Typhoid conjugate vaccines (TCV): GRADE tables for consideration by the Strategic Advisory Group of Experts (SAGE) on Immunization

Overarching question: The overarching question to be addressed when preparing the evidence to recommendations table is proposed below:

What is the optimal schedule and timing of typhoid conjugate vaccines in different epidemiological and programmatic settings?

Contents

Table	Initial rating	Limitation in study design	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Dose-response	Antagonistic bias& confounding	Final rating
Part 1. GRADE questions on the need for a booster dose of TCV										
1a. In children who have received a single dose of TCV at 6 months to 16 years of age, is there evidence of waning of duration of protection, indicating the need for a booster dose or revaccination?	4	Serious (-1)	Serious (-1)	None serious	Serious (-1)	None serious	Applicable (+1)	Not applicable	Not applicable	Low confidence ⊕⊕
1b. In children who have received a single dose of TCV at 6 to 23 months of age, is there evidence of waning of duration of protection, indicating a need for a booster dose or revaccination?	4	Serious (-1)	Serious (-1)	None serious	Very serious (-1)	None serious	Not applicable	Not applicable	Not applicable	Very low confidence ⊕
1c. In children who have received a single dose of TCV at 24 to 59 months of age, is there evidence of waning of duration of protection, indicating a need for a booster dose or revaccination?	4	Serious (-1)	Serious (-1)	None serious	Serious (-1)	None serious	Applicable (+1)	Not applicable	Not applicable	Low confidence ⊕⊕
1d. In children who have received a single dose of TCV at 5 to 16 years of age, is there evidence of waning of duration of protection, indicating a need for a booster dose or revaccination?	4	Serious (-1)	None serious	None serious	Serious (-1)	None serious	Applicable (+1)	Not applicable	Not applicable	Moderate confidence ⊕⊕⊕
2. In children who have received a single dose of TCV at 6 months to 16 years of age, does a second dose extend the duration of protection?	4	Serious (-1)	None serious	Serious (-1)	None serious	None serious	Not applicable	Not applicable	Not applicable	Low confidence ⊕⊕
Part 2 – GRADE questions on the safety of a booster dose of TCV										

3a: In children who have received a single dose of TCV at 6 months to 16 years of age, what is the safety of a second dose with respect to serious adverse events?	4	None serious	None serious	None serious	Serious (-1)	None serious	Not applicable	Not applicable	Not applicable	Moderate confidence ⊕⊕⊕

Part 1. GRADE questions on the need for a booster dose to optimize the duration of protection of a single dose of TCV against typhoid fever in recipients up to 16 years of age.

GRADE TABLE 1a: In children who have received a single dose of TCV at 6 months to 16 years of age, is there evidence of waning of duration of protection?

Population: Children who have received the first dose of TCV between 6 months up to 16 years of age.
Intervention: A single dose of TCV administered between 6 months and 16 years of age.
Comparison: No vaccination.
Outcome: Efficacy/effectiveness[1] against blood culture-confirmed typhoid 4 or more years after administration of the first dose.

In children who have received a single dose of TCV between 6 months to 16 years of age, is there evidence of waning of duration of protection, indicating the need for a booster dose or revaccination?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		3 RCTs[2] [1-3]	4
	Factors decreasing confidence	Limitation in study design	Serious[3]	-1
		Inconsistency	Serious[4]	-1
		Indirectness	None serious	0
		Imprecision	Serious[5]	-1

[1] Immunogenicity data could be used as a surrogate for efficacy, where required.
[2] The Typhoid Vaccine Acceleration Consortium (TyVAC) has conducted three randomized controlled trials of Typbar-TCV® (Vi polysaccharide conjugated to tetanus toxoid): two individually randomized trials in Nepal (ages 9 months–15 years, n=20,019) and Malawi (ages 9 months–12 years, n=28,130), and one cluster-randomized trial in Bangladesh (ages 9 months–15 years, n=61,756). Cross-over vaccination was conducted in Nepal and Bangladesh. Control vaccines were meningococcal A conjugate (MenA) in Nepal and Malawi, and JE in Bangladesh. Immunogenicity sub-studies were embedded in all three trials. Across sites, a single dose of TCV was shown to be highly efficacious (80–85%) against blood culture–confirmed *S.* Typhi over 18–24 months, with consistent protection across age groups. Longer-term follow-up from Malawi demonstrated an overall efficacy of 78.3% (95% CI 66.3–86.1) at 4.3 years post-vaccination (Patel et al. 2024).
In the Bangladesh trial (Qadri et al. 2024), crossover design only allowed direct comparison between previous-TCV (vaccinated 2018–2019) and recent-TCV recipients (vaccinated in 2021). Previous-TCV recipients had higher typhoid incidence than recent-TCV (adjusted IRR 3.10, 95%CI 1.53-6.29), yielding an extrapolated VE estimate of 50% (95%CI -13-78) in years 3-5. Effectiveness estimates using a nested test-negative analysis comparing incidence rates among vaccinated vs unvaccinated children showed vaccine protection of 84% (95% CI 74–90) among recent-TCV recipients and 55% (95% CI 36–68) among previous-TCV recipients, consistent with waning protection after 3–5 years. In Nepal, estimated vaccine effectiveness among previous-TCV recipients (vaccinated 2017/2018) was 58% (95% CI 9-80, p=0.03) as compared to recent-TCV recipients (vaccinated in 2020/2021), among whom estimated VE was 79% (95%CI 49-91, p=0.0005).
[3] In the Nepal and Bangladesh studies, cross-over vaccination occurred, so the comparator data for VE at ≥4 y is earlier vs later vaccination with TCV rather than TCV vaccination compared to no TCV. Thus, one point is deducted for limitation in study design (applies to all Part 1 GRADE questions).
[4] Estimated VE varies by site (see above); thus, one point is deducted for inconsistency.
[5] In Bangladesh, the estimated VE in years 3-5 was 50% (95%CI -13 -78). In the test-negative analysis, estimated VE was 55% (95%CI 36-68) for previous-TCV recipients as compared to 84% (95%CI 74-90) for recent-TCV recipients. In Malawi, overall VE with median follow-up of 4.5 years was 78.3% (95%CI 66.3-86.1). In Nepal, estimated VE was 58% (95%CI 9-80) among previous-TCV recipients and 79% (95%CI 49-91) among recent-TCV recipients. One level was downgraded for imprecision due to wide confidence intervals that cross clinically relevant thresholds.

		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[6]	+1
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			2
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **low level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion			Low-certainty evidence suggests that a single dose of TCV provides strong protection in the first 2 years and sustained protection through 4–5 years after vaccination. Reduced effectiveness has been observed in some settings beyond 3–5 years, but evidence is heterogeneous and imprecise.

[6] Overall VE at 4.3 years is 78% (95%CI 66-86) in Malawi and vaccine protection at 3-5 years (previous-TCV group) is 55% (95%CI 36-68) in Bangladesh. Estimated VE in Nepal among previous-TCV recipients was 51% (95%CI -9- 78) and 74% (95%CI 36-90) among recent-TCV recipients. These point estimates exceed 50%, so one point was added for large effect size.

GRADE TABLE 1b: In children who have received a single dose of TCV at 6 to 23 months of age, is there evidence of waning of duration of protection?

Population: Children who have received the first dose of TCV between 6 and 23 months of age.
Intervention: A single dose of TCV administered between 6 and 23 months of age.
Comparison: No vaccination.
Outcome: Efficacy/effectiveness[2] against blood culture-confirmed typhoid 4 or more years after administration of the first dose.

In children who have received a single dose of TCV between 6 and 23 months of age, is there evidence of waning of duration of protection, indicating the need for a booster dose or revaccination?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		3 RCTs[3] [1-3]	4
	Factors decreasing confidence	Limitation in study design	Serious[3]	-1
		Inconsistency	None serious[7]	0
		Indirectness	None serious	0
		Imprecision	Very serious[8]	-2
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[9]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			1
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **very low level of confidence** that the true effect lies close to the estimate of the effect on health outcome.

[7]Estimated VE varies by setting in this age group, but these variations are not statistically significant; thus, there is no deduction for **inconsistency**.
[8] In Malawi, among children vaccinated at <2 years of age with TCV, VE was 70.6% after 4.3 years, but with a very wide confidence interval (95%CI 6.4-93.0). In Bangladesh, in the "previous-TCV" group who were vaccinated with TCV at <2 years of age in 2018/2019, VE was 24% after 3-5 years (test-negative analysis) with a wide confidence interval that crosses zero (95%CI -29-55). In Nepal, 6% VE (95%CI -800-90, p-0.96) was observed among children under 2 between year 3 and year 7; 42% VE (95%CI -574-95, p=0.66) was observed in this group Y1-Y4. Thus, two points are deducted for imprecision.
[9] In Malawi, among children vaccinated at <2 years of age with TCV, VE was 70.6% (95%CI 6.4-93.0) after 4.3 years. This is a large effect size (<50%), but with a wide confidence interval. In addition, no large effect size was observed in Bangladesh (see above footnote), so no point is added for effect size.

	Conclusion	Very low-certainty evidence suggests that protection following a single TCV dose administered before 2 years of age may decline beyond 3–5 years. Estimates vary across settings and are highly imprecise, limiting confidence in the extent of waning in this age group.

GRADE TABLE 1c: In children who have received a single dose of TCV at 24 to 59 months of age, is there evidence of waning of duration of protection?

Population: Children who have received the first dose of TCV between 24 and 59 months of age.
Intervention: A single dose of TCV administered between 24 and 59 months of age.
Comparison: No vaccination.
Outcome: Efficacy/effectiveness[2] against blood culture-confirmed typhoid 4 or more years after administration of the first dose.

In children who have received a single dose of TCV between 24 and 59 months of age, is there evidence of waning of duration of protection?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		3 RCTs[3] [1-3]	4
	Factors decreasing confidence	Limitation in study design	Serious[3]	-1
		Inconsistency	Serious[10]	-1
		Indirectness	None serious	0
		Imprecision	Serious[11]	-1
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[12]	+1
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			2
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **low level of confidence** that the true effect lies close to the estimate of the effect on health outcome.

[10] Estimated VE varies by setting in this age group (see below); thus, one point is deducted for inconsistency.
[11] In Malawi, among children who received TCV at 2-4 years of age, VE was high (79.6%) after 4.3 years, but with a wide confidence interval (95%CI 45.8-93.9). In Bangladesh, VE among children who received TCV between ages 2 and 4 was 59% after 3-5 years, but also with a wide confidence interval (95%CI 12-81). In Nepal, VE among children who received TCV between 2 and 4 years of age was 21% (95%CI -210-80, p-0.74) between years 3 and year 7 and 54% (95%CI -101-89, p=0.30) between year 1 and year 4. Thus, one point was deducted for imprecision.
[12] In Malawi, among children who received TCV at 2-4 years of age, VE was 79.6% (95%CI 45.8-93.3) at the end of follow-up (4.3 years). In Bangladesh, in the "previous-TCV" group who were vaccinated with TCV between 2 and 4 years of age in 2018/2019, VE was estimated as 59% (95%CI 12-81) via test-negative analysis 3-5 years following vaccination. Each of these point estimates exceeds 50%; thus, one point is added for effect size. VE was low in Nepal but case numbers were small.

	Conclusion	Low-certainty evidence suggests that a single TCV dose administered at 2–4 years of age provides protection through at least 4 years after vaccination. Reduced effectiveness has been observed in some settings beyond 3–5 years, but estimates remain heterogeneous and imprecise.

GRADE TABLE 1d: In children who have received a single dose of TCV at 5 to 16 years of age, is there evidence of waning of duration of protection?

Population: Children who have received the first dose of TCV between 5 and 16 years of age.
Intervention: A single dose of TCV administered between 5 and 16 years of age.
Comparison: No vaccination.
Outcome: Efficacy/effectiveness[2] against blood culture-confirmed typhoid 4 or more years after administration of the first dose.

In children who have received a single dose of TCV between 5 and 16 years of age, is there evidence of waning of duration of protection, indicating the need for a booster dose or revaccination?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		3 RCTs[3] [1-3]	4
	Factors decreasing confidence	Limitation in study design	Serious	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	Serious[13]	-1
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[14]	+1
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			3
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **moderate level of confidence** that the true effect lies close to the estimate of the effect on health outcome.

[13] In Malawi, in children who received TCV between 5 and 12 years of age, VE was 79.3% but with a moderately wide confidence interval (95%CI 63.5-89.0) after 4.3 years. In Bangladesh, in previous-TCV recipients ages 5-9 years of age, estimated VE was 74% (95%CI 41-89) after 3-5 years and 85% (95%CI 51-95) among previous-TCV recipients ages 10-14 years of age after 3-5 years. In Nepal, 79% VE (95%CI 24-94) was observed among vaccine recipients between years 3 and 7, and 93% VE (95%CI 64-99) was observed between years 1 and year 4. These are all moderately wide confidence intervals, so one point is deducted for imprecision.

[14] In Malawi, in children who received TCV between 5 and 12 years of age, VE was 79.3% (95%CI 63.5-89.0) after 4.3 years. In Bangladesh, in previous-TCV recipients (recieved TCV in 2018/2019) ages 5-9 years of age, estimated VE was 74% (95%CI 41-89) after 3-5 years and 85% (95%CI 51-95) among previous-TCV recipients vaccinated with TCV at ages 10-14 years of age after 3-5 years. These are large effects (±80%), so one point is added for effect size.

	Conclusion	Moderate-certainty evidence indicates that a single TCV dose administered at 5 years of age or older provides sustained protection through at least 4–5 years after vaccination. Evidence of waning in this age group is less pronounced than in younger children.

GRADE TABLE 2: The need for a booster dose to extend the duration of protection in children who received a single dose of TCV up to age 16 years.

Population: Children who have received the first dose of TCV from 6 months up to 16 years of age.
Intervention: A second dose of TCV given at least 1 year after the first dose.
Comparison: A single dose of TCV.
Outcome: Extended protection[2] against blood culture-confirmed typhoid following a booster dose.

In children who have received a single dose of TCV at 6 months to 16 years of age, does a second dose extend the duration of protection?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		5 initial RCTs (observational extensions)[15] [4-6]	4
	Factors decreasing confidence	Limitation in study design	Serious[16]	-1
		Inconsistency	None serious	0
		Indirectness	Serious[17]	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			1

[15] Booster-dose immunogenicity (≥1 year post-primary) data derive from six observational extensions of Phase 2 or Phase 3 randomized trials conducted in Malawi, Burkina Faso, Nepal (Typbar-TCV and Vi-DT), India, and Indonesia. Participants were re-enrolled and boosted without new randomisation at the time of the second dose. In Malawi (Typbar-TCV Phase 3 extension; N=136, 72 boosted), children primed at 9–11 months were boosted 4–5 years later; approximately 100% achieved ≥4-fold seroconversion at Day 28, with GMT increasing 375.7-fold (18.8 to 6867.9 EU/mL). In Burkina Faso (Typbar-TCV Phase 2b extension), children primed at 9–23 months received a heterologous Vi-CRM197 booster 5–6 years later; 100% seroconverted, with day-28 GMT 5140 EU/mL and GMFRs of 238–375. In Nepal, a heterologous Vi-CRM197 booster given ~2 or ~4 years after Typbar-TCV priming resulted in higher antibody concentrations with the longer interval. In the SK Bioscience Vi-DT Phase 2 extension (N=285 enrolled; 268 followed), infants primed at 6–23 months received a booster ~2 years post-primary; 100% seroconverted, with a 64-fold GMT increase (5.5 to 351.8 IU/mL), and seroconversion remained ≥96%, 93%, and 90% at years 3, 4, and 5, respectively. In India (Typbar-TCV Phase 3 extension), a booster ~2 years post-primary elicited ≥10-fold rises with increased avidity; 71% of boosted children retained seroconversion at 7 years compared with 44% of non-boosted children. In Indonesia (BioFarma Vi-DT Phase 2 extension), 58/64 (90.6%) of primed children maintained ≥4-fold seroconversion three years post-primary; after a booster at ~3 years, 64/64 (100%) achieved ≥4-fold responses at Day 28, and ≥96% maintained seroconversion through three years post-booster, with no serious adverse events reported. No safety signals were reported in these extension studies.

[16] Although the primary trials were randomized, booster allocation occurred in open-label extension phases without re-randomisation at the time of the second dose. Participants were re-enrolled several years after priming, introducing potential selection bias and confounding. Therefore, one level was downgraded for study limitations.

[17] Immunogenicity is used as a surrogate for efficacy/effectiveness data, so one point is deducted for indirectness.

Summary of Findings	Statement on the certainty of evidence	Evidence supports a **very low level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion	Low-certainty evidence indicates that a booster dose of TCV administered ≥1 year after primary vaccination induces strong and sustained immunologic responses across vaccine platforms and settings. However, as evidence is based on immunogenicity endpoints rather than clinical efficacy data, the extent to which boosting provides additional long-term protection against typhoid remains uncertain.

Part 2. GRADE questions on the safety of a booster dose of TCV

GRADE TABLE 3: Safety of a booster dose of TCV with respect to serious adverse events in recipients up to 16 years of age.

Population: Children who have received the first dose of TCV from 6 months to 16 years of age.
Intervention: A second dose of TCV at least 1 year after the first dose.
Comparison: No second dose of TCV.
Outcome: Serious adverse events determined to be causally related to TCV after the second TCV dose.

What is the safety of a second dose of TCV with respect to serious adverse events in recipients 6 months to 16 years of age?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT, 4 observational studies[18] [4-7]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	Serious[19]	-1
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			3
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **moderate level of confidence** that the true effect lies close to the estimate of the effect on health outcome.

[18] Safety data for a booster dose of TCV administered ≥12 months after the primary dose derive from one randomized Phase 2 trial and five observational extensions conducted in Nepal, India, Malawi, Burkina Faso, and Indonesia. In Nepal (Vi-DT Phase 2 trial; Capeding et al., 2022), 114 children in the late-booster arm (primed at 6–23 months) received a booster at ~96–110 weeks post-primary; no serious adverse events (SAEs) were assessed as causally related to vaccination. Long-term follow-up through 5 years showed comparable safety profiles between early- and late-booster groups. In India (Typbar-TCV Phase 3 extension; Vadrevu et al., 2021), approximately 100 children received a booster ~2 years post-primary; no vaccine-related SAEs were identified. In Malawi (TyVAC Phase 3 extension; Nampota-Nkomba et al., 2025), 72 children received a booster 4–5 years post-primary and were followed for 6 months; no SAEs were deemed causally related. In Burkina Faso (TyVAC Phase 2b extension), 87 children received a heterologous Vi-CRM197 booster 5–6 years post-primary; no vaccine-related SAEs were identified during 28-day follow-up. In Indonesia (BioFarma Vi-DT Phase 2 extension), 64 children primed at 6–23 months received a booster ~3 years post-primary; no SAEs were reported within 28 days.

[19] Across these studies, <1000 booster recipients have been documented without vaccine-related serious adverse events. However, the total exposed population remains limited and studies were not powered to detect rare adverse events; therefore, one level was downgraded for imprecision.

	Conclusion	Moderate-certainty evidence indicates that a booster dose of TCV administered at least 12 months after the primary dose is well tolerated and has not been associated with vaccine-related serious adverse events in available studies. However, the total number of booster recipients remains limited, and rare adverse events cannot be excluded.

References

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