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Typhoid conjugate vaccines for preventing typhoid fever (enteric fever) (Review)

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[Intervention Review]

Typhoid conjugate vaccines for preventing typhoid fever (enteric fever)

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ABSTRACT

Rationale

Typhoid fever is a major cause of enteric disease-related morbidity and mortality. Vaccination reduces disease burden and prevents outbreaks, but policies and programmes should be informed by the most recent evidence as newer vaccines become available.

Objectives

To assess the benefits and harms of typhoid conjugate vaccines (TCVs) compared to no vaccine, placebo, typhoid-inactive agents (vaccines for another disease) or other typhoid vaccines for preventing morbidity and mortality associated with typhoid fever in adults and children.

Search methods

In April 2024, we searched the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, CINAHL, Global Index Medicus, United States Advisory Committee on Immunization Practices and the World Health Organization vaccine repository for randomised controlled trials (RCTs), with no restrictions. We also searched clinical trial registries for ongoing trials (www.clinicaltrials.gov and the WHO International Clinical Trials Registry Platform), grey literature, bibliographic citations of reviews and key articles for additional studies. We contacted study authors for information about ongoing studies.

Eligibility criteria

We included RCTs and cluster-RCTs of children and adults living in typhoid-endemic areas or travelling to typhoid-endemic areas. We included studies comparing TCVs to controls (i.e. no vaccine, placebo or vaccines for another disease), non-conjugated typhoid vaccines or other TCVs.

Outcomes

Outcomes included acute typhoid fever, defined by laboratory-confirmed isolation of *Salmonella typhi*, all-cause mortality, adverse events (AEs) and serious adverse events (SAEs).

Risk of bias

Review authors independently assessed risk of bias for all outcomes, using the Cochrane RoB 2 tools. We resolved disagreements through discussion or adjudication. We assessed the intention-to-treat effect and used the overall RoB judgement to assess the certainty of evidence for each outcome.

Synthesis methods

Three review authors independently screened titles and abstracts for eligible studies, followed by full-text assessment. Disagreements were resolved through discussion or adjudication by a fourth author. Four authors independently extracted characteristics of included studies and outcome data using a piloted, standardised data extraction form.

We synthesised results for each outcome where possible, using the Mantel-Haenszel statistical method and random-effects analysis model. Where meta-analysis was not possible due to the nature of the data, we planned to synthesise results based on direction of effect. We used GRADE to assess the certainty of evidence for each outcome, assessing risk of bias, inconsistency, indirectness, imprecision and other bias.

Included studies

We included 19 trials (17 RCTs and two cluster-RCTs). The 19 trials enrolled 395,650 participants, with ages ranging from six weeks to 60 years. Vaccines were delivered as a single dose in 14 studies; two doses, ranging from four to 24 weeks apart, in six studies; and three doses, four weeks apart, in one study. Comparators included: no vaccine, placebo and other vaccines. Seven studies compared TCV with non-conjugated typhoid vaccines. Six studies compared one TCV to another TCV.

Synthesis of results

TCV compared to control may result in a large reduction in acute typhoid fever (risk ratio (RR) 0.20, 95% confidence interval (CI) 0.12 to 0.32; I^2 = 70%; 6 studies, 101,896 participants; low-certainty evidence) and probably results in little to no difference in all-cause mortality (RR 0.80, 95% CI 0.35 to 1.85; I^2 = 52%; 4 studies, 100,337 participants; moderate-certainty evidence). TCV results in little to no difference in AEs when compared to control (RR 0.91, 95% CI 0.76 to 1.09; I^2 = 0%; 3 studies, 29,465 participants; high-certainty evidence) and a slight reduction in SAEs compared to control (RR 0.82, 95% CI 0.71 to 0.95; I^2 = 0%; 6 studies, 89,625 participants; high-certainty evidence).

TCV compared to non-conjugated typhoid vaccines may result in little to no difference in acute typhoid fever (RR 0.90, 95% CI 0.48 to 1.69; 1 study, 78 participants; low-certainty evidence). There were no deaths in the included studies. When compared to non-conjugated typhoid vaccines, TCV likely results in little to no difference in AEs (RR 1.00, 95% CI 0.77 to 1.31; I^2 = 0%; 3 studies, 244 participants; moderate-certainty evidence) and likely results in a slight reduction in SAEs (RR 0.30, 95% CI 0.05 to 1.88; I^2 = 0%; 2 studies, 732 participants; moderate-certainty evidence).

For TCV compared to another TCV, none of the studies reported on acute typhoid fever. Vi tetanus toxoid vaccine (Vi-TT) may result in little to no difference in all-cause mortality compared to a different TCV (RR 5.19, 95% CI 0.54 to 49.80; I^2 = 0%; 2 studies, 2422 participants; low-certainty evidence). Vi-TT likely results in little to no difference in AEs compared to another TCV (RR 1.18, 95% CI 0.92 to 1.51; I^2 = 39%; 4 studies, 2916 participants; moderate-certainty evidence) and may result in little to no difference in SAEs (RR 2.48, 95% CI 0.74 to 8.36; I^2 = 0%; 3 studies, 2866 participants; low-certainty evidence).

The certainty of evidence was consistently reduced due to imprecision, indirectness and bias.

Authors' conclusions

This review highlights that TCVs, compared to controls, are effective in preventing typhoid fever, and may confer protection for up to four years. TCVs compared to non-conjugated typhoid vaccines may result in little to no difference in acute typhoid fever and AEs, and likely result in a slight reduction in SAEs. Vi-TT compared to another TCV may result in little to no difference in all-cause mortality or SAEs, and likely results in little to no difference in AEs.

Funding

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Registration

Protocol available via doi.org/10.1002/14651858.CD015746

PLAIN LANGUAGE SUMMARY

Do typhoid conjugate vaccines prevent acute typhoid fever and are they safe?

Key messages

- Compared to a control (no vaccine, placebo ('dummy') or vaccine for another disease), typhoid conjugate vaccines (TCVs) may result in a large decrease in acute typhoid fever cases.
- We are uncertain whether TCVs, compared to other typhoid vaccines, decrease acute typhoid cases.
- There may be little to no difference in death from any cause, and unwanted effects, when TCVs are compared to a control, a non-conjugated typhoid vaccine or a different TCV. There is a slight decrease in serious unwanted effects when TCV is compared to a control, but may be little to no difference when compared to other TCVs.
- More robust research in typhoid-endemic countries (countries where typhoid occurs regularly) in this area is needed.

What are TCVs?

Typhoid conjugate vaccines (TCVs) are designed to protect against typhoid fever, sometimes known as enteric fever, caused by the bacteria *Salmonella typhi* (*S typhi*). The bacteria have an outer layer of sugar molecules (called the Vi polysaccharide). To help the body make a strong immune response, the Vi polysaccharide is attached to a protein. This helps the immune system recognise and fight *S typhi* more effectively. The TCVs assessed include Vi tetanus toxoid (Vi-TT), Vi diphtheria toxoid (Vi-DT), Vi-CRM_{197} and Vi-rEPA.

Why are TCVs important?

Typhoid fever causes sickness and death in people in low- and middle-income countries (LMICs) - mostly sub-Saharan Africa, South- and Southeast Asia. It is passed from person-to-person through faecal-oral transmission (germs spread through contact with human faeces). People with typhoid may have a high fever, body aches, headache, nausea and vomiting, poor appetite and, later, stomach ache. Typhoid should be diagnosed with a laboratory test but is often diagnosed based on symptoms. It can be treated with antibiotics, but there is growing antibiotic resistance. Vaccination, together with interventions like access to clean water, handwashing and improved hygiene, helps to prevent typhoid fever. The World Health Organization (WHO) recommends typhoid vaccination in routine immunisation programmes for children in high-risk areas. Unlike other typhoid vaccines, TCVs can be given to children under two years old.

What did we want to find out?

We wanted to find out how well typhoid conjugate vaccines prevent acute typhoid fever and death from any cause, and how safe they are.

What did we do?

We searched for studies that compared TCVs to a control (no vaccine, a placebo or a vaccine for another disease), other typhoid vaccines and other TCVs. We summarised the results and rated our confidence in the evidence.

What did we find?

We found 19 studies with 395,650 participants and included 394,790 in our analysis. Participants were aged between six weeks and 60 years. The smallest study included 75 participants and the largest 326,794. The studies were conducted mostly in LMICs with most in Asia.

Main results

Compared to no vaccine, placebo or vaccine for another disease, TCV vaccination may result in a large decrease in typhoid fever and probably results in little to no difference in deaths from any cause. TCV vaccination results in little to no difference in unwanted effects and in a slight decrease in serious unwanted effects. TCV vaccination compared to control likely results in a longer duration of protection, with one study showing lower rates of acute typhoid fever for up to four years.

Compared to non-conjugated typhoid vaccines, TCVs may result in little to no difference in acute typhoid fever and likely result in little to no difference in unwanted effects. There is a slight decrease in serious unwanted effects when TCV is used instead of non-conjugate typhoid vaccines. None of the studies reported deaths for this comparison.

Compared to other TCVs, no studies reported on typhoid fever. There is little to no difference in deaths from any cause when comparing one TCV (Vi-TT) to another. Vaccination with Vi-TT likely results in little to no difference in unwanted effects and may result in little to no difference in serious unwanted effects compared to another TCV.

Our confidence in some of the evidence was decreased because it was not always precise, did not always fully apply to our question and there were potential biases.

What are the limitations of the evidence?

Death was not always reported and, when it was, the number was low. This may have led to fewer deaths being reported than occurred. No studies compared the effectiveness of one TCV to another in preventing typhoid fever. Unwanted effects are not defined identically by study authors. We reported these as a combined outcome instead of as specific effects like nausea or rash, which may limit the use of these results by healthcare practitioners.

How up-to-date is this evidence?

The review is current to 19 April 2024.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings table - TCV compared to control (no vaccine, placebo or vaccines for another disease) for preventing typhoid fever

TCV compared to control (no vaccine, placebo or vaccines for another disease) for preventing typhoid fever

Patient or population: preventing typhoid fever
Setting: South and Southeast Asia (the Philippines, Indonesia, Vietnam, India, Bangladesh and Nepal), Africa (Malawi) and Europe (the United Kingdom)
Intervention: TCV
Comparison: control (no vaccine, placebo or vaccines for another disease)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control (no vaccine, placebo or vaccines for another disease)	Risk with TCV				
Acute typhoid fever - total follow-up: range 1 months to 4 years	8 per 1000	**2 per 1000** (1 to 2)	**RR 0.20** (0.12 to 0.32)	101896 (6 RCTs)	⊕⊕⊖⊖ Low[a,b]	TCV may result in a large reduction in acute typhoid fever when compared to control.
All-cause mortality - total follow-up: range 2 years to 4 years	1 per 1000	**1 per 1000** (0 to 1)	**RR 0.80** (0.35 to 1.85)	100337 (4 RCTs)	⊕⊕⊕⊖ Moderate[c,d]	TCV probably results in little to no difference in all-cause mortality when compared to control.
Adverse events - total follow-up: range 28 days to 6 months	6 per 1000	**5 per 1000** (4 to 6)	**RR 0.91** (0.76 to 1.09)	29465 (3 RCTs)	⊕⊕⊕⊕ High[e]	TCV results in little to no difference in adverse events when compared to control.
Serious adverse events - total follow-up: range 1 months to 2 years	9 per 1000	**7 per 1000** (6 to 8)	**RR 0.82** (0.71 to 0.95)	89625 (6 RCTs)	⊕⊕⊕⊕ High	TCV results in a slight reduction in serious adverse events when compared to control.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_447740485326135986.

[a] Downgraded by one level for serious risk of bias: two of six studies had high risk of bias or some concerns due to deviations from intended interventions; one had high risk due to missing outcome data.
[b] Downgraded by one level for inconsistency. Substantial heterogeneity (I2 = 70%; P = 0.006) likely driven by Jin 2017. When excluded in sensitivity analysis, the I2 changes to 12% (P = 0.34).
[c] Downgraded by one level for inconsistency. Some evidence of heterogeneity (I2 = 52%; P = 0.10), likely driven by Qadri 2021.
[d] Whilst the confidence interval appears wide, due to the large sample size, coupled with the absolute effect of 5 fewer to 6 more per 10,000, we did not rate down for imprecision.
[e] Capeding 2020 and Carlos 2022 reported unsolicited adverse events up to 28 days whilst Patel 2024 reported adverse events for 30 mins post vaccination. They all found similar AE rates and we have not downgraded for indirectness.

Summary of findings 2. Summary of findings table - TCV compared to non-conjugated typhoid vaccines (ViPS) for preventing typhoid fever

TCV compared to non-conjugated typhoid vaccines (ViPS) for preventing typhoid fever

Patient or population: preventing typhoid fever
Setting: South and Southeast Asia (the Philippines, Pakistan and India) and Europe (the United Kingdom and Belgium)
Intervention: TCV
Comparison: non-conjugated typhoid vaccines (ViPS)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with non-conjugated typhoid vaccines (ViPS)	Risk with TCV				
Acute typhoid fever follow-up: 28 days	351 per 1000	**316 per 1000** (169 to 594)	**RR 0.90** (0.48 to 1.69)	78 (1 RCT)	⊕⊕⊖⊖ Low[a,b]	TCV may result in little to no difference in acute typhoid fever when compared to non-conjugate typhoid vaccines.
Mortality - not reported	-	-	-	-	-	
Adverse events follow-up: range 28 days to 42 days	451 per 1000	**451 per 1000** (347 to 591)	**RR 1.00** (0.77 to 1.31)	244 (3 RCTs)	⊕⊕⊕⊖ Moderate[c,d]	TCV likely results in little to no difference in adverse events when compared to non-conjugate typhoid vaccines.

Serious adverse events follow-up: range 28 days to 90 days	11 per 1000	**3 per 1000** (1 to 21)	**RR 0.30** (0.05 to 1.88)	732 (2 RCTs)	⊕⊕⊕⊖ Moderate[e,f]	TCV likely results in a slight reduction in serious adverse events when compared to non-conjugate typhoid vaccines.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_447740500957782709.

[a] Downgraded one level for serious risk of bias: Jin 2017 was judged as high risk of bias due to deviations from intended interventions and bias due to missing outcome data.
[b] Downgraded one level for imprecision: the small sample size failed to meet the optimal information size.
[c] We did not downgrade for risk of bias: one study (Capeding 2018) showed some concerns of bias arising from the randomisation process but this was not sufficient to downgrade this domain.
[d] Downgraded one level for imprecision as the small sample sizes of the studies, with few events, decreases our confidence in the results.
[e] Downgraded one level for risk of bias: we judged Jin 2017 at high risk of bias due to deviations from intended interventions (per protocol analysis) and missing outcome data.
[f] With a low event rate (rare events) and an adequate sample size, rating down for imprecision becomes inappropriate.

Summary of findings 3. Summary of findings table - Vi-TT compared to other TCVs (Vi-DT or Vi-CRM197) for preventing typhoid fever

Vi-TT compared to other TCVs (Vi-DT or Vi-CRM197) for preventing typhoid fever

Patient or population: preventing typhoid fever
Setting: South and Southeast Asia (the Philippines, India and Nepal)
Intervention: Vi-TT
Comparison: other TCVs (Vi-DT or Vi-CRM197)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with other TCVs (Vi-DT or Vi-CRM197)	Risk with Vi-TT				

Acute typhoid fever - not reported	-	-	-	-	-	
All-cause mortality follow-up: range 42 days to 24 weeks	0 per 1000	**0 per 1000** (0 to 0)	**RR 5.19** (0.54 to 49.80)	2422 (2 RCTs)	⊕⊕⊖⊖ Low[a]	Vi-TT may result in little to no difference in all-cause mortality when compared to a different TCV.
Adverse events follow-up: range 28 days to 42 days	174 per 1000	**206 per 1000** (160 to 263)	**RR 1.18** (0.92 to 1.51)	2916 (4 RCTs)	⊕⊕⊕⊖ Moderate[b]	Vi-TT likely results in little to no difference in adverse events when compared to another TCV.
Serious adverse events follow-up: range 28 days to 24 weeks	3 per 1000	**6 per 1000** (2 to 21)	**RR 2.48** (0.74 to 8.36)	2866 (3 RCTs)	⊕⊕⊖⊖ Low[c]	Vi-TT may result in little to no difference in serious adverse events when compared to another TCV.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_447740507837489848.

[a] Downgraded by two levels for imprecision: mortality is a rare event, and in this case there is a very low event rate in both arms, with no events in the comparator arms for both included studies. However, the very wide confidence interval decreases our confidence in the precision.
[b] Downgraded by one level for inconsistency: evidence of heterogeneity (I2 = 39%), which is driven by Thuluva 2022, without a clear explanation for the heterogeneity.
[c] Downgraded by two levels for imprecision: serious adverse events are rare, and in this case there is a very low event rate in both arms, with no events in the comparator arms for both included studies. However, the very wide confidence interval decreases our confidence in the precision.

BACKGROUND

Description of the condition

Typhoid and paratyphoid fevers, collectively known as enteric fever, are caused by *Salmonella enterica* serovar *typhi* (*S typhi*) and *Salmonella enterica* serovar *paratyphi* A, B and C [1, 2, 3], which are rod-shaped, Gram-negative, facultative anaerobic bacteria [4]. They are a major cause of enteric disease-related morbidity and mortality, predominantly in children (peak incidence aged five to 15 years [5]) in low-and-middle-income countries (LMICs) [6]. In 2021, there were an estimated 9.2 million (95% confidence interval (CI) 7.3 to 11.9 million) cases of typhoid fever, with an associated 107,000 (95% CI 54,400 to 188,000) deaths globally [5].

Infection with *S typhi* is known as typhoid fever. *S typhi* is shed in the stools of infected persons, who may be acutely ill or healthy carriers of *S typhi* [7]. Faecal-oral transmission occurs through two mechanisms: (1) short-cycle, with food and water contaminated through poor sanitation and hygiene measures from temporary or chronic carriers of *S typhi,* or (2) long-cycle, with larger environmental contamination (water polluted with sewerage, inadequate water treatment, or use of raw human faeces or sewerage as fertiliser for crops [4, 7]). Transmission is through ingestion of *S typhi* in contaminated food or water. The bacterium penetrates the intestinal epithelium and is disseminated by the lymphatic system and bloodstream to multiply in the lymph nodes, gallbladder, liver and spleen [8].

Presentation is often non-specific, but includes a high temperature, up to 40°C, flu-like symptoms, such as headache, chills, malaise and myalgia, and abdominal symptoms, such as loss of appetite, nausea and vomiting. Abdominal pain may develop later in the clinical course [9, 10, 11, 12]. Complications of untreated typhoid fever include encephalopathy, gastrointestinal bleeding, hepatitis, psychosis, myocarditis, cholecystitis and intestinal perforation, with prevalence rates of 27% amongst a hospitalised population [13].

Diagnosis is complicated, as symptoms overlap with other causes of fever, and is dependent on isolation of the bacterium in blood, through culture or polymerase chain reaction [9, 14]. Blood culture is limited by a sensitivity of 61% (95% CI 52 to 70) [9]. Stool, urine and bone-marrow culture can also be used. Clinical diagnosis is often used, with administration of antibiotics whilst awaiting culture results. Early antibiotic treatment shortens disease duration and prevents complications [15], but can contribute to antimicrobial resistance [16]. Together with water, sanitation and hygiene (WASH) interventions [17], typhoid vaccination has proven effective in preventing typhoid fever and reducing the disease burden [18]. The World Health Organization (WHO) recommends typhoid vaccination in routine immunisation programmes in high-risk populations [4, 19].

Description of the intervention and how it might work

Different typhoid vaccines to prevent *S typhi* infection have been developed: non-conjugated typhoid vaccines, which include a live-attenuated, oral vaccine (Ty21a) and an unconjugated Vi polysaccharide (ViPS) injectable vaccine, and conjugated typhoid vaccines (TCVs). TCVs induce a vigorous immune response to bacterial capsular polysaccharides [20]. There are no vaccines available against *S paratyphi,* although there are several under development [21, 22].

TCVs licenced by the WHO include Typbar-TCV™, with tetanus toxoid as carrier, and Vi-CRM_{197}, with CRM_{197}, a non-toxic mutant of diphtheria toxin, as carrier. TCVs are preferred for all ages due to their improved immunological properties, suitability for use in children under two, and sustained duration of protection compared to non-conjugated typhoid vaccines. Safe co-administration of specific TCVs with other routine vaccines in children has shown no immune interference and to be well tolerated, supporting their inclusion in national immunisation schedules, specifically in endemic countries [23]. The Centers for Disease Control and Prevention (CDC) recommends either Ty21a or ViPS for people travelling to endemic areas, as TCVs are not yet licenced or available in the USA [24].

The TCVs included in this review are Vi tetanus toxoid (Vi-TT), Vi-CRM_{197}, Vi-diphtheria toxoid (Vi-DT) and Vi-rEPA, with details summarised in Table 1.

Vaccine protection is complex. Factors that may influence the immune response include intrinsic host factors, perinatal host factors, extrinsic actors, behaviour, nutrition, environment, vaccine and administration factors. Intrinsic host factors shown to influence vaccine response include age, sex, genetics and comorbidities [25]. Comorbidities influencing immune response include coeliac disease, diabetes, chronic renal disease and chronic liver disease [25]. Extrinsic factors include infections, e.g. HIV or malaria, or medical treatment [25]. This informed our subgroup analysis.

Why it is important to do this review

It is important that the most recent evidence be available to inform policies and programmes for the prevention of typhoid fever. Since 2018, when the WHO recommended the incorporation of TCVs into routine immunisation programmes for endemic regions, only six countries have implemented this directive [26, 27]. This review may inform the WHO's recommendations.

The availability of different TCVs is critical to ensure widespread, equitable vaccine access [28]. The previous Cochrane review noted three ongoing trials on TCVs [29]. Two of these trials have concluded, and the results are available in peer-reviewed publications.

This is an update of the previous Cochrane review, published in 1998, and updated in 2019 [29]. This updated version is restricted to TCVs.

OBJECTIVES

To assess the benefits and harms of TCVs compared to no vaccine, placebo, typhoid-inactive agents (vaccines for another disease) or other typhoid vaccines for preventing morbidity and mortality associated with typhoid fever in adults and children.

METHODS

We followed the Methodological Expectations of Cochrane Intervention Reviews (MECIR) [30] and the PRISMA 2020 guidelines [31].

Amendments made to the review since the publication of the protocol, including aspects of the protocol not implemented, are detailed in Supplementary material 9.

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), including cluster-RCTs (cRCTs). We did not include quasi-randomised studies.

Types of participants

We included studies on children and adults:

- living in typhoid-endemic areas; or
- accessing vaccination prior to travelling to typhoid-endemic areas.

No age, demographic or other restrictions were included.

Types of interventions

We included studies using the following TCVs:

- Vi-TT (Vi tetanus toxoid, including Typbar-TCV, Zyvac-TCV, Pedatyph)
- Vi-DT (Vi diphtheria toxoid)
- Vi-CRM_{197} (non-toxic mutant of diphtheria toxoid including TYPHIBEV)
- Other TCV vaccines (including Vi-rEPA)

We included the following comparisons:

- TCV versus no vaccine
- TCV versus placebo
- TCV versus typhoid-inactive agents (vaccines for another disease)
- TCV versus non-conjugated typhoid vaccines (e.g. unconjugated Vi polysaccharide (ViPS) and live-attenuated Ty21a vaccines)
- TCV versus other TCV vaccines

We combined the first three comparisons (no vaccines, placebo and vaccines for other diseases) into one: 'TCV versus control'.

Outcome measures

We measured the benefits and harms of TCVs.

Critical outcomes

- Acute typhoid fever, defined by laboratory-confirmed isolation of *S typhi* (e.g. blood cultures or stool sample)
- All-cause mortality

Important outcomes

- Adverse events (including fever, complications at injection site)
- Serious adverse events (any untoward medical occurrence that at any dose results in death, is life-threatening, requires or prolongs hospitalisation, results in persistent or significant disability or incapacity)

Search methods for identification of studies

We attempted to identify all relevant studies regardless of language, publication status or publication date limit.

Electronic searches

We searched the following databases on 19 April 2024 for primary studies:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2024, Issue 3);
- MEDLINE Ovid (1946 to 18 April 2024);
- Embase Ovid (1974 to 19 April 2024);
- CINAHL EbscoHost (Cumulative Index to Nursing and Allied Health Literature; 1982 to 19 April 2024);
- Global Index Medicus (1993 to 19 April 2024).

The search histories are in Supplementary material 1.

Searching other resources

We searched for ongoing trials on 19 April 2024 at www.clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP; trialsearch.who.int/). We also checked the Centers for Disease Control Advisory Committee on Immunization Practices (ACIP) and the WHO vaccine repository up to 19 April 2024 for additional trial reports. We searched grey literature of relevant conference abstracts via PubMed, checked reference lists of reviews, retrieved articles for additional studies and performed citation searches on key articles. We contacted study authors for additional information where necessary, and contacted relevant individuals and organisations for information about unpublished or ongoing studies.

On 19 November 2024, we searched Retraction Watch, using the authors, title and DOI of each included study. We also searched PubMed for errata linked to included studies using the PMID.

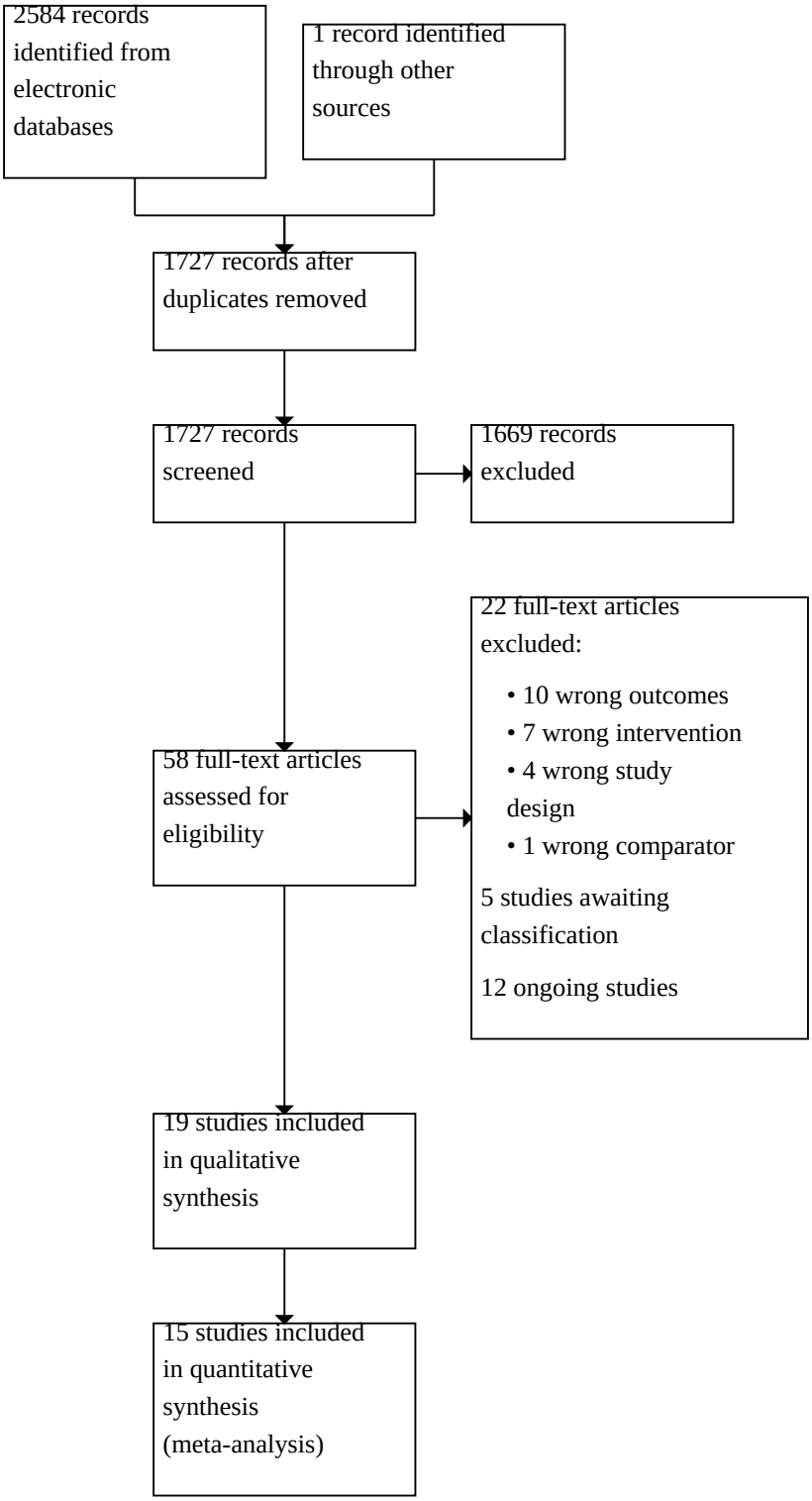
Data collection and analysis

We uploaded the search results to Covidence [32] and removed duplicates. Where relevant, we contacted authors for missing information to confirm the eligibility of studies. We present all comparisons and outcomes in the summary of findings tables.

Selection of studies

Three review authors (NG, MM, TL) independently screened titles and abstracts for potentially eligible studies and obtained full-text copies. NG, MM and TL independently identified studies for inclusion based on the eligibility criteria. In the event of disagreement, a fourth author (TK) adjudicated. We included a PRISMA flowchart (Figure 1) [31, 33] and a table of 'Characteristics of the included studies' (Supplementary material 2). We provide a table listing the excluded studies with justifications (Supplementary material 3).

Figure 1.



Data extraction and management

Four authors (NG and MM; TL and CI) independently extracted characteristics of included studies and outcome data, and entered them into a standard, piloted data extraction form. We extracted the following:

- Methods: study design, number of study centres and locations, study setting, withdrawals, date of study and length of follow-up.
- Participants: number, mean age and range, gender, inclusion and exclusion criteria, country and other relevant characteristics.
- Intervention: type of TCV, dose, schedule, route of administration, clinical trial phase and data on fractional doses, where applicable.
- Comparison: type of comparison - no vaccine, placebo, other non-typhoid vaccine or other typhoid vaccine.
- Outcome measures: study outcomes and time points reported (number of participants and of events per arm), number of participants randomised in each arm and with adverse events in each arm, number who withdrew, were lost to follow-up or were excluded.

Where the authors did not provide these data, we proceeded as explained under Dealing with missing data.

Any outcome data that could not be synthesised were reported in the 'Characteristics of included studies' table. Any disagreements were resolved through consensus, or by involving an additional author (TK).

Risk of bias assessment in included studies

Four authors (NG, MM, TL and CI) independently assessed the risk of bias for all relevant outcomes, using the Cochrane risk of bias (RoB) 2 tools for RCTs and cRCTs [34, 35]. Disagreements were resolved through discussion, or through adjudication (TK/PdK). We used the RoB 2 Excel tools for RCTs and cRCTs [35], and assessed the risk of bias for reported primary and secondary outcomes, using the intention-to-treat effect. Outcomes were measured at various time points with acute typhoid fever measured between one month to four years post-vaccination, all-cause mortality reported between 42 days and 27 months post-vaccination, adverse events (AEs) reported between 28 days and four years post-vaccination and serious adverse events (SAEs) reported between 21 days and four years post-vaccination. The follow-up periods for the outcomes reported per trial are in Table 2.

We assessed bias across the following domains.

- Bias arising from the randomisation process (whether the allocation concealment was random and maintained, and if baseline differences between groups suggested randomisation issues).
- Bias arising from deviations from the intended interventions (effect of assignment to intervention; knowledge of interventions by participants, carers or researchers; deviations due to trial context influencing outcomes and whether these deviations were balanced between groups; whether an appropriate method was used to analyse the effect of assignment to intervention; and whether there was a potential impact on the outcome due to failing to analyse participants in their assigned groups).
- Bias due to missing outcome data (whether data were available for the specific outcome for all or nearly all randomised participants; there was evidence that missing data could bias the results; and/or the missing data could be due to participants' health status or reasons related to the outcome).
- Bias in outcome measurement (whether the method of measuring the outcome was appropriate; the measurement differed between intervention groups; and/or outcome assessors were aware of interventions allocated to participants, which may affect the assessment).
- Bias from selection of the reported results (whether data analysis was performed according to a prespecified plan; and the numerical result was selected based on results of multiple eligible measurements or data analyses).

For cRCTS, we assessed the additional component of bias arising from identification or recruitment of individual participants within clusters.

We used the signalling questions and tool algorithms available in the RoB 2 tool to determine if an outcome was at high risk, had some concerns or was at low risk of bias. We defined bias as 'low risk' when all domains were judged as low risk, 'some concerns' when at least one domain was judged to raise some concerns of bias and 'high risk' when at least one domain was judged as high risk. We did not exclude studies due to high risk of bias, but we reported and considered the risk when presenting and interpreting the results for the relevant outcomes (see Sensitivity analysis).

We applied the overall risk of bias judgement when assessing the certainty of the evidence for each outcome, following the GRADE recommendations.

Measures of treatment effect

We reported risk ratios (RR), with 95% confidence intervals (CIs) for dichotomous data. We did not anticipate any continuous data for the specified outcomes. We planned to present time-to-event outcomes as hazard ratios (HR) with 95% CIs.

Unit of analysis issues

For cRCTs, we adjusted for the effects of randomisation prior to including effect estimates in our meta-analysis. When a cRCT did not adjust for clustering, we extracted unadjusted primary data, and adjusted these using the intra-cluster correlation coefficient (ICC). If the ICC was not reported, we planned to contact study authors, or use an ICC value from a similar study, or estimate the ICC. If an extrapolated or estimated ICC was used, we conducted sensitivity analyses to investigate the robustness of our conclusions [36]. We used an ICC of 0.0013, as calculated by the authors of Qadri 2021 [37, 38, 39, 40, 41], when adjusting data for the two included cRCTs.

For trials with multiple arms, we considered each pair-wise comparison and included those relevant to the review objectives. We described these in the 'Characteristics of included studies' table (Supplementary material 2). There were no instances where one study with multiple intervention groups was included in a meta-analysis more than once.

Dealing with missing data

We analysed all outcomes on an intention-to-treat basis. We contacted the authors of the included studies for missing data and information, where relevant. Where it was not possible to obtain the missing data, we reported the gaps, and considered how the certainty of evidence was impacted. When needed, we planned to impute missing data to report intention-to-treat analyses [42]. We planned to describe any assumptions and imputations used to deal with missing data, and to explore the effect of imputation with a sensitivity analysis (e.g. best- and worst-case scenarios). When numbers of participants and events were not available, but an effect estimate was reported, we planned to use the generic inverse variance method to include these data in meta-analysis, provided measures of uncertainty (e.g. standard error, P value or 95% CI) were available [43].

Reporting bias assessment

We planned to assess publication bias using funnel plots if 10 or more studies were included in a meta-analysis for a given outcome.

Synthesis methods

We analysed the data using Review Manager Web (RevMan Web) [44]. We synthesised results for each outcome using meta-analysis, where possible, using the Mantel-Haenszel method with a random-effects analysis model. Where this was not possible due to the nature of the data, we planned to synthesise results using direction of effect, using the SWiM reporting guideline [45]. The primary analysis included all eligible studies.

We assessed heterogeneity by inspecting the forest plots for overlapping 95% CIs, the Chi^2 test, P value and the I^2 statistic [46]. Thresholds for I^2 may be misleading - we classified heterogeneity as: 0% to 40% may not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and 75% to 90% may represent considerable heterogeneity.

Where studies reported no events in either arm, we excluded them from the meta-analysis but reported the results narratively [47]. When comparing TCVs, we selected Vi-TT as the intervention, as it was the most frequently utilised intervention in the included studies. We used GRADE to assess the certainty of the evidence for each outcome.

Investigation of heterogeneity and subgroup analysis

We conducted subgroup analyses for heterogeneity. When statistical heterogeneity was significant and unexplained, we interpreted the meta-analysis correspondingly, and downgraded the certainty of evidence in the summary of findings tables, as per GRADE recommendations.

We planned to perform subgroup analyses based on the following anticipated effect modifiers. However, the available data were sparse and insufficient.

- Endemicity (travellers versus routine vaccination for those living in typhoid-endemic areas)
- Age groups
  - Young children (one to 23 months old)
  - Older children (two to 12 years old)
  - Adolescents (12 to 17 years old)
  - Adults (18 years and older)
- Immunosuppression (participants with comorbid conditions causing immunosuppression, such as HIV and malnutrition) [25]

We added a post hoc subgroup analysis assessing the length of protection conferred by TCVs against acute typhoid fever compared to a control.

Equity-related assessment

We did not pre-plan a health equity assessment but applied the PROGRESS-Plus framework to guide data extraction and analysis [48]. This helped us identify health disparities across PROGRESS-Plus factors in the relevant trials to consider the impact of interventions on health equity. PROGRESS-Plus variables captured included research setting, which speaks to place of residence and socio-economic status, personal characteristics associated with discrimination, features of relationships and time-dependent relationships.

Sensitivity analysis

We undertook sensitivity analyses to assess the effect of high risk of bias in any included studies, and the effect of the trial phase (excluding phase I and II trials from the overall meta-analysis) on the outcomes. Further, as mentioned in the Unit of analysis issues and Dealing with missing data sections, we conducted sensitivity analyses to investigate the robustness of our conclusions if we extrapolated or estimated the ICC for cluster-randomised trials, and planned to explore the effect of any imputation performed for missing data [36].

Certainty of the evidence assessment

Three authors (NG, TL and TK) conducted the GRADE assessment with all authors reviewing and providing input. We summarised the results of the analysis in the summary of findings tables, and presented summary effect estimates for all outcomes, using the GRADE framework to assess the certainty of evidence [49]. We considered five domains for decreasing our confidence in the results: risk of bias, inconsistency, indirectness, imprecision and publication bias. We resolved any disagreements through discussion, and justified downgrading decisions in footnotes. We reported each comparison in a separate summary of findings table. Duration of follow-up differed from under 12 months to four years. We did not pre-specify timeframes for follow-up of focus but conducted a sensitivity analysis, which found little difference in the effect size, and we therefore synthesised all the studies regardless of their duration of follow-up.

Consumer involvement

Whilst we did not pre-specify consumer involvement in our protocol, we asked a lay person to review our plain language summary.

RESULTS

Description of studies

See Supplementary material 2 for the characteristics of the included studies, as well as Table 2 for the 'Overview of synthesis and included studies (OSIS)' table illustrating key characteristics of studies, outcomes and analyses. A complete record of all

comparisons and analyses can be found in Supplementary material 7 and a full data package is available in Supplementary material 8.

Results of the search

Searches were conducted on 18 May 2023 and 18 April 2024. We searched the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, CINAHL, Global Index Medicus, clinicaltrials.gov and WHO ICTRP, as well as ACIP and the WHO vaccine repository. The search strategies are in Supplementary material 1. The search yielded 2584 records, of which 857 were duplicates. We excluded 1669 records at title and abstract screening. We assessed 58 full-text studies for eligibility, of which 22 were excluded, 12 were ongoing studies, five are awaiting classification and 19 were included. Our search of Retraction Watch and PubMed for errata yielded no results related to the included studies.

The PRISMA flow chart illustrates the process (Figure 1). We describe the excluded studies in Supplementary material 3, the studies awaiting classification in Supplementary material 4 and the ongoing studies in Supplementary material 5.

Included studies

Of the 19 included studies, 17 were randomised at the individual participant level and two were cRCTs (Mitra 2016 [50, 51]; Qadri 2021). Table 2 is a summary of included trials; study characteristics that are important for interpreting the syntheses and full details of the included studies are in Supplementary material 2.

Six studies were conducted in the Philippines (Bhutta 2014 [52, 53, 54]; Capeding 2018 [55, 56]; Capeding 2020 [57, 58, 59, 60]; Carlos 2022 [61, 62]; Choi 2021 [63, 64]; Ok Baik 2023 [65, 66]); five in India (Bhutta 2014; Kundu 2020 [67]; Mitra 2016; Mohan 2015 [68, 69]; Thuluva 2022 [70, 71]); two in Indonesia (Koesnoe 2024 [72, 73, 74, 75]; Medise 2019 [76, 77]); two in Nepal (Kumar Rai 2022 [78, 79, 80, 81]; Shakya 2021 [82, 83, 84]); and one each in Pakistan (Bhutta 2014), Vietnam (Lin 2001 [85, 86]), Bangladesh (Qadri 2021), Malawi (Patel 2024 [87, 88, 89, 90, 91, 92]), Belgium (van Damme 2011 [93, 94, 95]) and the United Kingdom (Jin 2017 [96, 97, 98]).

Three studies were Phase I trials (Capeding 2018; Choi 2021; Medise 2019); one was a Phase I/II trial (van Damme 2011); four were Phase II trials (Bhutta 2014; Capeding 2020; Jin 2017; Koesnoe 2024); three were Phase II/III trials (Kundu 2020; Ok Baik 2023; Thuluva 2022); five were Phase III trials (Carlos 2022; Kumar Rai 2022; Mohan 2015; Patel 2024; Shakya 2021); one was a Phase IV trial (Mitra 2016); and for two (Lin 2001; Qadri 2021), the trial phase was not specified. Jin 2017 is a human oral-challenge study where, after vaccination, participants ingested *S typhi* orally and were then assessed with daily blood cultures over a two-week period to diagnose acute typhoid infection. When we found the trial linked to Jin 2017, we contacted the authors to confirm whether the results had been published and the authors shared the publication link.

Participants

The 19 studies enrolled 395,650 participants, of whom 394,790 were included in our meta-analysis. Sample sizes ranged from 75 (Choi 2021) to 326,794 participants (Qadri 2021), with ages ranging from six weeks to 60 years.

Interventions

Included TCVs were Vi-TT, Vi-CRM_{197}, Vi-DT and Vi-rEPA. Vi-TT was an intervention or comparison in 10 studies (Jin 2017; Kumar Rai 2022; Kundu 2020; Mitra 2016; Mohan 2015; Ok Baik 2023; Patel 2024; Qadri 2021; Shakya 2021; Thuluva 2022), Vi-DT in six studies (Capeding 2018; Capeding 2020; Carlos 2022; Koesnoe 2024; Kumar Rai 2022; Medise 2019), Vi-CRM_{197} in four studies (Bhutta 2014; Choi 2021; Ok Baik 2023; Thuluva 2022; van Damme 2011), and Vi-rEPA in one study (Lin 2001), where Vi-rEPA was compared to placebo in children aged two to five years. When comparing TCVs, we chose to use Vi-TT as the intervention as this was the most common intervention in the included studies. Vaccines were delivered as a single dose in 14 studies (Bhutta 2014; Carlos 2022; Choi 2021; Jin 2017; Kumar Rai 2022; Kundu 2020; Koesnoe 2024; Mohan 2015; Ok Baik 2023; Patel 2024; Qadri 2021; Shakya 2021; Thuluva 2022; van Damme 2011); in two doses, ranging from four to 24 weeks apart, in six studies (Bhutta 2014; Capeding 2018; Capeding 2020; Lin 2001; Medise 2019; Mitra 2016); and in three doses, four weeks apart, in one study (Bhutta 2014). In Bhutta 2014, the number of doses (one, two or three) was determined by age (see Supplementary material 2).

Comparators

TCV was compared to inactive comparators in 10 studies - TCV was compared to no vaccine in one (Mitra 2016), to placebo in two (Capeding 2020; Lin 2001) and to typhoid-inactive agents (i.e. including inactivated polio, Japanese encephalitis, meningococcal capsular group A conjugate and influenza vaccines) in seven (Bhutta 2014; Carlos 2022; Jin 2017; Koesnoe 2024; Patel 2024; Qadri 2021; Shakya 2021). Seven studies compared TCV with non-conjugated typhoid vaccines (Bhutta 2014; Capeding 2018; Choi 2021; Jin 2017; Medise 2019; Mohan 2015; van Damme 2011). Six studies compared one TCV to another (Carlos 2022; Choi 2021; Kumar Rai 2022; Kundu 2020; Ok Baik 2023; Thuluva 2022).

Outcomes

All outcomes reported are noted in the 'Characteristics of included studies' table (Supplementary material 2). Those relevant to this review are summarised below.

Acute typhoid fever, defined by laboratory-confirmed isolation of *S typhi*

Six studies reported on typhoid fever identified by isolating *S typhi* from blood cultures (Jin 2017; Lin 2001; Mitra 2016; Patel 2024; Qadri 2021; Shakya 2021). No studies reported typhoid fever diagnosed through stool culture.

All-cause mortality

Eleven studies reported all-cause mortality (Bhutta 2014; Carlos 2022; Choi 2021; Kumar Rai 2022; Lin 2001; Ok Baik 2023; Patel 2024; Qadri 2021; Shakya 2021; Thuluva 2022; van Damme 2011). Of these, four reported mortality but noted that there were no deaths (Bhutta 2014; Choi 2021; Ok Baik 2023; van Damme 2011).

Adverse events (AEs)

All included studies except Lin 2001 reported AEs.

Serious adverse events (SAEs)

All included studies except Mitra 2016 reported SAEs.

Excluded studies

We excluded 22 studies. Of these, 10 were excluded for assessing the wrong outcomes (CTRI/2016/01/006476 [99]; CTRI/2016/05/006975 [100]; CTRI/2018/01/011500 [101]; CTRI/2021/09/036577 [102]; EUCTR2011-000381-35-GB [103]; Jin 2021 [104]; Khanam 2023a [105]; Khanam 2023b [106]; NCT04741828 [107]; Voysey 2018 [108]), seven for using the wrong intervention (NCT00131833 [109]; NCT00679172 [110]; NCT05771779 [111]; Saluja 2022 [112]; Sirima 2020 [113, 114]; Sirima 2021 [115]; Wahid 2012 [116]), four for having the wrong study design (Haselbeck 2021 [117]; NCT05119426 [118]; Olaru 2019 [119] Schwartz 2009 [120]) and one for using the wrong comparator (EUCTR2011-001448-31-BE [121]). The 'Characteristics of excluded studies' table is in Supplementary material 3.

Studies awaiting classification

We categorised five studies as awaiting classification (EUCTR2010-021874-12-BE [122]; EUCTR2011-003653-26-GB [123]; Patel 2023 [124]; Szu 1998 [125]; Tesema 2018 [126]). More information is available in the 'Characteristics of studies awaiting classification' table (Supplementary material 4).

Ongoing studies

We identified 12 ongoing studies (CTRI/2019/04/018634 [127]; CTRI/2022/03/041314 [128]; CTRI/2022/06/043608 [129]; NCT04051268 [130]; NCT04852185 [131]; NCT05475379 [132]; NCT05480800 [133]; NCT05500482 [134]; NCT05613205 [135]; NCT05784701 [136]; PACTR202011804563392 [137]; PACTR202112680671189 [138]), summarised in the 'Characteristics of ongoing studies' table (Supplementary material 5)

Two studies compare TCV to no vaccine - these are both cRCTs (CTRI/2022/03/041314; NCT05500482); two compare TCV to placebo (NCT05480800; NCT05784701); four compare TCV to typhoid-inactive agents (NCT04852185; NCT05480800; NCT05613205; PACTR202011804563392), two of which are cRCTs (NCT04852185; PACTR202011804563392); four compare TCV to a non-TCV typhoid vaccine (CTRI/2019/04/018634; NCT04051268; NCT05480800; NCT05613205); and six compare TCV to a different TCV (CTRI/2022/06/043608; NCT04051268; NCT05475379; NCT05480800; NCT05784701; PACTR202112680671189). One study compares a bivalent conjugate vaccine to Vi-TT TCV (CTRI/2022/06/043608).

Risk of bias in included studies

We assessed the risk of bias in the 15 trials contributing to the meta-analyses (Capeding 2018; Capeding 2020; Carlos 2022; Choi 2021; Jin 2017; Kumar Rai 2022; Lin 2001; Mitra 2016; Mohan 2015; Ok Baik 2023; Patel 2024; Qadri 2021; Shakya 2021; Thuluva 2022; van Damme 2011). We rated the risk of bias as high for two outcomes in a human oral-challenge study (Jin 2017), and as unclear for two outcomes in two studies (Capeding 2018; Mitra 2016).

We evaluated the risk of bias for the outcomes: acute typhoid fever, all-cause mortality, AEs and SAEs. For a confirmed diagnosis of acute typhoid fever, we judged one trial as high risk of bias overall (Jin 2017), and another had some concerns of bias (Mitra 2016). For all-cause mortality, AEs and SAEs, we judged all trials as low risk of bias. See Supplementary material 6 for detailed risk of bias assessment data. Risk assessment per domain is summarised below.

RoB summary per domain

Random sequence generation and allocation concealment

We judged this domain as low risk of bias for all trials except Capeding 2018, which reported insufficient information to assess risk.

Deviations from the intended interventions

We judged this domain as high risk in one trial for the outcomes of acute typhoid fever and SAEs (Jin 2017), as unblinding was required to account for expired investigational vaccine (Vi-TT). There were some concerns of bias for the outcome of acute typhoid fever for the cRCT by Mitra 2016. It was uncertain if participants were identified and recruited before randomisation of clusters, and in the vaccination group, those in higher quintiles had better access to sanitation and drinking water in the vaccination group. Data were not adjusted and analysed per protocol. We assessed the other trials as low risk of bias for this domain across outcomes.

Missing outcome data

Included trials had minimal missing outcome data overall, except Jin 2017 where outcome data for the intervention and control groups for acute typhoid fever and SAEs were incomplete and analysed per protocol. The authors did not report whether sensitivity analyses were performed to assess the impact of the missing data on the results (Jin 2017). We judged the trial as high risk of bias for this domain.

Measurement of the outcome

We deemed the reporting of mortality, SAEs and AEs not to be subject to bias. Although AEs were self-reported, these were limited, of mild to moderate severity and mostly comparable between vaccination and control groups.

Selective reporting

For AEs, SAEs and mortality, despite the uncertainty about whether all trials were prospectively registered, reporting these trial outcomes is standard good clinical practice. Thus, we judged all trials as low risk of bias.

Other bias

We had no concerns about any other aspects of the trials, and assessed all as low risk of bias for this domain.

Synthesis of results

There were three comparisons: 1) TCV versus control, 2) TCV versus non-conjugated typhoid vaccine and 3) TCV versus other TCVs, summarised in Table 3. The findings are reported by outcome below. More information for each comparison is available in Supplementary material 7 and Supplementary material 8. The absolute and relative effects of outcomes with their GRADE ratings are summarised in Summary of findings 1, Summary of findings 2 and Summary of findings 3. Data not included are summarised in Table 4.

Comparison 1: TCV versus control

Nine studies compared TCV to control (Capeding 2020; Carlos 2022; Jin 2017; Koesnoe 2024; Lin 2001; Mitra 2016; Patel 2024; Qadri 2021; Shakya 2021). We considered a comparator to be a

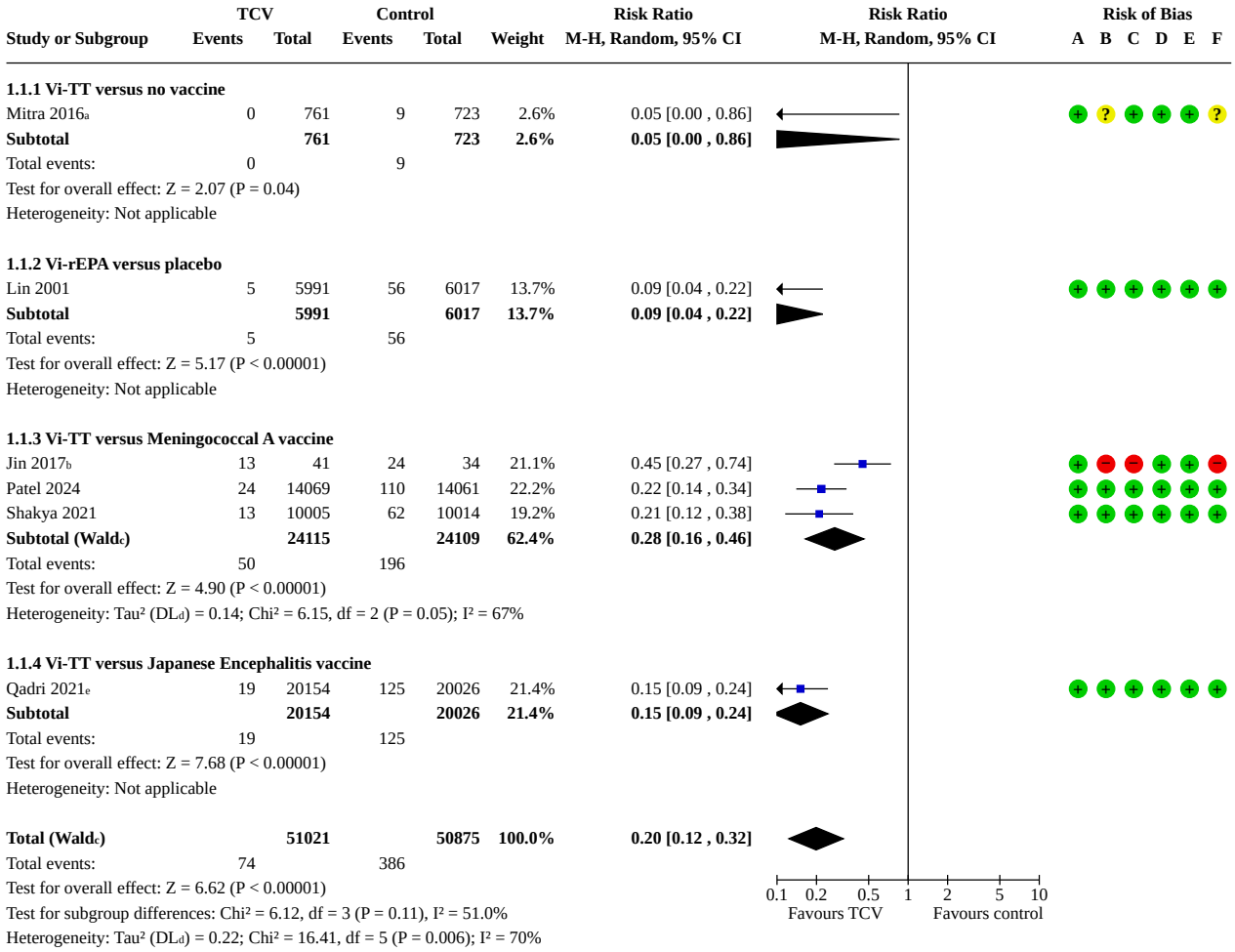
control if TCV was compared to an agent unrelated to typhoid, i.e. no vaccine, placebo or to a vaccine for a non-typhoid condition (e.g. meningococcal A vaccine). One study compared Vi-TT to no vaccine (Mitra 2016), two compared TCV to placebo (Capeding 2020; Lin 2001) and six compared TCV to a vaccine for a different illness (Carlos 2022; Jin 2017; Koesnoe 2024; Patel 2024; Qadri 2021; Shakya 2021). More details around the certainty of evidence are available in Summary of findings 1. Data not included are summarised in Table 4.

Critical outcomes

1.1. Acute typhoid fever

Six studies reported this outcome and were included in the meta-analysis (Jin 2017; Lin 2001; Mitra 2016; Patel 2024; Qadri 2021; Shakya 2021). TCV may result in a large reduction in acute typhoid fever when compared to control (risk ratio (RR) 0.20, 95% confidence interval (CI) 0.12 to 0.32; I^2 = 70%; 6 studies, 101,896 participants; low-certainty evidence; Analysis 1.1; Figure 2). We downgraded the certainty of the evidence by one level for serious risk of bias and one level for serious inconsistency.

Figure 2. TCV may result in a large reduction in acute typhoid fever when compared to control



Footnotes

[a]Adjusted using an intracluster correlation coefficient (ICC) of 0.0013 from Qadri 2021
[b]Human challenge study
[c]CI calculated by Wald-type method.
[d]Tau² calculated by DerSimonian and Laird method.
[e]Adjusted using an ICC of 0.0013 from Qadri 2021

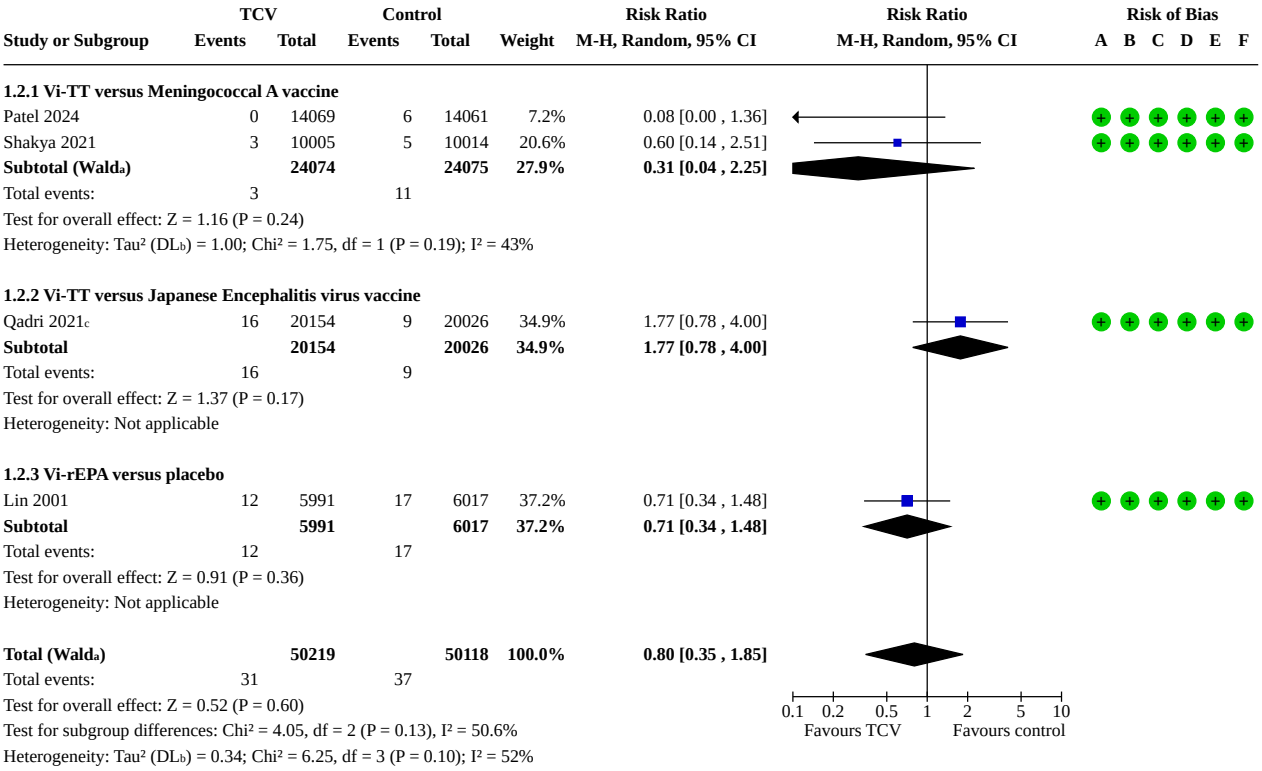
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

1.2 All-cause mortality

Four studies reported this outcome and were included in the meta-analysis (Lin 2001; Patel 2024; Qadri 2021; Shakya 2021). TCV probably results in little to no difference in all-cause mortality when compared to control (RR 0.80, 95% CI 0.35 to 1.85; I^2 = 52%; 4 studies, 100,337 participants; moderate-certainty evidence; Analysis 1.2; Figure 3). We downgraded the certainty of the evidence by one level for serious unexplained inconsistency.

Figure 3. TCV probably results in little to no difference in all-cause mortality when compared to control



Footnotes

[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.
[c]Adjusted using an ICC of 0.0013 from Qadri 2021

Risk of bias legend

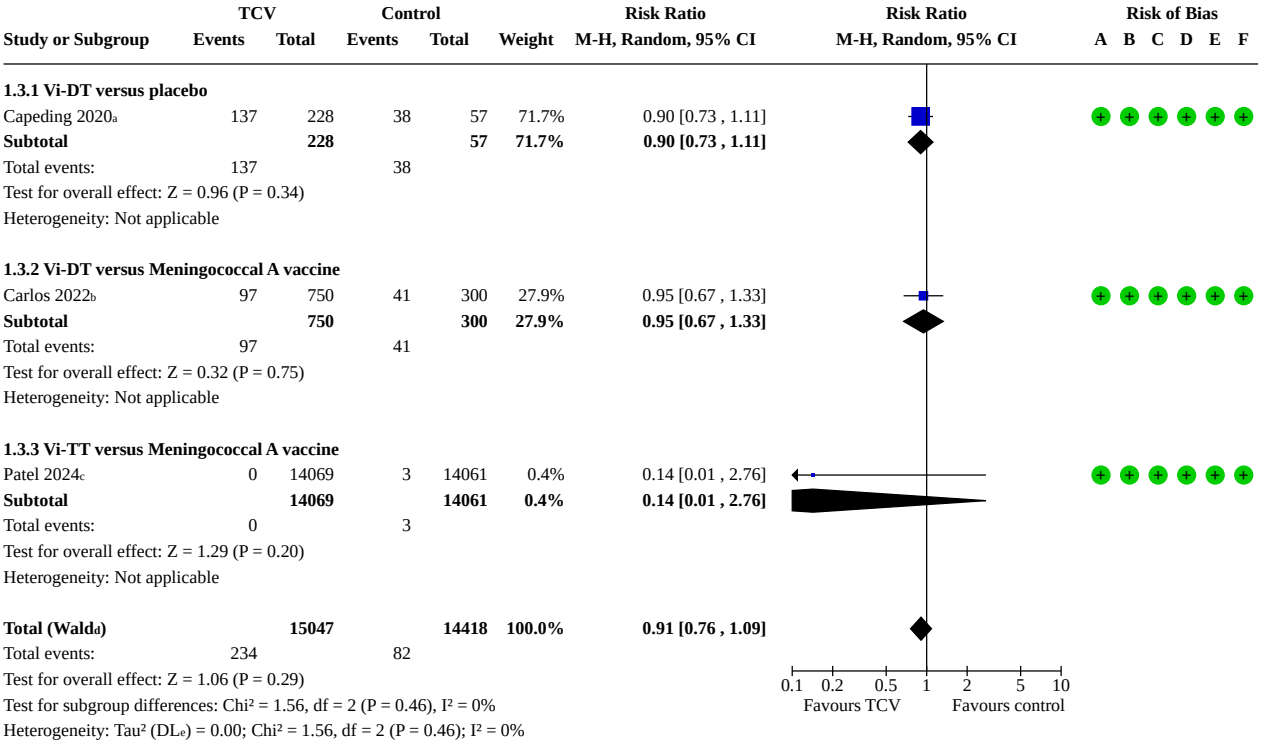
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Important outcomes

1.3 Adverse events

Seven studies reported this outcome (Capeding 2020; Carlos 2022; Koesnoe 2024; Mitra 2016; Patel 2024; Qadri 2021; Shakya 2021). Three were included in the meta-analysis (Capeding 2020; Carlos 2022; Patel 2024). TCV results in little to no difference in adverse events when compared to control (RR 0.91, 95% CI 0.76 to 1.09; I^2 = 0%; 3 studies, 29,465 participants; high-certainty evidence; Analysis 1.3; Figure 4). Koesnoe 2024 was not included as the reporting of adverse events was unclear. In Mitra 2016, adverse events were only reported for the intervention and not the control group. Qadri 2021 reported the overall incidence of adverse events for both groups (not per arm). Shakya 2021 listed adverse events by specific event but not overall per group and, as such, was not included.

Figure 4. TCV results in little to no difference in adverse events when compared to control



Footnotes

[a]Unsolicited adverse events reported within 28 of receiving the vaccine
[b]Unsolicted adverse events recorded within 28 days of vaccination
[c]Adverse events within 30 minutes after vaccination
[d]CI calculated by Wald-type method.
[e]Tau² calculated by DerSimonian and Laird method.

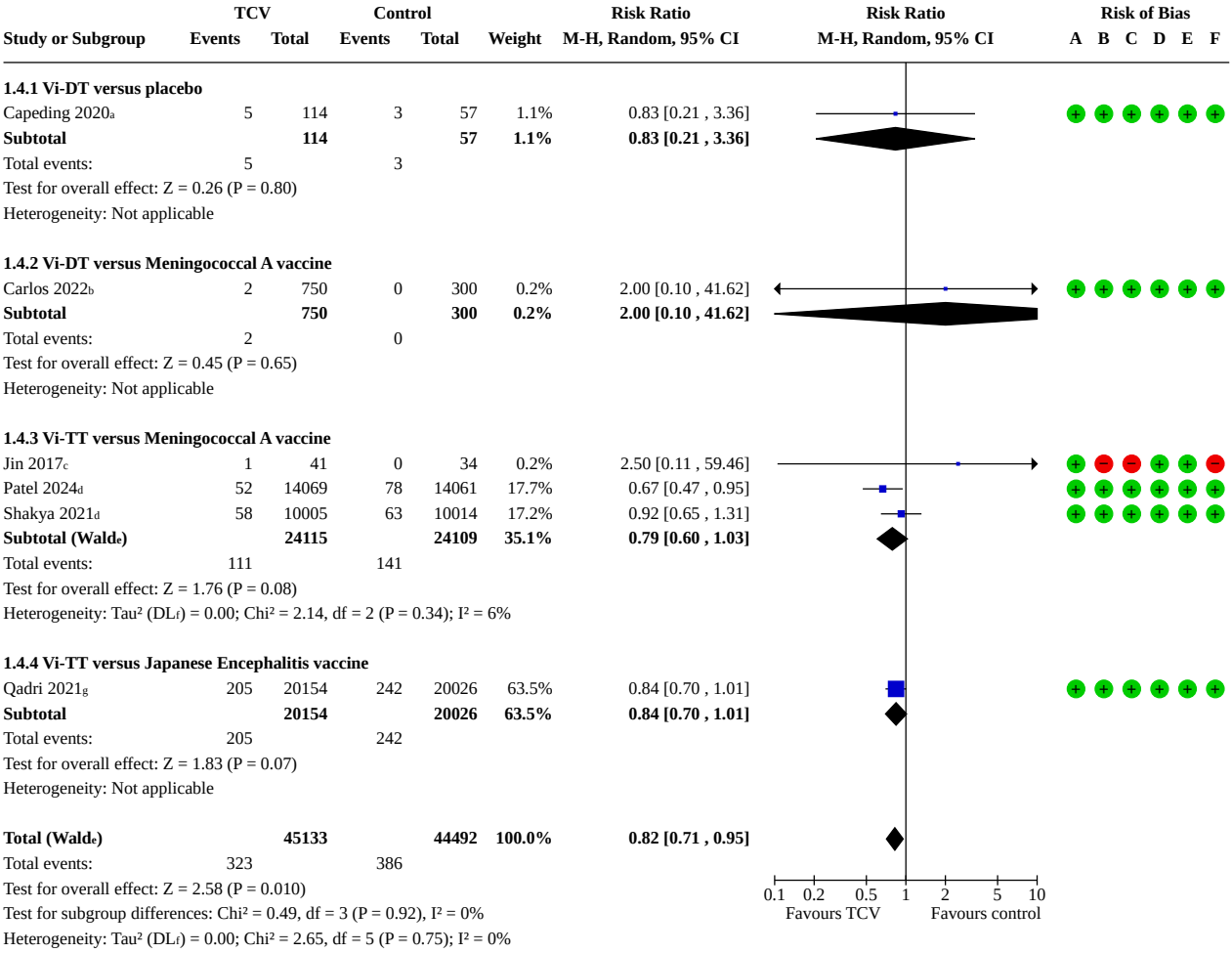
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

1.4 Serious adverse events

Eight studies reported this outcome (Capeding 2020; Carlos 2022; Jin 2017; Lin 2001; Koesnoe 2024; Patel 2024; Qadri 2021; Shakya 2021). Six were included in the meta-analysis (Capeding 2020; Carlos 2022; Jin 2017; Patel 2024; Qadri 2021; Shakya 2021). TCV results in a slight reduction in serious adverse events compared to control (RR 0.82, 95% CI 0.71 to 0.95; I^2 = 0%; 6 studies, 89,625 participants; high-certainty evidence; Analysis 1.4; Figure 5). Lin 2001 and Koesnoe 2024 reported this outcome, but as there were no events in either study, the data were not included.

Figure 5. TCV results in a slight reduction in serious adverse events compared to control



Footnotes

aSAEs reported up to 28 weeks from vaccination. Participants in Groups A and C received one dose of Vi-DT or saline, respectively, followed by a dose of fluquadri at 24 weeks.
bThis comparison excludes data from the Vi-DT multidose arm
cHuman challenge study
dSAEs reported within six months of vaccination
eCI calculated by Wald-type method.
fTau² calculated by DerSimonian and Laird method.
gData were adjusted using the ICC of 0.013 from Qadri 2021. SAEs were reported from vaccination up until the end of the study period.

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 2: TCV versus non-conjugated typhoid vaccines

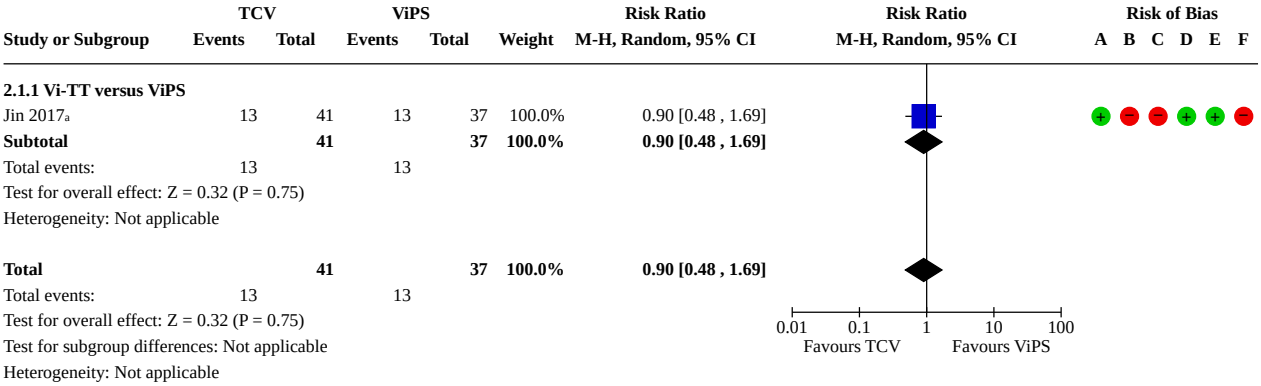
Six studies compared TCV to non-conjugated typhoid vaccines (Bhutta 2014; Capeding 2018; Choi 2021; Jin 2017; Mohan 2015; van Damme 2011). All six compared TCV to an unconjugated Vi polysaccharide vaccine (ViPS) and none compared TCV to the live-attenuated vaccine (Ty21a). More details around the certainty of evidence are available in Summary of findings 2. Data not included are available in Table 4.

Critical outcomes

2.1 Acute typhoid fever

One study reported this outcome and was included in the meta-analysis (Jin 2017). TCV may result in little to no difference in acute typhoid fever when compared to non-conjugated typhoid vaccines (RR 0.90, 95% CI 0.48 to 1.69; 1 study, 78 participants; low-certainty evidence; Analysis 2.1; Figure 6). We downgraded the certainty of the evidence by two levels for serious risk of bias and imprecision.

Figure 6. TCV may result in little to no difference in acute typhoid fever when compared to non-conjugated typhoid vaccines



Footnotes

[a]Human challenge study

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

2.2 All-cause mortality

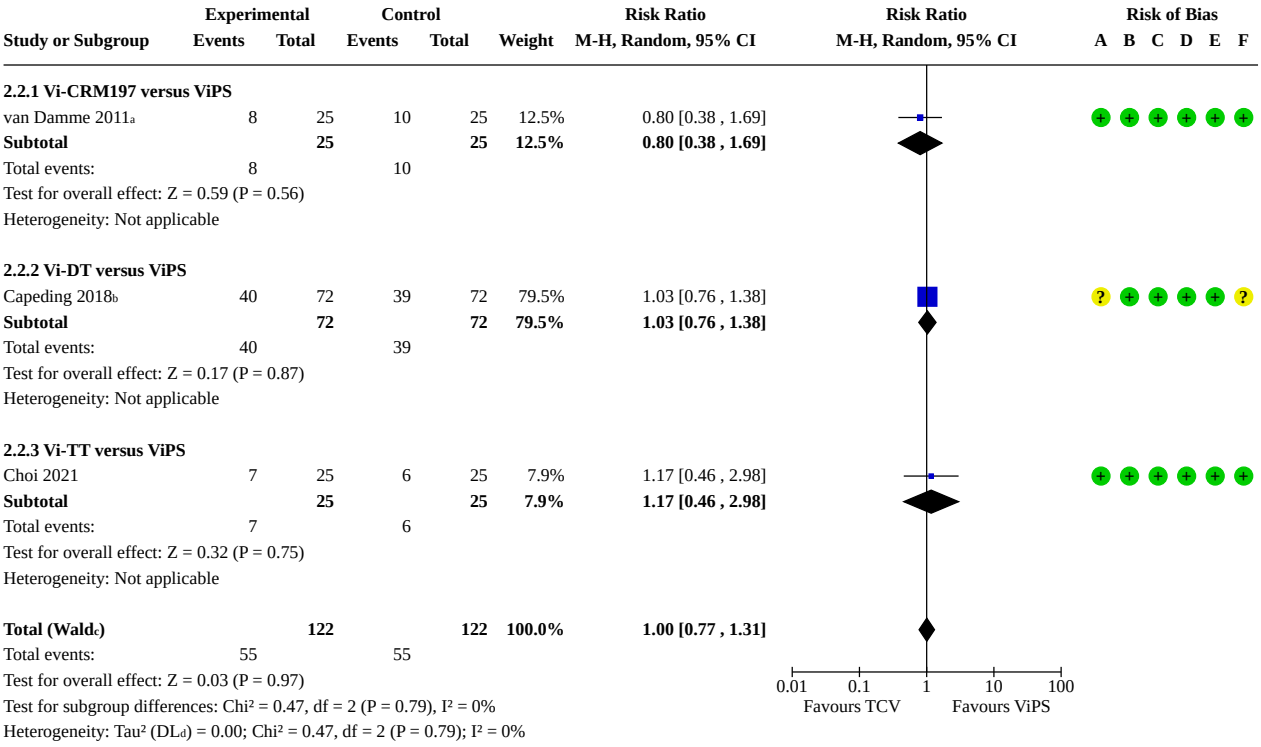
Two studies, both comparing Vi-CRM$_{197}$ to ViPS, reported this outcome, but as there were no events, these were not included in a meta-analysis (Bhutta 2014; van Damme 2011).

Important outcomes

2.3 Adverse events

Four studies reported this outcome (Capeding 2018; Choi 2021; Mohan 2015; van Damme 2011). Three were included in the meta-analysis (Capeding 2018; Choi 2021; van Damme 2011). TCV likely results in little to no difference in adverse events when compared to non-conjugated typhoid vaccines (RR 1.00, 95% CI 0.77 to 1.31; I^2 = 0%; 3 studies, 244 participants; moderate-certainty evidence; Analysis 2.2; Figure 7). We downgraded the certainty of the evidence by one level for imprecision. Mohan 2015 reported adverse events by specific event, e.g. fever or headache, as opposed to overall adverse events, and so was not included.

Figure 7. TCV likely results in little to no difference in adverse events when compared to non-conjugated typhoid vaccines



Footnotes

[a]Any adverse event reported up to 28 days from vaccine

[b]Unsolicited adverse events reported within 28 days after any dose

[c]CI calculated by Wald-type method.

[d]Tau² calculated by DerSimonian and Laird method.

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions

(C) Bias due to missing outcome data

(D) Bias in measurement of the outcome

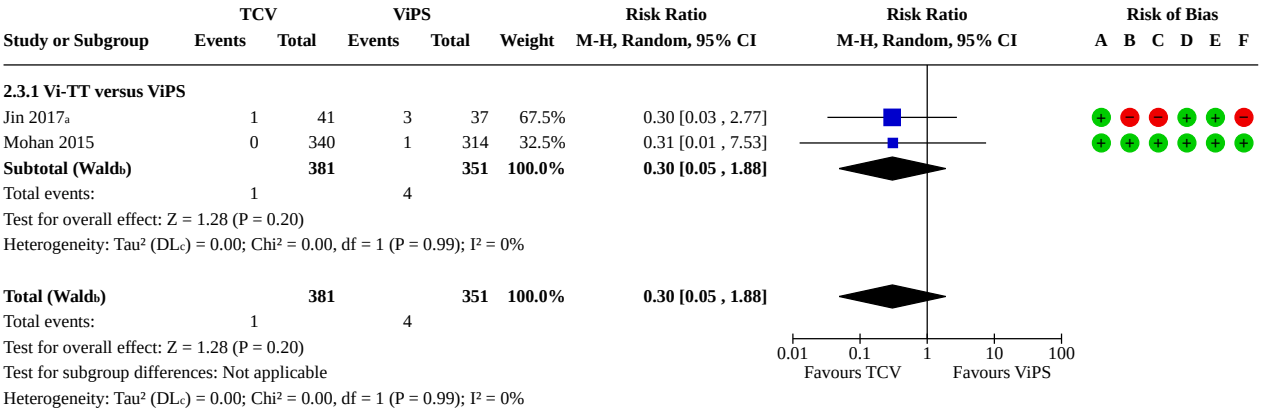
(E) Bias in selection of the reported result

(F) Overall bias

2.4 Serious adverse events

Three studies reported this outcome (Jin 2017; Mohan 2015; van Damme 2011). Two were included in the meta-analysis (Jin 2017; Mohan 2015). TCV likely results in a slight reduction in serious adverse events when compared to non-conjugated typhoid vaccines (RR 0.30, 95% CI 0.05 to 1.88; I^2 = 0%; 2 studies, 732 participants; moderate-certainty evidence; Analysis 2.3; Figure 8). We downgraded the certainty of the evidence by one level for serious risk of bias. van Damme 2011 reported zero events in both arms and was not included.

Figure 8. TCV likely results in a slight reduction in serious adverse events when compared to non-conjugated typhoid vaccines



Footnotes

[a]Human challenge study
[b]CI calculated by Wald-type method.
[c]Tau² calculated by DerSimonian and Laird method.

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 3: TCV versus other TCVs

Five studies compared one TCV to another TCV (Choi 2021; Kumar Rai 2022; Kundu 2020; Ok Baik 2023; Thuluva 2022). More details around the certainty of evidence are available in Summary of findings 3. Data not included are available in Table 4.

Critical outcomes

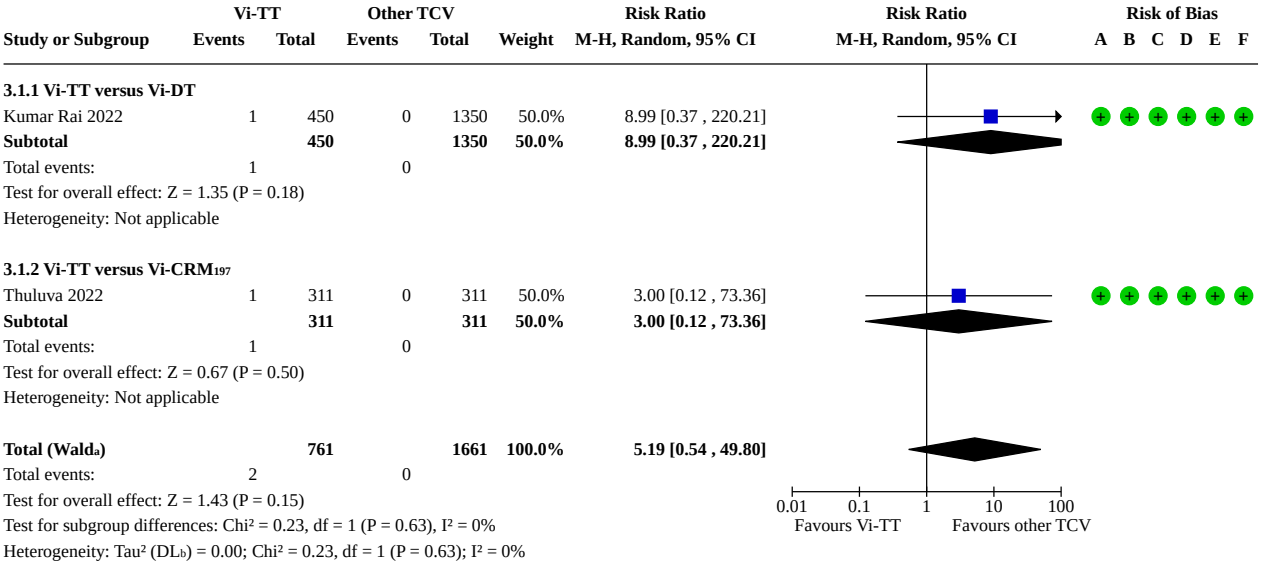
3.1 Acute typhoid fever

No studies reported this outcome.

3.2 All-cause mortality

Four studies reported this outcome (Choi 2021; Kumar Rai 2022; Ok Baik 2023; Thuluva 2022). Two were included in the meta-analysis (Kumar Rai 2022; Thuluva 2022). Vi-TT may result in little to no difference in all-cause mortality compared to a different TCV vaccine (RR 5.19, 95% CI 0.54 to 49.80; I^2 = 0%; 2 studies, 2422 participants; low-certainty evidence; Analysis 3.1; Figure 9). We downgraded the certainty of the evidence by two levels for imprecision. Ok Baik 2023 and Choi 2021 reported this outcome but, as there were no events, they were not included.

Figure 9. Vi-TT may result in little to no difference in all-cause mortality compared to a different TCV vaccine



Footnotes

[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Risk of bias legend

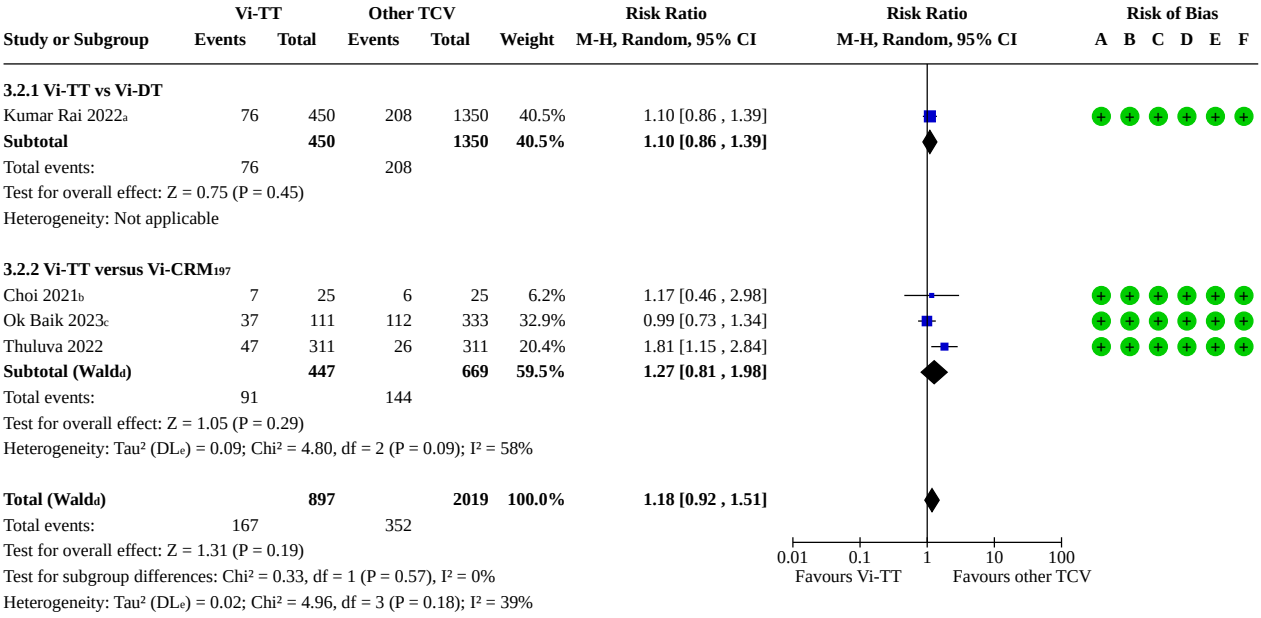
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Important outcomes

3.3 Adverse events

Five studies reported this outcome (Choi 2021; Kumar Rai 2022; Kundu 2020; Ok Baik 2023; Thuluva 2022). Four were included in the meta-analysis (Choi 2021; Kumar Rai 2022; Ok Baik 2023; Thuluva 2022). Vi-TT likely results in little to no difference in adverse events when compared to another TCV (RR 1.18, 95% CI 0.92 to 1.51; I^2 = 39%; 4 studies, 2916 participants; moderate-certainty evidence; Analysis 3.2; Figure 10). We downgraded the certainty of the evidence by one level for serious inconsistency. We did not include Kundu 2020 as the reporting was unclear on whether adverse events were solicited or unsolicited - this was reported in a supplement, which was not available.

Figure 10. Vi-TT likely results in a slight increase in adverse events when compared to another TCV



Footnotes

[a]Any adverse events within 4 week of vacccine
[b]Treatment emergent adverse events up to 42 days after vaccination
[c]Treatment emergent adverse events reported up to 168 days after vaccination
[d]CI calculated by Wald-type method.
[e]Tau² calculated by DerSimonian and Laird method.

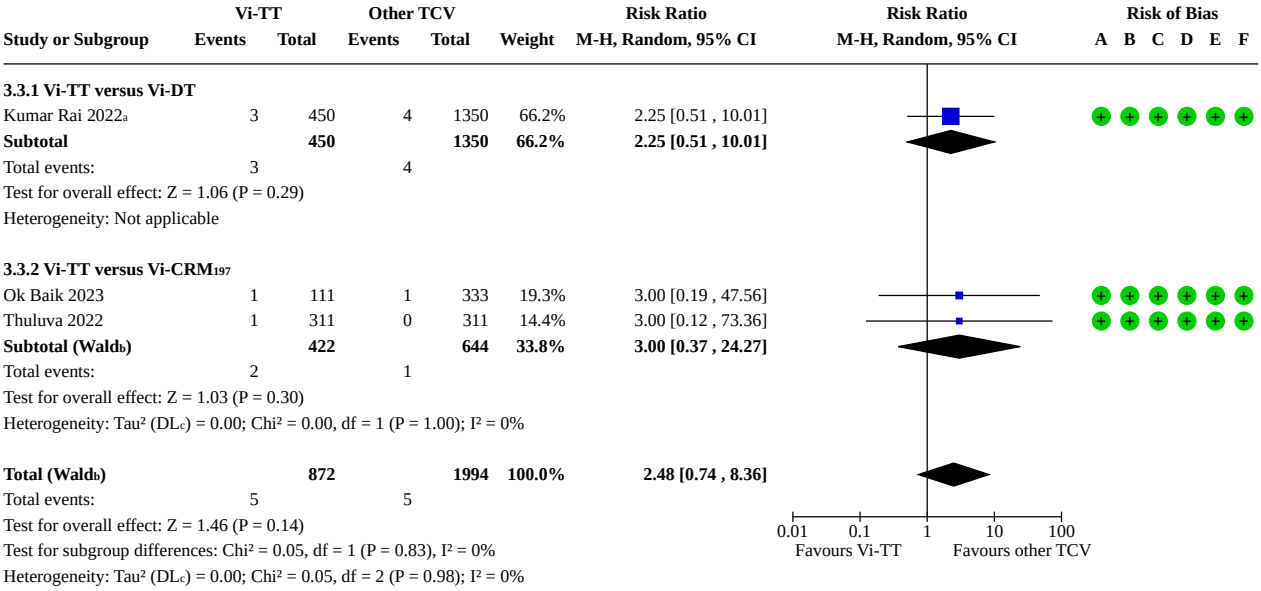
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

3.4 Serious adverse events

Five studies reported this outcome (Choi 2021; Kumar Rai 2022; Kundu 2020; Ok Baik 2023; Thuluva 2022). Three were included in the meta-analysis (Kumar Rai 2022; Ok Baik 2023; Thuluva 2022). Vi-TT may result in little to no difference in serious adverse events compared to other TCV vaccines (RR 2.48, 95% CI 0.74 to 8.36; I^2 = 0%; 3 studies, 2866 participants; low-certainty evidence; Analysis 3.3; Figure 11). We downgraded the certainty of the evidence by two levels for imprecision. Both Choi 2021 and Kundu 2020 reported this outcome but, as there were no events in either arm, they were not included.

Figure 11. Vi-TT may result in little to no difference in serious adverse events compared to other TCV vaccines



Footnotes

[a]SAEs reported during the 24 weeks study period
[b]CI calculated by Wald-type method.
[c]Tau² calculated by DerSimonian and Laird method.

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Prespecified sensitivity analyses

Where we identified high risk of bias, or Phase I and II trials, we conducted sensitivity analysis to explore whether the findings were affected by the inclusion of study outcomes with high risk of bias or by the inclusion of results from Phase I and II trials. We also carried out sensitivity analysis to assess the robustness of our conclusions when using an ICC for cRCTs.

1. TCV versus control

Critical outcomes

1.1. Acute typhoid fever

There was evidence of significant heterogeneity (I^2 = 70%) for this comparison. When we excluded studies with high risk of bias (Jin 2017), the RR decreased and precision increased from 0.20 (95% CI 0.12 to 0.32) to 0.17 (95% CI 0.13 to 0.23). Heterogeneity improved with the I^2 changing from 70% to 12%. Jin 2017 was also the only Phase I or II study for this outcome and is a human oral-challenge study. The forest plot is available in Analysis 4.1 in Supplementary material 7.

We also conducted sensitivity analyses to investigate the robustness of our conclusions where we estimated the ICC for cluster-randomised trials. For Mitra 2016 and Qadri 2021, the forest plots demonstrate that if clustering is not taken into account (ICC = 0), the risk of acute typhoid fever is lower in the TCV group compared to the control group. When a small amount of clustering is taken into account, this remains true, as can be seen in Analysis 5.1 and Analysis 5.2 in Supplementary material 7.

1.2 All-cause mortality

There were no studies with a high risk of bias or in Phase I or II included in this outcome. There was evidence of significant heterogeneity (I^2 = 52%; P = 0.10), driven by Qadri 2021. Qadri 2021 is a cRCT - we adjusted the data using an ICC of 0.0013 as used by the authors. When excluded from the meta-analysis, the point estimate decreased and the precision increased from RR 0.80 (95% CI 0.35 to 1.85) to RR 0.59 (95% CI 0.27 to 1.25). The I^2 changed from 52% to 12%. The forest plot is available in Analysis 4.2 in Supplementary material 7.

Sensitivity analyses to investigate the robustness of our conclusions where we estimated the ICC for cluster-randomised trials showed for Qadri 2021 that the forest plot demonstrates that if clustering is not taken into account (ICC = 0), the risk of death is higher in the TCV group compared to the control group but crosses the line of no effect. When a small amount of clustering is taken into account, this remains true, as can be seen in the forest plot (Analysis 5.3) in Supplementary material 7.

Important outcomes

1.3 Adverse events

There were no studies with a high risk of bias included in this outcome. When Capeding 2020 (Phase II trial) was excluded, the point estimate and precision decreased from RR 0.91 (95% CI 0.76 to 1.09) to RR 0.66 (95% CI 0.15 to 2.85), whilst I^2 increased from 0% to 36%. The forest plot is available in Analysis 4.3 in Supplementary material 7.

1.4 Serious adverse events

When we excluded studies with a high risk of bias or Phase I or II trials (Jin 2017), there was no change to the RR, 95% CI or I^2 statistic, available in Analysis 4.4 in Supplementary material 7. Sensitivity analyses to investigate the robustness of our conclusions where we estimated the ICC for cluster-randomised trials showed for Qadri 2021 that the forest plot demonstrates that if clustering is not taken into account (ICC = 0), the risk of serious adverse events is slightly lower in the TCV group compared to the control group. When a small amount of clustering is taken into account, this remains true, but confidence intervals cross the line of no effect, as can be seen in the forest plot available in Analysis 5.4 in Supplementary material 7.

2. TCV versus non-conjugated typhoid vaccines

Critical outcomes

2.1 Acute typhoid fever

Only one study is included in this outcome (Jin 2017), which was both at high risk of bias and a human oral-challenge study, so sensitivity analysis was not performed.

2.2 All-cause mortality

No studies were included in this outcome.

Important outcomes

2.3 Adverse events

There were no studies at high risk of bias and all three included studies were Phase I or II trials (Capeding 2018; Choi 2021; van Damme 2011).

2.4 Serious adverse events

When we excluded studies with high risk of bias or those that were a Phase I or II trial, or oral-challenge study (Jin 2017), there was a slight increase in the point estimate and a decrease in precision from RR 0.30 (95% CI 0.05 to 1.88) to RR 0.31 (95% CI 0.01 to 7.53). The forest plot is available in Analysis 6.1 in Supplementary material 7.

3. TCV versus other TCV vaccines

Critical outcomes

3.1 Acute typhoid fever

No studies were included in this outcome.

3.2 All-cause mortality

Both studies included were at low or unclear risk of bias and Phase II/III (Thuluva 2022) or III (Kumar Rai 2022) trials.

Important outcomes

3.3 Adverse events

None of the included studies were at high risk of bias. When Choi 2021 was excluded (Phase I trial), the point estimate increased slightly and precision decreased slightly from RR 1.18 (95% CI 0.92 to 1.51) to RR 1.19 (95% CI 0.89 to 1.60) with the I^2 statistic increasing from 36% to 60%. The forest plot is available in Analysis 7.1 in Supplementary material 7. When considering heterogeneity, when Thuluva 2022 was excluded, the point estimate decreased slightly and precision increased from RR 1.18 (95% CI 0.92 to 1.51) to RR 1.06 (95% CI 0.88 to 1.27) with the I^2 statistic decreasing from 39% to 0%. The forest plot is available in Analysis 7.2 in Supplementary material 7.

3.4 Serious adverse events

Studies included in this outcome were either at low or unclear risk of bias. All three included studies were either Phase II/III (Ok Baik 2023; Thuluva 2022) or Phase III (Kumar Rai 2022) trials.

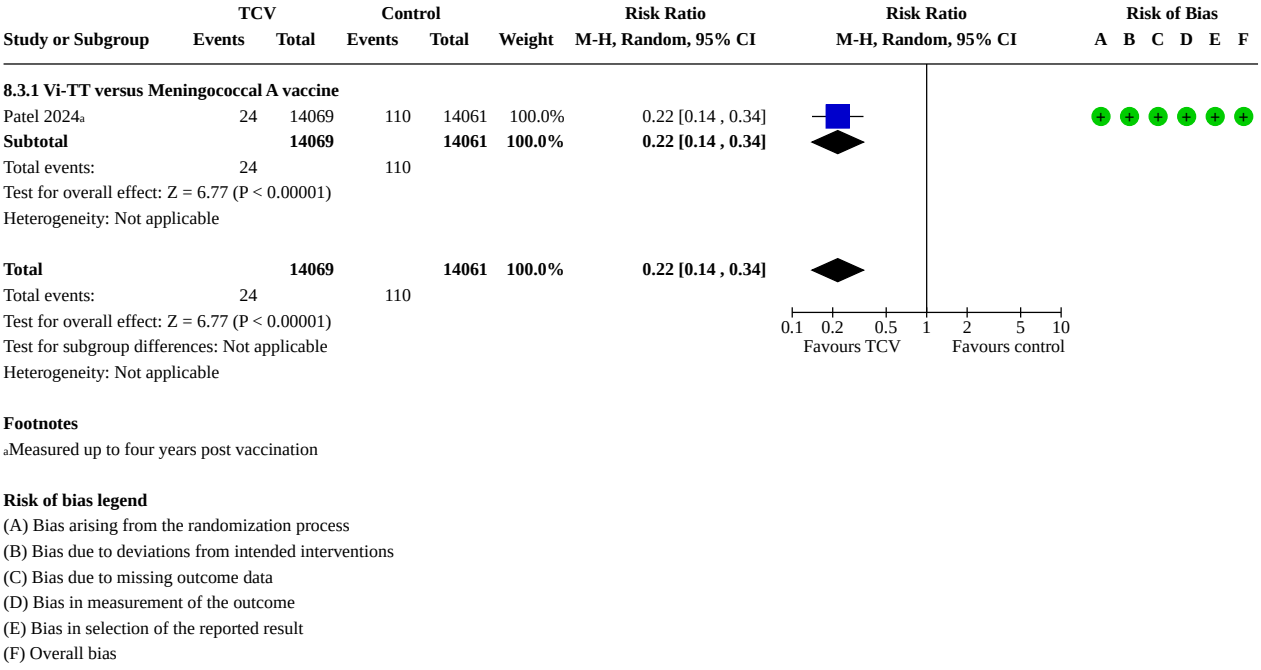
Prespecified subgroup analyses

There were insufficient data per outcome to perform the prespecified subgroup analyses for endemicity, age group and immunosuppression. Eleven studies did not report results stratified by age group (Bhutta 2014; Capeding 2018; Capeding 2020; Carlos 2022; Kumar Rai 2022; Mitra 2016; Mohan 2015; Ok Baik 2023; Patel 2024; Shakya 2021; Thuluva 2022). Kumar Rai 2022 reported adverse events by age group but not mortality or serious adverse events. Qadri 2021 reported events of culture-positive typhoid fever by age group but did not provide group sizes. Koesnoe 2024 reported specific, not overall, adverse events and so could not be included in a subgroup analysis. Medise 2019 reported results for the age groups of two to five years and 18 to 40 years, but these were not included as the reporting of adverse events was unclear. This is summarised in Table 5.

Other subgroup analyses

We performed subgroup analysis to evaluate the length of protection from acute typhoid fever when TCV is compared to a control. One study assessed events of acute typhoid fever up to 12 months post vaccination (RR 0.05, 95% CI 0.00 to 0.86; 1 study, 1484 participants in Supplementary material 7) (Mitra 2016). Three studies assessed events of acute typhoid fever from 12 to 24 months (RR 0.16, 95% CI 0.11 to 0.23; I^2 = 17%; 3 studies, 72207 participants in Supplementary material 7) (Lin 2001; Qadri 2021; Shakya 2021). One study assessed acute typhoid fever events up to four years (RR 0.22, 95% CI 0.14 to 0.34; 1 study, 28130 participants; Figure 12) (Patel 2024).

Figure 12. Acute typhoid fever more than two years post vaccination



Footnotes

[a]Measured up to four years post vaccination

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Equity assessment

Fourteen RCTs took place in LMICs, one in a low-income country, two in upper-middle-income countries and two in high-income countries, as classified by the World Bank [139]. Most were conducted in South and Southeast Asia, with one in sub-Saharan Africa. The ages of participants ranged from six weeks to 60 years. No adults older than 60 were included. Two cRCTs (Qadri 2021; Mitra 2016) and one RCT (Lin 2001) reported on socioeconomic status and lifestyle.

We did not collect data on other PROGRESS-PLUS variables such as occupation, gender, social capital, sexual orientation and disability. These were also not reported in the included studies. We judged one study as having some concerns of bias in the randomisation process (Capeding 2018); poor randomisation may speak to baseline imbalance across PROGRESS-PLUS factors.

Reporting biases

We aimed to explore publication bias, but there were insufficient studies with shared outcomes to create funnel plots.

DISCUSSION

Summary of main results

We evaluated the benefits and harms of typhoid conjugate vaccines compared to control, non-conjugated typhoid vaccines and other TCVs. We included 19 studies with 395,650 participants.

Compared to control, TCV may result in a large reduction in acute typhoid fever, and likely results in little to no difference in all-cause mortality. Subgroup analysis showed that the reduction in acute typhoid fever remains up to 12 months, two years and beyond two years (up to four years). For outcomes related to harms, TCV results in little to no difference in adverse events and a slight reduction in serious adverse events (Summary of findings 1).

When compared to non-conjugated typhoid vaccines, TCV may result in little to no difference in acute typhoid fever. Mortality was reported, but there were no events in either arm of the relevant studies. TCV likely results in little to no difference in adverse events and likely results in a slight reduction in serious adverse events (Summary of findings 2).

When TCV (Vi-TT) is compared to other TCVs, none of the included studies reported on acute typhoid fever. Vi-TT may result in little to no difference in all-cause mortality compared to a different TCV. Vi-TT likely results in little to no difference in adverse events when compared to another TCV and may result in little to no difference in serious adverse events (Summary of findings 3).

Limitations of the evidence included in the review

For the comparison of TCV versus control, we rated down the certainty of evidence for the outcome acute typhoid fever for serious risk of bias and inconsistency. The driver of bias and inconsistency was Jin 2017, an oral-challenge study in the United Kingdom (Analysis 1.1; Analysis 1.4; Analysis 2.1; Analysis 2.3). The high risk of bias was in the domains of deviation from intended interventions and missing outcome data.

When comparing different TCVs, there were no studies that compared cases of acute typhoid fever, defined by laboratory-confirmed isolation of *S typhi* (e.g. blood cultures or stool sample), which limits our ability to comment on the benefits of one TCV versus another. Considering that all included TCVs were shown to be effective compared to control, affordability may be the deciding factor for country adoption.

Mortality was not always reported and, when it was, event numbers were low. It is also possible that, due to the short follow-up of some of the studies, deaths may not have been reported.

Different authors define adverse events differently, which leads to confusion. We defined adverse events as "an unfavourable or harmful outcome that occurs during, or after, the use of a drug or other intervention, but is not necessarily caused by it" [140]. A further challenge with adverse events and serious adverse events is that many are uncommon or only occur once the trial is completed. However, self-reported adverse events were limited, of mild-to-moderate severity and mostly comparable between vaccination and control groups, except for slightly higher local reactogenicity reactions associated with the intervention. As we reported on composite measures of adverse events and not on specific events, e.g. nausea or rash, the clinical application may be limited.

The certainty of evidence was consistently reduced due to challenges with imprecision and indirectness, as well as some challenges with bias, which affected internal validity. Specifically, in the analysis comparing TCVs to control for acute typhoid fever, the relative risk was 0.20, with a 95% confidence interval from 0.12 to 0.32. However, the certainty was compromised by significant risks of bias, such as deviations from intended interventions, and inconsistencies predominantly associated with methodological concerns in studies like Jin 2017. Sensitivity analysis excluding this study (Jin 2017) confirmed the uncertainty. Furthermore, the internal validity issues were exacerbated by potential conflicts of interest amongst the authors, impacting the objectivity of the findings. External validity concerns also arose, highlighting issues with the applicability and generalisability of the results - additional research across diverse socio-economic and geographical settings is needed.

Equity considerations

Most included trials were conducted in South and Southeast Asia. Only one trial was conducted in Africa, despite evidence suggesting that disease incidence and mortality rates are similar (or higher) than in Asia [141]. Three of the identified ongoing trials are based in Africa. This may affect the generalisability of the results and highlights potential equity issues when applying non-African research to African settings.

The age range of participants was six weeks to 60 years. Typhoid has been shown to disproportionately affect children with a peak incidence between five and < 15 years old [4]. Excluding those aged above 60 years old may affect the generalisability. However, given the peak incidence in children, with the relevant age groups included in the trials, we do not anticipate this as a large limiting factor in terms of equity.

There was no indication of baseline imbalances across the PROGRESS-Plus factors. Typhoid elimination requires vaccination to be complemented with access to good-quality water, sanitation and hygiene, and waste-management facilities (WASH). Studies investigating the combined impact of TCVs and WASH interventions on reducing typhoid fever incidence can provide evidence for integrated public-health strategies addressing multiple health determinants.

Limitations of the review processes

We chose to pool all TCV vaccines into one intervention (divided by subgroups) to compare TCVs overall with control, non-conjugated typhoid vaccines and other TCVs. This may have excluded small nuances in the benefits of specific TCVs. Nonetheless, given the findings that indicate little to no significant difference in mortality, adverse events and serious adverse events amongst the pooled TCV groups, we are confident that this approach was justified. This pooling strategy allowed for a broader understanding of TCV benefits and harms but may have overlooked specific variations in vaccine performance that could be critical for optimising vaccination strategies.

Our review did not account for variations in dosing schedules, which are vital for interpreting vaccine benefits and the longevity of protection. This oversight might have affected outcomes, such as all-cause mortality, potentially influencing recommendations for booster doses. We assessed the length of vaccine protection against acute typhoid fever as part of a subgroup analysis. Data were only available for Comparison 1, so we could not assess long-term protection of TCVs compared to non-conjugated typhoid vaccines. The methodologies we employed, including a comprehensive search strategy, meticulous data extraction and thorough bias assessments, were aimed at ensuring a robust analysis. Yet, these methods required certain trade-offs, such as modifying comparison groups and analytical frameworks, which might have influenced the subtleties of our findings. We also did not explore how TCVs would integrate into Expanded Programme on Immunisation schedules, an aspect that varies widely by context and merits detailed investigation to grasp its broader public health implications. These gaps underline the need for more targeted research to refine global policy recommendations on the use of TCVs.

Agreements and disagreements with other studies or reviews

We identified two related reviews. Our findings add to the results from Milligan et al [29], as we identified 17 additional trials. We also identified a systematic review by Batool et al, evaluating the efficacy of typhoid vaccines against culture-confirmed *S typhi* [142]. Aligned with our results, they reported that TCV is likely to be effective in preventing typhoid fever, and suggest that TCV should be included in routine immunisation programmes in typhoid-endemic settings.

Our review supports the most recent WHO position paper on typhoid vaccines [4], published in 2018, which recommends programmatic use of typhoid vaccines to control typhoid fever. The WHO recommends that vaccines should be implemented with interventions such as health promotion, sanitation, access to clean water and improved hygiene, as well as training of healthcare professionals in the diagnosis and treatment of typhoid fever, which our review did not consider. The most recent guidance from the CDC recommends the use of ViPS or Ty21a vaccines as prophylaxis for travellers visiting typhoid-endemic regions [24]. Whilst we planned to stratify our analysis by endemicity (travellers versus routine vaccination for those living in typhoid-endemic areas), there were no studies reviewing typhoid prophylaxis for travellers.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence from trials of children and adults confirms that the use of typhoid conjugate vaccines (TCVs) compared to control may result in a large reduction in acute typhoid fever. This finding supports the broader implementation of TCVs in public health vaccination programmes, particularly in typhoid-endemic areas.

The World Health Organization (WHO) recommends routine typhoid vaccination in endemic countries, not only to decrease the disease burden but also to lessen the need for antibiotics to stem the increase in antibiotic resistance [143].

The certainty and strength of the evidence comparing TCVs with non-conjugated typhoid vaccines is lower, posing potential challenges for decision-making in contexts where multiple vaccine options are available. Decisions on selecting specific TCV products must be guided by availability, cost considerations and regulatory approvals rather than direct benefit comparisons where the data are of lower certainty. Thus, ongoing education and guideline updates will be essential as evidence emerges, ensuring that healthcare policy practice aligns with the latest research to maximise public health outcomes.

Equity-related implications for practice

Diseases like typhoid fever are linked to unsafe drinking water, inadequate sanitation and hygiene practices (WASH), and can be exacerbated by increased flooding and climate change. These diseases disproportionately affect the poorest, most disadvantaged populations. This is largely driven by inadequate access to safe WASH, especially in low- and middle-income countries (LMICs) and particularly in rural populations and low socioeconomic groups [144]. In 2022, UNICEF published the *Typhoid Conjugate Vaccine: Supply and Demand Update*, where it was noted that TCV uptake has been slow due to other competing priorities. The local epidemiology of typhoid is also difficult to define, making it difficult for endemic countries to commit to typhoid control [145].

Vaccines help to prevent morbidity and mortality from serious infections, aid in eradicating infectious diseases, promote herd immunity, reduce the incidence of secondary infections that complicate vaccine-preventable illnesses, prevent certain cancers and help to prevent antimicrobial resistance. There are also economic benefits such as cost-saving and productivity gains, as well as social benefits including healthcare equity improvement and strengthening of health and social care infrastructure [146]. This review shows that, compared to control, TCVs may result in a large reduction in acute typhoid fever. Vaccination would likely lead to an improvement in the burden of disease and reduce the burden of morbidity and mortality on disadvantaged communities, as well as improve equity through improved health outcomes and other benefits.

Implications for research

As new TCVs are developed, ongoing systematic reviews across diverse LMICs to assess their benefits and harms are needed. Given this review's low certainty in key outcomes, due to bias, inconsistency and imprecision, future research should focus on enhancing the methodological rigour of trials. This involves improving study design, ensuring adherence to intervention protocols and refining outcome measurements to strengthen the evidence base.

Contemplating whether further studies might alter the review conclusions, it is plausible that significant new findings could emerge, particularly as vaccine technologies evolve and new epidemiological data become available. Continued research into the development of bivalent vaccines that are also active against *S paratyphi* is also critical in addressing enteric fever as a whole.

Moreover, there is a critical need for research focused on the implementation aspects of TCV deployment. Investigating the operational challenges, integrating TCVs into existing public health infrastructures and understanding their acceptance across cultural and socioeconomic contexts are essential. This would not only confirm the practical utility of TCVs but also enhance their effectiveness globally, ensuring that recommendations are scientifically robust and practically implementable.

Further research should also include investigations into the need for TCV boosters, optimising the timing of vaccinations and geographic variation.

Equity-related implications for research

The findings indicate significant equity-related implications for research on TCVs. Despite the assurance of reducing typhoid fever incidence, the current evidence base does not fully address the different impacts of TCVs across demographic and socioeconomic groups. Future studies should prioritise inclusivity by ensuring diverse participant representation that reflects the global burden of typhoid, particularly in low-resource settings.

Research must also extend to evaluating the accessibility and acceptability of TCVs amongst different populations, including barriers faced by marginalised communities. This would help identify disparities in coverage and effectiveness, guiding tailored interventions that improve equity in vaccine distribution and administration.

Furthermore, future investigations should consider the implications of integrating TCVs into national immunisation programmes, particularly in countries with varying health infrastructure capabilities. Research should explore how TCV implementation strategies can be adapted to local contexts to ensure equitable access and effectiveness, including collaborating with local health authorities and communities to develop culturally and economically appropriate vaccination strategies that uphold equity and justice.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD015746.

Supplementary material 1 Search strategies

Supplementary material 2 Characteristics of included studies

Supplementary material 3 Characteristics of excluded studies

Supplementary material 4 Characteristics of studies awaiting classification

Supplementary material 5 Characteristics of ongoing studies

Supplementary material 6 Risk of bias

Supplementary material 7 Analyses

Supplementary material 8 Data package

Supplementary material 9 Amendments to the protocol

ADDITIONAL INFORMATION

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Michael Eisenhut, Luton & Dunstable University Hospital, United Kingdom.
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Contributions of authors

NG, TL, CI, PdK, TK and CW contributed to the conceptualisation, methodology and writing (original draft, review and editing) of the protocol.

NG, TL, MM, CI, PdK, TK and CW contributed to the enactment of the protocol, formal analysis, methodology and writing (original draft, review and editing) of the review.

Declarations of interest

NG, TL, MM, CI and PdK have no competing interests to declare.

CSW has declared the following competing interests:

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Data, code and other materials

As part of the published Cochrane review, the following are made available for download for users of the *Cochrane Library*: Full search strategies for each database; full citations of each unique report for all studies included, ongoing or awaiting classification, or excluded at the full-text screen, in the final review; study data, including study information, study arms and study results or test data;

consensus risk of bias assessments; and analysis data, including overall estimates and settings, subgroup estimates and individual data rows. Appropriate permissions have been obtained for such use. Analyses and data management were conducted within Cochrane's authoring tool, RevMan, using the inbuilt computation methods. Template data extraction forms from Excel are available from the authors on reasonable request.

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ADDITIONAL TABLES

Table 1. Summary of available vaccines for typhoid fever

	Type	Trade name	Manufacturer	Pre-qualified by WHO	Administration	Adverse events	Additional notes
Typhoid conjugate vaccines (TCV)	25 µg of Vi-capsular polysaccharide conjugated to a non-toxic tetanus toxoid carrier (Vi-TT)	Typbar-TCV	Bharat BioNTech	Yes	Parenteral administration; single dose; children ≥ 6 months old	Fever Local, non-specific reactions	First developed in India in 2013 for a single intramuscular (IM) dose of 0.5 mL for ages 6 months to 45 years. It was pre-qualified for use in December 2017 [147], and recommended as the preferred vaccine to prevent typhoid fever by the WHO due to the improved immunological properties, suitability for use in young children and anticipated longer duration of activity compared to ViPS and Ty21a vaccines. Vi-TT vaccines stimulate specialised T-cells in the body, with sustained protective immunity allowing vaccination from six months old with other routine vaccines [23]. The WHO recommends inclusion in routine administration of other childhood vaccines at nine months, or in the second year of life [4]. Strict cold-chain management may be challenging in resource-poor settings.
		PEDATYPH	Biomed	No			Consists of 5 µg of Vi-capsular polysaccharide from *S typhi*, conjugated to 5 µg of tetanus toxoid protein in isotonic saline, and was the first TCV to be developed in India [148]. It is recommended to be administered IM to children older than two years on a two-dose schedule, with four to eight weeks between doses, and a manufacturer-recommended booster every 10 years. For children between three and 23 months, a booster dose is recommended at 24 to 30 months and then repeated every 10 years.
		ZYVAC-TCV	Zydus Cadila	No			
	25 µg of Vi-capsular polysaccharide conjugated to 16.7 µg to 100 µg of CRM_{197} (Vi-CRM_{197})	TYPHIBEV	Biological E Limited	Yes			TYPHIBEV® was first pre-qualified by the WHO in December 2020 [147]. CRM_{197} is a non-toxic mutant of diphtheria toxoid. This vaccine is given as a single dose of 0.5 mL intramuscularly. It is indicated for use in children aged six months or older, and adolescents and adults aged 45 and younger [149]. Protection occurs two to

Table 1. Summary of available vaccines for typhoid fever *(Continued)*

							three weeks after immunisation. There are no clinical data on co-administration of TYPHIBEV® with other medicinal products or vaccines. It is not recommended in routine immunisation schedules for children. The vaccine must be stored under cold-chain management (2 °C to 8 °C [147]).
	25 µg of Vi-capsular polysaccharide conjugated to 37 µg of diphtheria toxin (Vi-DT) [150, 151]	SKYTyphoid Multi Inj.	SK Bioscience	Yes			Vi-DT (SKYTyphoid Multi Inj) was pre-qualified by the WHO in February 2024 [28, 152, 153] and has been shown to be safe and immunogenic in people aged six months to 45 years [28].
	25 µg of Vi-capsular polysaccharide conjugated to 25 µg of *Pseudomonas aeruginosa* exoprotein A (Vi-rEPA) [154, 155]	None		No			This vaccine is given as two intramuscular doses, six weeks apart, in children older than two years [154]. This vaccine has not been commercialised [29].
Non-TCV	Live attenuated vaccine (Ty2 strain of *S typhi;* no Vi antigen; Ty21a)	Vivotif	Emergent Biosolutions	Yes	Oral administration (enteric-coated capsules); children ≥ 5 years and adults; 3-dose or 4-dose (North America) regimen, every other day Protection starts 10 to 14 days after 3rd dose.	Fever Erythema and localised pain Gastrointestinal events (more common in Ty21a)	
	Unconjugated Vi polysac-	Typhim VI	Sanofi Pasteur	Yes	Parenteral administration; children		

Table 1. Summary of available vaccines for typhoid fever *(Continued)*

	charide vaccine (ViPS)	Typherix	GlaxoSmithKline	≥ 2 years and adults; single dose

IM: intramuscular; TCV: typhoid conjugate vaccine; Vi-DT: Vi-diphtheria toxoid; Vi-CRM_{197}: Vi-capsular polysaccharide conjugated to CRM_{197} Vi-TT: Vi tetanus toxoid; Vi-rEPA: Vi-capsular polysaccharide conjugated to *Pseudomonas aeruginosa* exoprotein A; ViPS: Vi polysaccharide vaccine; WHO: World Health Organization

Table 2. Overview of Synthesis and Included Studies (OSIS) table illustrating key characteristics of studies, outcomes and analyses, sorted alphabetically

No.	Study name (country of conduct)	Study design	Population (sample size: intervention/comparator 1/comparator 2)	Intervention	Comparator(s)	Outcome domains with available data (follow-up period)	Included in meta-analysis	If clustered, was clustering accounted for?
1	Bhutta 2014 (Pakistan, India and the Philippines)	Phase II RCT	Study A: adults and children (200: 100/60/40) Study B: children (120/20/40)	Vi-CRM_{197}	Study A: ViPS PNC-13 Study B: ViPS PNC-13	AEs (28 days) SAEs (28 days)	No	N/A
2	Capeding 2018 (the Philippines)	Phase I RCT	Adults and children (144: 72/72)	Vi-DT	ViPS	AEs (28 days) SAEs (28 days)	Yes	N/A
3	Capeding 2020 (the Philippines)	Phase II RCT	Children (285: 114/114/57	V-DT (single dose) +FluQuadri	Vi-DT (two doses) Placebo+FluQuadri	AEs (6 months) SAEs (6 months)	Yes	N/A
4	Carlos 2022 (the Philippines)	Phase III RCT	Adults and children (1800: 750/750/300)	Vi-DT (single-dose vial)	Vi-DT (multi-dose vial) MCV (Nimenrix®, Pfizer)	AEs (6 months) SAEs (6 months)	Yes	N/A

Table 2. Overview of Synthesis and Included Studies (OSIS) table illustrating key characteristics of studies, outcomes and analyses, sorted alphabetically *(Continued)*

5	Choi 2021 (the Philippines)	Phase I RCT	Adults (75: 25/25/25)	Vi-CRM_{197}	ViPS Vi-TT	AEs (42 days) SAEs (42 days)	No	N/A
6	Jin 2017 (United Kingdom)	Phase IIb RCT (oral challenge study)	Adults (112: 41/37/34)	Vi-TT	ViPS MCV (MENVEO, GSK)	Acute typhoid fever (1 month) *AEs (21 days) SAEs (21 days)	Yes	N/A
7	Koesnoe 2024 (Indonesia)	Phase II RCT	Children (200: 100/100)	Vi-DT	IPV	AEs (28 days) SAEs (28 days)	No	N/A
8	Kumar Rai 2022 (Kathmandu and Nepal)	Phase III RCT	Adults and children (1800: 1350/450)	Vi-DT	Vi-TT	All-cause mortality (24 weeks) AEs (28 days) SAEs (24 weeks)	Yes	N/A
9	Kundu 2020 (India)	Phase II/III RCT	Adults and children (240: 119/121)	Vi-TT (test vaccine)	Vi-TT	AEs (6 weeks) SAEs (6 weeks)	No	N/A
10	Lin 2001 (Vietnam)	RCT	Children (12,008: 5991/6017)	Vi-rEPA	Saline placebo	Acute typhoid fever (27 months) All-cause mortality (27 months) *AEs (27 months) *SAEs (27 months)	Yes	N/A
11	Medise 2019 (Indonesia)	Phase 1 RCT	Adults and children (100: 50/25/25)	Vi-DT	ViPS + influenza vaccine (adults) PCV (children)	*AEs (6 months) *SAEs (6 months)	No	N/A
12	Mitra 2016 (India)	Phase IV cRCT	Children (1765: 905/860)	Vi-TT	No vaccine	Acute typhoid fever (12 months) *AEs (12 months)	Yes	We used an ICC of 0.0013

Table 2. Overview of Synthesis and Included Studies (OSIS) table illustrating key characteristics of studies, outcomes and analyses, sorted alphabetically *(Continued)*

13	Mohan 2015 (India)	Phase III RCT	Adults and children (654: 340/314)	Vi-TT	ViPS	*AEs (90 days) SAEs (90 days)	Yes	N/A
14	Ok Baik 2023 (The Philippines)	Phase II/III RCT	Adults and children (445: 333 (pooled arms A-C)/111)	Vi-CRM_{197} (3 batches pooled)	Vi-TT	AEs (28 days) SAEs (28 days)	Yes	N/A
15	Patel 2024 (Malawi)	Phase III RCT	Children (28,130: 14,069/14,061)	Vi-TT	MenA	Acute typhoid fever (4 years) All-cause mortality (4 years) AEs (28 days) SAEs (6 months)	Yes	N/A
16	Qadri 2021 (Bangladesh)	cRCT	Children (326,794: 163,421/163,373)	Vi-TT	JE vaccine	Acute typhoid fever (24 months) All-cause mortality (24 months) *AEs (24 months) SAEs (24 months)	Yes	We used an ICC of 0.0013
17	Shakya 2021 (Nepal)	Phase III RCT	Children (20,019: 10,005/10,014)	Vi-TT	MenA	Acute typhoid fever (2 years) All-cause mortality (2 years) *AEs (2 years) SAEs (2 years)	Yes	N/A
18	Thuluva 2022 (India)	Phase II/III RCT	Adults and children (622: 311/311)	Vi-CRM_{197}	Vi-TT	All-cause mortality (42 days) AEs (42 days) SAEs (42 days)	Yes	N/A
19	van Damme 2011 (Belgium)	Phase I/II RCT	Adults (Phase 1: 50: 25/25; Phase 2: 88: 22/22/22/22)	Vi-CRM_{197} Phase II: different concentrations	ViPS	AEs (28 days) SAEs (28 days)	Yes	N/A

Table 2. Overview of Synthesis and Included Studies (OSIS) table illustrating key characteristics of studies, outcomes and analyses, sorted alphabetically *(Continued)*

													of Vi-CRM_{197} delivered

AEs: adverse events; cRCT: cluster-RCT; ICC: intracluster correlation coefficient; IPV: inactivated polio vaccine; JE: Japanese encephalitis; MCV: meningococcal conjugate vaccine; MenA: meningococcal capsular group A conjugate vaccine; N/A: not applicable; PNC-13: pneumococcal conjugate vaccine 13; RCT: randomised controlled trial; SAEs: serious adverse events; Vi-CRM_{197}: 25 µg of typhoid Vi-capsular polysaccharide conjugated to 16.7 µg to 100 µg of CRM_{197}; Vi-DT: 25 µg of purified Vi *S typhi* polysaccharide conjugated to 37 µg of diphtheria toxoid; Vi-rEPA: 22.5 µg of Vi conjugated to 22 µg of rEPA; Vi-TT: 25 µg of Vi-capsular polysaccharide conjugated to a non-toxic tetanus toxoid carrier; ViPS: Vi polysaccharide vaccine

*Outcomes not included in meta-analysis

Table 3. Comparisons delineated by interventions, comparators and studies

Comparison	TCV Vaccine	Comparator	Study
1 TCV versus control	Vi-TT	No vaccine	Mitra 2016
		Meningococcal A vaccine	Jin 2017; Patel 2024; Shakya 2021
		Japanese encephalitis vaccine	Qadri 2021
	Vi-DT	Placebo	Capeding 2020
		Meningococcal A vaccine	Carlos 2022
		Inactivated polio vaccine	Koesnoe 2024
	Vi-rEPA	Placebo	Lin 2001
2 TCV versus non-conjugated typhoid vaccines	Vi-TT	ViPS	Choi 2021; Jin 2017; Mohan 2015
	Vi-DT	ViPS	Capeding 2018
	Vi-CRM_{197}	ViPS	Bhutta 2014; van Damme 2011
3 TCV versus other TCV vaccines	Vi-TT	Vi-DT	Kumar Rai 2022
		Vi-CRM_{197}	Choi 2021; Ok Baik 2023; Thuluva 2022
		V-TT (test vaccine)	Kundu 2020

TCV: typhoid conjugate vaccine; Vi-DT: Vi-diphtheria toxoid; ViPS: Vi polysaccharide vaccine; Vi-TT: Vi tetanus toxoid; Vi-CRM_{197}: Vi-capsular polysaccharide conjugated to CRM_{197}; Vi-rEPA: Vi-capsular polysaccharide conjugated to *Pseudomonas aeruginosa* exoprotein A

Table 4. Summary of data not included in the meta-analysis per comparison and outcome

Comparison	Outcome	Study	Data limitation
TCV versus control	Adverse events	Koesnoe 2024	The reporting of adverse events was unclear: solicited and unsolicited adverse events were counted together [72] and another publication within this study reports systemic and local AEs from vaccination to 28 days, but it is unclear if there is double counting and so was reported narratively [73, 74].
		Mitra 2016	Adverse events were only reported for the intervention and not the control group.
		Qadri 2021	Authors reported the overall incidence of adverse events for both groups (not per arm).
		Shakya 2021	Authors reported adverse events by specific event, e.g. fever or headache, as opposed to overall adverse events per arm.

Table 4. Summary of data not included in the meta-analysis per comparison and outcome *(Continued)*

	Serious adverse events	Lin 2001	Authors reported this outcome, but as there were no events, the data were not included in the meta-analysis.
		Koesnoe 2024	Authors reported this outcome, but as there were no events, the data were not included in the meta-analysis.
TCV versus non-conjugated typhoid vaccines	All-cause mortality	Bhutta 2014	Authors reported this outcome, but as there were no events, the data were not included in the meta-analysis.
		van Damme 2011	Authors reported this outcome, but as there were no events, the data were not included in the meta-analysis.
	Adverse events	Mohan 2015	Authors reported adverse events by specific event, e.g. fever or headache, as opposed to overall adverse events per arm.
	Serious adverse events	van Damme 2011	Authors reported this outcome, but as there were no events, the data were not included in the meta-analysis.
TCV versus other TCVs	All-cause mortality	Choi 2021	Authors reported this outcome, but as there were no events, the data were not included in the meta-analysis.
		Ok Baik 2023	Authors reported this outcome, but as there were no events, the data were not included in the meta-analysis.
	Adverse events	Kundu 2020	Reporting was unclear on whether adverse events were solicited or unsolicited - this was reported in a supplement that was not available for review.
	Serious adverse events	Choi 2021	Authors reported this outcome, but as there were no events, the data were not included in the meta-analysis.
		Kundu 2020	Authors reported this outcome, but as there were no events, the data were not included in the meta-analysis.

AEs: adverse events; TCV: typhoid conjugate vaccine

Table 5. Data stratified by age group

Study	Outcome	Age range	Relevant results/comments
Bhutta 2014	AEs SAEs	**Study A age range** Children: 24 to 59 months; Older infants: 9 to 12 months; Infants: 6 to 8 weeks **Study B age range** Children: 24 to 59 months; Older infants: 9 to 12 months; Infants: 6 to 8 weeks	Not reported per age group
Capeding 2018	AEs SAEs	**Age range:** 2 to 45 years Three cohorts: 18 to 45 years, 6 to 17 years, and 2 to 5 years	Not reported per age group

Table 5. Data stratified by age group *(Continued)*

Capeding 2020	AEs	**Age range:** 6 to 23 months	Not reported per age group
	SAEs		
Carlos 2022	AEs	**Age range:**	Not reported per age group
	SAEs	Strata 1 - 18 to 45 years Strata 2 - 2 to <18 years Strata 3 - 6 months to < 2 years	
Choi 2021	AEs	**Age range:** 18 to 45 years	Adult population only
Jin 2017	Acute typhoid fever	**Age range:** 18 to 60 years	Adult population only
	SAEs		
Koesnoe 2024	AEs	**Age range:** 12 to 40 years	Reported per adverse event, not overall
	SAEs		No events
Kumar Rai 2022	All-cause mortality	**Age range:** 6 months to 45 years	Not reported per age group
	AEs		**Solicited within 7 days:** *Six months to < 2 years:* Vi-DT n = 97 (21.6%) Vi-TT n = 42 (28.0%) *Two years to < 18 years:* Vi-DT n = 70 (15.3%) Vi-TT n = 34 (22.7%) *18 to 45 years:* Vi-DT n = 93 (30.7%) Vi-TT n = 39 (26.0%) **Unsolicited within 4 weeks** *Six months to < 2 years:* Vi-DT n = 137 (30.4%) Vi-TT n = 54 (36.0%) *Two years to < 18 years:* Vi-DT n = 45 (10.0%) Vi-TT n = 16 (10.7%) *18 to 45 years* Vi-DT n = 26 (5.8%) Vi-TT n = 6 (4.0%)

Table 5. Data stratified by age group *(Continued)*

	SAEs		Not reported per age group
Kundu 2020	AEs	**Age range:** 6 months to 45 years	Reporting was unclear on whether adverse events were solicited or unsolicited
	SAEs		No events
Lin 2001	Acute typhoid fever	**Age range:** 2 to 5 years	Included in meta-analysis
	All-cause mortality		
	SAEs		No events reported
Medise 2019	AEs	**Age ranges:** 2 to 5 years and 18 to 40 years	Poor definition of adverse events, unable to include in meta-analysis
Mitra 2016	Acute typhoid fever	**Age range:** 6 months to 12 years	Results not reported per age group
	AEs		Adverse events were only reported for the intervention and not the control group
Mohan 2015	AEs	**Age range:** 2 to 45 years	Results not reported per age group
	SAEs		
Ok Baik 2023	AEs	**Age range:** 6 months to 45 years	Results not reported per age group
	SAEs		
Patel 2024	All-cause mortality	**Age range:** 9 months to 12 years	Results not reported per age group
	AEs		
	SAEs		
Qadri 2021	Acute typhoid fever	**Age range:** 9 months to < 16 years	Reported events of culture-positive typhoid fever by age group but did not provide group sizes
Shakya 2021	Acute typhoid fever	**Age range:** 9 months to < 16 years	Results not reported per age group
	All-cause mortality		Results not reported per age group
	AEs		Authors reported adverse events by specific event, e.g. fever or headache, as opposed to overall adverse events per arm
Thuluva 2022	All-cause mortality	**Age range:** ≥ 6 months to < 64 years	Results not reported per age group
	AEs		
	SAEs		
van Damme 2011	All-cause mortality	**Age range:** 18 to 40 years	No events
	AEs		Adult population only

Table 5. Data stratified by age group *(Continued)*

	SAEs	No events

AEs: adverse events; IQR: interquartile range; SAEs: serious adverse events