 (0.13 to 1.21) |
| | 3 | | | | 1.036 | 8/21,400 | 6/5286 | 0.33 (0.11 to 0.95) |
| Wahdan 1980a EGY | 1 | Liquid formulation (3) | 0.0015 | 37 | 1.054 | 0/13,980 | 7/15,087 | 0.07 (0.00 to 1.26) |
| | 2 | | | | 1.054 | 0/13,980 | 8/15,087 | 0.06 (0.00 to 1.10) |
| | 3 | | | | 1.054 | 0/13,980 | 7/15,087 | 0.07 (0.00 to 1.26) |
| Levine 1987i CHL | Cumulative incidence 2.5 to 3 years | Enteric capsules (3) | 0.0015 | 25 | 1.036 | 33/20,847 | 16/5286 | 0.52 (0.29 to 0.95) |
| Levine 1987ii CHL | Cumulative incidence 2.5 to 3 years | Enteric capsules (3) | 0.0015 | 25 | 1.036 | 22/21,400 | 16/5286 | 0.34 (0.18 to 0.65) |
| Levine 1990ii CHL | Cumulative incidence 2.5 to 3 years | Enteric capsules (3) | 0.0015 | 15 | 1.021 | 62/33,982 | 14/4752 | 0.62 (0.35 to 1.11) |
| Wahdan 1980a EGY | Cumulative incidence 2.5 to 3 years | Liquid formulation (3) | 0.0015 | 37[b] | 1.054 | 0/13,980 | 21/15,087 | 0.03 (0.00 to 0.41) |
| Levine 1990i CHL | Cumulative incidence 2.5 to 3 years | Liquid formulation (3) | 0.0015 | 15 | 1.021 | 23/35,870 | 14/5338 | 0.24 (0.13 to 0.47) |
| Levine 1987iii CHL | Cumulative incidence 2.5 to 3 years | Gelatin capsules (3) | 0.0015 | 25 | 1.036 | 44/20,792 | 16/5286 | 0.70 (0.39 to 1.24) |
| Levine 1987iv CHL | Cumulative incidence | Gelatin capsules (3) | 0.0015 | 26 | 1.0375 | 54/21,570 | 16/5279 | 0.83 (0.47 to 1.44) |

**Table 1. Cluster-randomized trials: efficacy of oral Ty21a (3 doses) versus control; adjusted results** *(Continued)*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2.5 to 3 years | | | | | | | |
| Levine 1990i CHL | Cumulative incidence<br>5 years | Liquid formulation (3) | 0.015 | 15 | 1.021 | 33/35,870 | 21/5338 | 0.23 (0.14 to 0.40) |
| Levine 1987ii CHL | Cumulative incidence<br>7 years | Enteric capsules (3) | 0.015 | 25 | 1.036 | 48/21,400 | 32/5286 | 0.37 (0.24 to 0.58) |

Abbreviations: CI: confidence interval; ICC: intracluster correlation coefficient.
[a]ICC calculated from Sur 2009 IND.
[b]Average cluster size for Wahdan 1980a EGY calculated using pilot trial cluster size information.

**Table 2. Cluster-randomized trials: efficacy of oral Ty21a vaccine: unadjusted results[a]**

| Trial | Year | Preparation (N doses) | RR (95% CI)[b] | Efficacy[c] |
|---|---|---|---|---|
| Black 1990ii CHL | 1 | Enteric capsules (1) | 0.75 (0.48 to 1.18) | 25% (−18% to 52%) |
| | 2 | | 0.65 (0.36 to 1.18) | 35% (−18% to 64%) |
| | 3 | | 1.04 (0.47 to 2.31) | −4% (−131% to 53%) |
| | 4 | | 1.06 (0.56 to 2.00) | −6% (−100% to 44%) |
| | 5 | | 1.17 (0.51 to 2.68) | −17% (−168% to 49%) |
| | Cumulative 3 years | | 0.76 (0.55 to 1.06) | 24% (−6% to 45%) |
| | Cumulative 5 years | | 0.85 (0.65 to 1.12) | 15% (−12% to 35%) |
| Black 1990i CHL | 1 | Enteric capsules (2) | 0.48 (0.29 to 0.79) | 52% (21% to 71%) |
| | 2 | | 0.29 (0.14 to 0.60) | 71% (40% to 86%) |
| | 3 | | 0.74 (0.33 to 1.65) | 26% (−65% to 67%) |
| | 4 | | 0.81 (0.42 to 1.58) | 19% (−58% to 58%) |
| | 5 | | 0.88 (0.39 to 1.99) | 12% (-99% to 61%) |
| | Cumulative 3 years | | 0.46 (0.32 to 0.66) | 54% (34% to 68%) |
| | Cumulative 5 years | | 0.57 (0.42 to 0.76) | 43% (24% to 58%) |
| Levine 1987ii CHL | 1 | Enteric capsules (3) | 0.29 (0.10 to 0.86) | 71% (14% to 90%) |
| | 2 | | 0.40 (0.13 to 1.21) | 60% (−21% to 87%) |
| | 3 | | 0.33 (0.11 to 0.95) | 67% (5% to 89%) |
| Wahdan 1980a EGY | 1 | Liquid formulation (3) | 0.07 (0.00 to 1.26) | 93% (−26% to 100%) |
| | 2 | | 0.06 (0.00 to 1.10) | 94% (−10% to 100%) |
| | 3 | | 0.07 (0.00 to 1.26) | 93% (−26% to 100%) |
| Levine 1987i CHL | Cumulative incidence 2.5 to 3 years | Enteric capsules (3) | 0.51 (0.28 to 0.91) | 49% (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%) |
| 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) | 0.02 (0.00 to 0.40) | 98% (60% to 100%) |

**Table 2. Cluster-randomized trials: efficacy of oral Ty21a vaccine: unadjusted results[a]** *(Continued)*

| | | | | |
|---|---|---|---|---|
| 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 5 years | Liquid preparation (3) | 0.23 (0.13 to 0.39) | 77% (61% to 87%) |
| Levine 1987ii CHL | Cumulative incidence 7 years | Enteric capsules (3) | 0.37 (0.24 to 0.58) | 63% (42% to 76%) |

Abbreviations: RR: risk ratio; CI: confidence interval.
[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% CIs.
[c]Efficacy = 1 − risk ratio.

**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. Efficacy of Vi-TT (PedaTyph); cluster unadjusted results; year 1**

| Trial | Number of doses | Follow-up | Vi-TT (PedaTyph) | | Control | | Risk ratio (96% CI) | Efficacy (95% CI) |
|---|---|---|---|---|---|---|---|---|
| | | | Events | Total | Events | Total | | |
| Mitra 2016 IND | 2 | 1 year | 0 | 765 | 11 | 860 | 0.05 (0.00 to 0.83%) | 95% (17% to 100%) |

Abbreviations: CI: confidence interval.

# APPENDICES

## Appendix 1. Search strategy

| Search set | CIDG SR[a] | CENTRAL | MEDLINE[b] | Embase[b] | LILACS[b] |
|---|---|---|---|---|---|
| 1 | typhoid fever | typhoid* ti,ab,kw | typhoid* [Title/Abstract] | typhoid* .ti or typhoid*.ab | typhoid fever |
| 2 | vaccine* | " typhoid fever*" ti,ab,kw | "typhoid fever" [Title/Abstract] | typhoid fever/ | vaccin$ |
| 3 | 1 and 2 | salmonell* ti,ab,kw | "Typhoid Fever"[Mesh] | "typhoid fever".ti. or "typhoid fever".ab. | 1 and 2 |
| 4 | — | 1 or 2 or 3 | salmonell* [Title/Abstract] | salmonell*.ti or salmonel-l*.ab | typhoid vaccin$ |
| 5 | — | vaccin* ti, ab, kw | 1 or 2 or 3 or 4 | 1 or 2 or 3 or 4 | paraty-phoid vaccin$ |
| 6 | — | 4 and 5 | vaccin* [Title/Abstract] | vaccin*.ti or vaccin*.ab | 3 or 4 or 5 |
| 7 | — | [Typhoid-Paraty-phoid Vaccines] Mesh | 5 and 6 | 5 and 6 | — |
| 8 | — | 6 or 7 | "Typhoid-Paratyphoid Vaccines"[Mesh] | typhoid vaccine/ | — |
| 9 | — | | "Ty21a typhoid vaccine" [Supplementary Concept] | typhoid paratyphoid vaccine/ | — |
| 10 | — | | Vi polysaccharide vaccine, typhoid [Sup-plementary Concept] | 7 or 8 or 9 | — |
| 11 | — | | "typhoid vaccine M01ZH09" [Supplemen-tary Concept] | _ | — |
| 12 | — | — | 7 or 8 or 9 or 10 or 11 | — | — |

[a]Cochrane Infectious Diseases Group Specialized Register.
[b]Search terms used in combination with the search strategy for retrieving trials developed by Cochrane.

## Appendix 2. Adverse events with Ty21a

### Serious adverse effects

| Trial | Ty21a vaccine | | Control | |
|---|---|---|---|---|
| | Events | People vaccinated | Events | People vaccinated |

(Continued)

| | | | | |
|---|---|---|---|---|
| **Enteric capsules** | | | | |
| Levine 1986i CHL | 0 | 172 | 0 | 367 |
| Simanjuntak 1991ii IDN | 0 | 311 | 0 | 291 |
| Subtotal | 0 | 483 | 0 | 658 |
| | | | | |
| **Liquid formulation** | | | | |
| Olanratmanee 1992 THA | 0 | 88 | 0 | 82 |
| Simanjuntak 1991i IDN | 0 | 333 | 0 | 255 |
| Wahdan 1980a EGY | 0 | 16486 | 0 | 15902 |
| Wahdan 1980b EGY | 0 | 413 | 0 | 417 |
| Subtotal | 0 | 17320 | 0 | 116656 |
| | | | | |
| **In milk with sodium bicarbonate** | | | | |
| Levine 1986ii CHL | 0 | 165 | 0 | 172 |
| Subtotal | 0 | 165 | 0 | 172 |
| | | | | |
| Total | 0 | 17968 | 0 | 117486 |

**Ty21a adverse events per dose of vaccine (cluster unadjusted)**

| Adverse event | Trial | Vaccine events/total (%) | Placebo events/total (%) |
|---|---|---|---|
| Vomiting | Wahdan 1980a EGY | 49/47037 (0.1%) | 21/45638 (0.05%) |
| | Wahdan 1980b EGY | 12/1159 (1.04%) | 2/1311 (0.15%) |
| Fever | Wahdan 1980a EGY | 1/47037 (0.002%) | 3/45638 (0.07%) |
| | Wahdan 1980b EGY | 1/1159 (0.01%) | 1/1311 (0.08%) |
| Nausea/ abdominal pain | Wahdan 1980a EGY | 14/47037 (0.03%) | 2/45638 (0.004%) |
| | Wahdan 1980b EGY | 3/1159 (0.26%) | 0/1311 (0%) |

## WHAT'S NEW

| Date | Event | Description |
|---|---|---|
| 3 May 2018 | New citation required and conclusions have changed | This review update includes one new trial, evaluating the Vi-polysaccharide tetanus-toxoid conjugate vaccine (Vi-TT PedaTyph). |
| 6 March 2018 | New search has been performed | This is an update of Anwar 2014 with a new search up to 14 February 2018. We have updated the Background and adjusted the protocol to make clear that the review does not include human challenge studies. We also updated the protocol to exclude adverse effects comparison trials using non-placebo vaccines as a control. We updated our methods to include in the meta-analysis cluster-randomized trials that we had previously described in separate tables. |

## HISTORY

Protocol first published: Issue 4, 1998
Review first published: Issue 4, 1998

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

RM: data collection and management, analysis, interpretation of results, and review writing.
AN: data collection, analysis, and review writing.
MR: data analysis, review writing.
MP: data analysis, review writing.
All review authors read and approved the final manuscript.

## DECLARATIONS OF INTEREST

RM has no known conflicts of interest.
MP has no known conflicts of interest.
MR has no known conflicts of interest.
AN has no known conflicts of interest.

## SOURCES OF SUPPORT

### Internal sources

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

### External sources

- Department for International Development (DFID), UK.

  Grant: 5242
- World Health Organization, Switzerland.

  WHO Agreement for Performance of Work (APW) Grant 2017 (number 702828-0)

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this update, we excluded trials that reported on adverse events where typhoid vaccines were compared to an alternative vaccine rather than placebo. This is because other vaccines may also have adverse events associated with them – such as fever or erythema at injection site – and would not enable a true assessment of adverse events associated with typhoid vaccines. We excluded human challenge trials; this had not been explicitly stated in the protocol but none were included in the previous review.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Incidence; Randomized Controlled Trials as Topic; Salmonella typhi [immunology]; Time Factors; Typhoid Fever [epidemiology] [immunology] [*prevention & control]; Typhoid-Paratyphoid Vaccines [adverse effects] [*therapeutic use]; Vaccines, Attenuated [adverse effects] [therapeutic use]

### MeSH check words

Adolescent; Adult; Child; Child, Preschool; Humans