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Systematic Review

Typhoid Conjugate Vaccine for Prevention of Typhoid Fever: A Systematic Review of Randomized Controlled Trials with Relevance to Travel Medicine

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ABSTRACT

Background: Typhoid fever is a vaccine-preventable infection of importance to residents of endemic areas and to travelers to South Asia and Africa. Typhoid conjugate vaccines (TCVs) have been evaluated in field randomized controlled trials (RCTs). This systematic review summarizes their efficacy and safety.

Methods: RCTs of Vi-conjugate typhoid vaccines in children, using a non-typhoid control vaccine and reporting blood-culture-confirmed typhoid fever, were eligible. Data were extracted and synthesized without meta-analysis following the SWiM reporting guideline, with qualitative risk-of-bias appraisal using RoB 2 domains.

Findings: Three RCTs (Nepal, Malawi, Bangladesh; more than 100,000 vaccinated or randomized children) were included. Vaccine efficacy against blood-culture-confirmed typhoid fever was 81.6% (95% CI 58.8–91.8) in Nepal, 80.7% (95% CI 64.2–89.6) in Malawi, and 85% (97.5% CI 76–91) total protection in Bangladesh. Serious adverse events were balanced between groups, and none were attributed to the vaccine in Malawi and Bangladesh; one vaccine-related event (pyrexia) was reported in Nepal.

Conclusion: TCV showed high efficacy and an acceptable safety profile in children in endemic settings. Direct evidence for adult travelers was not found in the trials reviewed.

INTRODUCTION

Typhoid fever, caused by Salmonella enterica serovar Typhi, remains an important cause of febrile illness in South Asia and sub-Saharan Africa, and it is also a recognized risk for travelers to these regions, particularly those visiting friends and relatives. Antimicrobial resistance has made prevention by vaccination increasingly important.

Older typhoid vaccines had limited use in young children. Typhoid conjugate vaccines (TCVs), which link the Vi polysaccharide to a carrier protein, were developed to provide immunogenicity in infants and young children. Three large field RCTs have reported efficacy in endemic settings: in Nepal [1], Malawi [2], and Bangladesh [3].

These trials were conducted in different populations and designs, including an

individually randomized design in Nepal and Malawi and a cluster-randomized design in Bangladesh. Their results are therefore best summarized side by side before drawing conclusions about their relevance to travel health.

This systematic review aims to summarize the efficacy and safety of typhoid conjugate vaccine compared with a control vaccine in randomized trials, and to discuss what these data imply for travel medicine.

METHODS

1. Design

This systematic review of RCTs was planned using the PICO framework. No protocol was prospectively registered. Results were synthesized without meta-analysis, following the principles of the SWiM reporting guideline [4].

2. Eligibility Criteria

Eligibility criteria are summarized in Table 1. RCTs published in peer-reviewed journals were eligible. Trials were grouped by randomization design: individually randomized trials (Nepal and Malawi) and a cluster-randomized trial (Bangladesh).

Table 1. Eligibility Criteria (PICO)

Element	Criterion
Population	Children (and adults where reported) in typhoid-endemic settings
Intervention	Vi-conjugate typhoid vaccine
Comparator	Non-typhoid control vaccine
Outcomes	Blood-culture-confirmed typhoid fever; adverse events
Design	Randomized controlled trial in a peer-reviewed journal

3. Information Sources and Search

Peer-reviewed literature indexed in PubMed was searched in November 2026 through a web search interface, using the terms “typhoid conjugate vaccine,” “typhoid fever,” and “randomized trial”. Publisher abstracts and verified secondary records were used to confirm the content of each trial report.

4. Study Selection

Records were screened against the eligibility criteria by title, abstract, and available full-text information. Selection was performed by a single reviewer.

5. Data Items

Sample size, age range, vaccine and control, follow-up, number of typhoid cases, vaccine efficacy with confidence intervals, immunogenicity where reported, and serious adverse events were extracted.

6. Risk-of-Bias Appraisal

Risk of bias was appraised qualitatively using the domains of the RoB 2 tool [5] (randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting), based on information in published abstracts and verified secondary records.

7. Effect Measures

Effect measures were reported as given by each trial, including hazard ratios, risk ratios, vaccine or treatment efficacy, absolute event rates, and mean differences, each with its 95% confidence interval where available. When a trial reported a confidence level other than 95%, this is stated in the text. Measures were not converted between scales, because conversion requires data that were not available in the records reviewed.

8. Missing and Unreported Data

When a result, confidence interval, or safety rate was not available in the records reviewed, it is stated as not available and was not estimated. Where a figure was derived by simple arithmetic from reported values, this is stated in the text and no confidence interval is given.

9. Certainty of the Evidence

A formal certainty-of-evidence rating was not performed. Instead, the consistency of results across trials, the precision of estimates, the directness of the evidence, and the potential for bias were considered narratively when interpreting the findings.

10. Ethical Considerations

This review used only published data from previously reported trials and did not involve new contact with patients. Ethical

approval was therefore not required, and the original trials reported their own ethical approvals and participant consent.

11. Synthesis

Because drugs, populations, durations, comparators, and outcomes differed, a pooled estimate was not calculated. Results are reported as provided by each trial and are tabulated and described narratively.

RESULTS

1. Study Selection

The search identified three RCTs that met the eligibility criteria [1–3]. All three used a Vi-conjugate typhoid vaccine and a non-typhoid control vaccine, and all assessed blood-culture-confirmed typhoid fever.

2. Characteristics of Included Trials

The Nepal trial randomized 20,019 children aged 9 months to 16 years to typhoid conjugate vaccine (n = 10,005) or meningococcal serogroup A conjugate vaccine (MenA; n = 10,014) [1]. The Malawi trial randomized 28,130 children aged 9 months to 12 years (14,069 and 14,061) to TCV or MenA [2]. The Bangladesh trial was cluster-randomized, with 150 clusters and 61,756 vaccinated participants (41,344 TCV and 20,412 Japanese encephalitis vaccine) [3].

Table 2. Characteristics of Included Trials

Trial	Design and population
Nepal [1]	20,019 children aged 9 months–16 years; TCV (n = 10,005) vs MenA (n = 10,014); individually randomized
Malawi [2]	28,130 children aged 9 months–12 years; TCV (n = 14,069) vs MenA (n = 14,061); individually randomized
Bangladesh [3]	150 clusters; 41,344 vaccinated with Vi-TT and 20,412 with a Japanese encephalitis control; cluster-randomized; mean follow-up 17.1 months

3. Efficacy against Typhoid Fever

3.1 Nepal

In Nepal, 7 cases of blood-culture-confirmed typhoid fever occurred in the TCV group (79 per 100,000 person-years) and 38 in the control group (428 per 100,000 person-years), giving a vaccine efficacy of 81.6% (95% CI 58.8–91.8) [1].

3.2 Malawi

In Malawi, 12 cases occurred with TCV and 62 with MenA. Efficacy was 80.7% (95% CI 64.2–89.6) in the intention-to-treat analysis and 83.7% (95% CI 68.1–91.6) in the per-protocol analysis [2].

3.3 Bangladesh

In Bangladesh, incidence was 96 per 100,000 person-years in the TCV group and 635 in the control group, corresponding to total protection of 85% (97.5% CI 76–91). Protection among children under 2 years was 81% (95% CI 39–94). Overall protection, including the effect in the whole cluster population, was 57% (97.5% CI 43–68), with incidence of 93 versus 213 per 100,000 person-years, and indirect protection was 19% (95% CI −12 to 41), which was not significant [3].

Table 3. Vaccine Efficacy by Trial

Trial	Efficacy (95% CI)
Nepal [1]	81.6% (58.8–91.8)
Malawi [2]	80.7% (64.2–89.6), intention-to-treat
Bangladesh [3]	85% total protection (76–91, 97.5% CI)

4. Immunogenicity

Immunogenicity data were available in the records reviewed only for Nepal, where seroconversion in the immunogenicity subset was 99% (677/683) with TCV and 2% (8/380) with the control vaccine [1].

5. Safety

In Nepal, 132 serious adverse events occurred in the first 6 months (61 with TCV and 71 with MenA), and one event, pyrexia, was considered vaccine-related. Fever in the first week occurred in 5.0% and 5.4%, respectively [1]. In Malawi, 130 serious adverse events were reported (52 with TCV and 78 with MenA); six deaths occurred, all in the MenA group, and none were vaccine-related [2]. In Bangladesh, no vaccine-related serious adverse events were

reported among about 4,800 participants monitored for safety [3].

Table 4. Selected Safety Findings

Trial	Safety finding
Nepal [1]	132 SAEs (61 vs 71); 1 vaccine-related (pyrexia); fever in first week 5.0% vs 5.4%
Malawi [2]	130 SAEs (52 vs 78); 6 deaths, all in control group; none vaccine-related
Bangladesh [3]	No vaccine-related SAEs among about 4,800 monitored

6. Risk-of-Bias Appraisal

All three trials were randomized and used an active control vaccine, which maintains blinding to the typhoid vaccine status. The Bangladesh trial was cluster-randomized, and the analysis therefore needed to account for clustering, which was reflected in its reporting of total, indirect, and overall protection. A domain-level RoB 2 judgement requires full-text and protocol review and was not completed.

Table 5. Qualitative Risk-of-Bias Summary

Trial	Appraisal
Nepal [1]	Randomized, double-blind, active-controlled; no major concerns evident
Malawi [2]	Randomized, double-blind, active-controlled; ITT and per-protocol reported
Bangladesh [3]	Cluster-randomized; clustering considered in analysis

DISCUSSIONS

1. Summary of Evidence

In all three trials, typhoid conjugate vaccine had high efficacy against blood-culture-confirmed typhoid fever, with point estimates of 81.6%, 80.7%, and 85% [1–3]. The consistency across three countries and two randomization designs strengthens confidence in the finding.

2. Consistency across Settings

The trials were conducted in Nepal, Malawi, and Bangladesh, in different transmission settings and with different circulating strains, yet the efficacy estimates were similar. This supports the generalizability of the vaccine's effect across endemic populations.

3. Young Children

In Bangladesh, protection in children under 2 years was 81% (95% CI 39–94), although the interval is wide [3]. Because conjugate vaccines are immunogenic in infants, this is an important difference from older polysaccharide vaccines, which are not recommended in young children.

4. Indirect Protection

In Bangladesh, indirect protection was estimated at 19% (95% CI −12 to 41), which was not statistically significant [3]. Population-level benefit beyond direct protection is therefore uncertain from these data.

5. Safety

Serious adverse events were balanced between groups, and few were attributed to the vaccine [1–3]. In Malawi, all six deaths occurred in the control group and none were considered vaccine-related [2]. The trials were not designed to detect rare adverse events.

6. Relevance to Travel Medicine

The included trials enrolled children living in endemic areas, not international travelers. The records reviewed did not include data on adult travelers, on protection duration beyond the follow-up period, or on recommendations for specific itineraries. Extrapolation to travelers should be made with caution and with reference to national travel-health guidance.

7. Implications for Practice

The findings support TCV as an effective vaccine against typhoid fever in children in endemic settings. Travel clinics should consider destination, duration of stay, and traveler characteristics, and should follow current national guidance when advising on vaccination.

8. Implications for Research

Future research should assess efficacy and duration of protection in adults and in travelers, effect on antimicrobial-resistant typhoid, and cost-effectiveness for travel and for national programs.

9. Strengths of the Review

This review focused on randomized controlled trials published in major peer-reviewed journals, which are the strongest design for estimating intervention effects. Each trial result was cross-checked against the published abstract or a verified secondary record, and the numbers reported here are those given by the trial authors. The reporting of synthesis without meta-analysis followed a published guideline, and limitations in the methods are described openly.

10. Certainty and Consistency of the Evidence

Considered narratively, the certainty of the evidence depends on three features: the number and size of the trials, the consistency of the direction and size of effects between trials, and the precision of the estimates. Where trials agree in direction and have narrow confidence intervals, the evidence is stronger; where trials disagree or have wide confidence intervals, the evidence is weaker and conclusions should be more cautious. A formal grading of certainty was not undertaken and would be needed before the findings are used to support a guideline recommendation.

11. Generalizability

Trial participants are selected by eligibility criteria and often receive closer monitoring than patients in routine care, so effects seen in trials may differ in practice. The populations in the included trials may differ from patients in Indonesia in baseline risk, access to care, and background treatment, and the findings should be applied with attention to local circumstances.

12. Recommendations for an Updated Review

An updated review suitable for journal submission should register a protocol in a public registry before the search, search several databases such as PubMed, Embase, and the Cochrane Library with an exportable strategy, and screen records independently in duplicate. Data should be extracted from full-text reports and trial registries, risk of bias should be assessed domain by domain with RoB 2, and, where trials are sufficiently similar, a random-effects meta-analysis with an assessment of heterogeneity should be performed. The certainty of evidence for each outcome should then be graded using the GRADE approach.

13. Limitations

Several limitations should be acknowledged. Searching was performed through a web interface rather than an exportable multi-database search and no protocol was registered, so relevant trials may have been missed. Selection and extraction were performed by one reviewer, using published abstracts and verified secondary records. A formal RoB 2 assessment was not completed and no pooled estimate was computed. Only three trials were included, all in children in endemic settings; no pooled estimate was computed, and duration of protection was not addressed. The review should be repeated with a documented multi-database search and independent duplicate review before the findings are used for clinical recommendations.

CONCLUSIONS

Typhoid conjugate vaccine showed efficacy of about 80–85% against blood-culture-confirmed typhoid fever in three large trials in children in endemic settings, with no vaccine-related safety signal identified. Direct evidence for adult travelers was not found.

Future work should include a pre-registered, multi-database systematic review with meta-analysis, formal risk-of-bias and certainty-of-evidence assessment, and trials addressing efficacy and duration of protection in adults and travelers.

Author Contribution Statement

The author performed all aspects of this study.

REFERENCES

[1] Shakya M, Colin-Jones R, Theiss-Nyland K, et al. Phase 3 efficacy analysis of a typhoid conjugate vaccine trial in Nepal. *N Engl J Med.*

2019;381(23):2209–2218. doi:10.1056/NEJMoa1905047

[2] Patel PD, Patel P, Liang Y, et al. Safety and efficacy of a typhoid conjugate vaccine in Malawian children. *N Engl J Med.* 2021;385(12):1104–1115. doi:10.1056/NEJMoa2035916

[3] Qadri F, Khanam F, Liu X, et al. Protection by vaccination of children against typhoid fever with a Vi-tetanus toxoid conjugate vaccine in urban Bangladesh: a cluster-randomised trial. *Lancet.* 2021;398(10301):675–684.

[4] Campbell M, McKenzie JE, Sowden A, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ.* 2020;368:l6890. doi:10.1136/bmj.l6890

[5] Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898.