GRADE tables

Systematic review and meta-analysis of immunogenicity, efficacy and safety data of Vi-TT typhoid conjugate vaccines Source: Cochrane Response and Cochrane Infectious Diseases Group

Summary of Findings 1.2: Vi-TT typhoid conjugate vaccines (2 doses) versus placebo, no intervention or control vaccine in children and adults [11]

Patients: 6 month to 12-year old children; 18-60 year old adults (efficacy and immunogenicity)
Setting: India, UK (efficacy), Vietnam, UK (immunogenicity)
Comparison: Vi-TT typhoid conjugate vaccine (Peda Typh™, 2 doses (6 week interval) or Typbar-TCV®, 1 dose) versus placebo, no intervention (normal vaccination course) or control vaccine (MENVEO®, 1 dose)

Outcome	Plain language summary	Vaccine type and doses	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
			Control	Vi-TT		
Incidence of typhoid fever in adults follow-up: <1 month	We do not know about the effects of 1 dose Typbar-TCV on incidence of typhoid fever compared with placebo at <1 month follow-up, evidence was of very low certainty.	Typbar-TCV 1 dose	419 per 1000	54.5 per 1000 (13 to 222)	RR 0.13 (0.03 to 0.53) 68 participants in 1 RCT	⨁◯◯◯ VERY LOW[2,3] due to serious indirectness and imprecision
Incidence of typhoid fever in children follow-up: Year 1	We do not know about the effects of 2 doses Pedatyph on incidence of typhoid fever compared with normal course of vaccination; evidence was of very low certainty.	Peda Typh 2 doses	13 per 1000	0.8 per 1000 (0 to 13)	RR 0.06 (0.00 to 1.01)[1] 1625 participants in 1 cluster RCT	⨁◯◯◯ VERY LOW[3,4,5] due to imprecision, indirectness, and risk of bias
Ratio of GMTs in adults follow up: <1 month	We do not know about the effects of 1 dose Typbar-TCV on GMTs compared with placebo at <1 month follow-up, evidence was of very low certainty.	Typbar-TCV 1 dose	Mean: 7.8 EU	Mean: 579.7 EU	Ratio 73.91 (43.89 to 124.47) 72 participants in 1 RCT	⨁◯◯◯ VERY LOW[2,3] due to serious indirectness and imprecision
Seroconversion in adults follow up: <1 month	We do not know about the effects of 1 dose Typbar-TCV on seroconversion compared with placebo at <1 month follow-up, evidence was of very low certainty.	Typbar-TCV 1 dose	0/33 (0%)	37/37 (100%)	RR 67.11 (4.28 to 1051.38) 72 participants in 1 RCT	⨁◯◯◯ VERY LOW[2,3] due to serious indirectness and imprecision
SAEs (RCTs) in children follow up: up to 1 month	Evidence from RCTs We do not know about the effect of 2 doses PedaTyph on SAEs compared with no treatment in children; evidence was of very low certainty.	Peda Typh 2 doses	0/860 (no treatment)	0/905	RR not estimable* 1765 participants in 1 RCT	⨁◯◯◯ VERY LOW[4,5,6] due to imprecision, indirectness, and risk of bias
SAEs (RCTs) in adults follow up: up to 1 month	Evidence from RCTs We do not know about the effect of 1 dose Typbar-TCV compared with control vaccine on SAEs in adults; evidence was of very low certainty.	Typbar-TCV 1 dose	0/34 (MENVEO)	1/41[a]	RR 2.50 (0.11 to 59.46) 75 participants in 1 RCT	⨁◯◯◯ VERY LOW[2,3] due to serious indirectness and imprecision

SAEs (NRCS) in children and adults follow-up: 3 months	Evidence from non-randomised comparison: We do not know about the effect of 1 dose Typbar-TCV on SAEs; evidence was of very low certainty.	Typbar-TCV 1 dose	One SAE was reported among 327 participants in a non-randomised arm of an RCT.[b]	⊕OOO VERY LOW[3,7,8] due to non-randomised comparison, imprecision and indirectness

CI= confidence interval; EU= enzyme-linked immunosorbent assay (ELISA) unit; GMT= Geometric mean titre; NRCS= non-randomised comparative study; MENVEO= Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine; RCT= randomised controlled trial; RR= risk ratio; Vi-TT= typhoid Vi antigen coupled to tetanus toxin carrier protein

* Effect could not be estimated because no events were reported

[1] Primary trial is not cluster adjusted. This estimate uses a small assumed intra-cluster correlation co-efficient of 0.0015. (Alternatively, assuming a large intra-cluster correlation co-efficient of 0.1 would give RR 0.85, 95% CI 0.04 to 20.08).

[2] Downgraded two levels for serious indirectness: evaluated by only one trial in adults in the UK; human challenge study design uses high levels of bacterial inoculum and controls timing of infection relative to vaccination.

[3] Downgraded one level for imprecision: small sample size.

[4] Downgraded one level for indirectness: evaluated by only one cluster trial in one setting (Kolkata, India) in children under 12 years.

[5] Downgraded one level for risk of bias: unblinded, unadjusted cluster trial with baseline difference between intervention and control groups.

[6] Downgraded one level for imprecision: no events were reported.

[7] Non-randomised comparisons start at moderate level evidence.

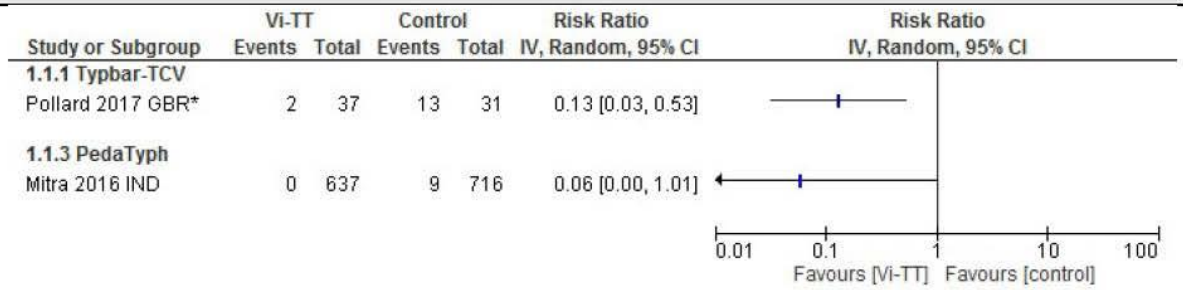
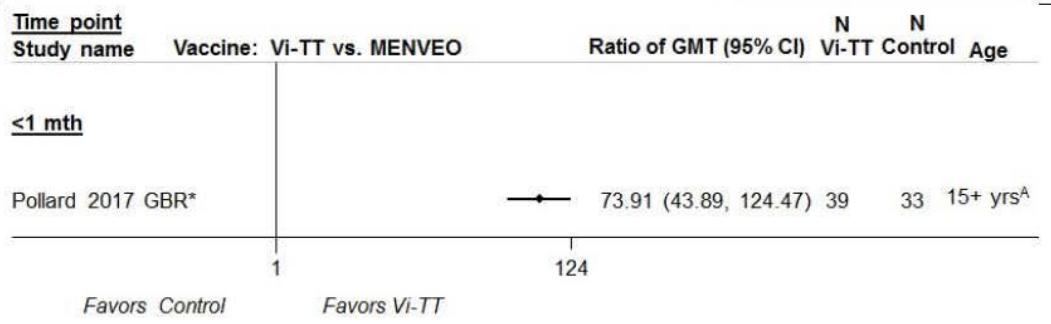
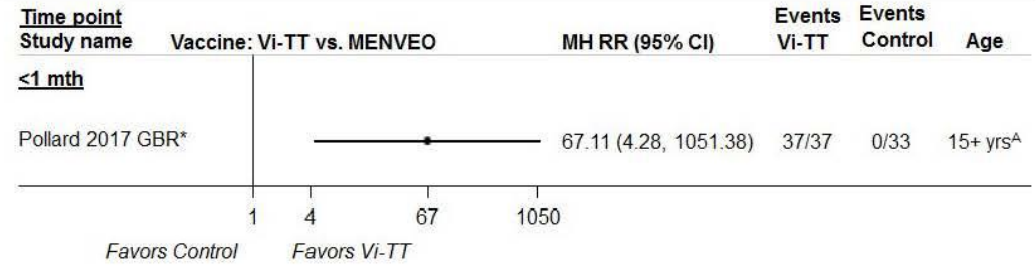
[8] Downgraded one level for indirectness: evaluated by only one trial in one setting (India).

[a] One hospitalisation for per-rectum bleeding and altered bowel habit, diagnosed with inflammatory bowel disease. Deemed not related to vaccination - onset of symptoms occurred prior to vaccination.

[b] Lower respiratory tract infection in an 18-month-old girl, resolved upon treatment, assessed by trialists as unrelated to vaccination.

Forest plots 1.2: Vi-TT typhoid conjugate vaccine versus placebo, no intervention or control vaccine in children and adults

Patients: 6 month to 12-year old children (efficacy); 18-60 year old adults (immunogenicity)
Setting: India (efficacy), Vietnam (immunogenicity)
Comparison: Vi-TT typhoid conjugate vaccine (Peda Typh™, 2 doses (6 week interval) or Typbar-TCV®, 1 dose) versus placebo, no intervention (normal vaccination course) or control vaccine (MENVEO®, 1 dose)

Outcome	Forest plot	Certainty of the evidence (GRADE)
Incidence of typhoid fever with 2 doses PedaTyph in infants and children (0.5 to 12 years) or 1 dose Typbar-TCV in adults follow up: <1 month (Pollard GBR); Year 1 (Mitra 2016 IND)		⊕OOO VERY LOW ⊕OOO VERY LOW
Ratio of GMTs with 1 dose Typbar-TCV in adults follow up: <1 month		⊕OOO VERY LOW
Seroconversion with 1 dose Typbar-TCV in adults follow up: <1 month		⊕OOO VERY LOW

		14
SAEs (RCTs)	Vi-TT vs no treatment: only 1 study (Mitra 2016 IND) included for this comparison. Tabulated in Appendix 1.2 (A.1.2.3)	⊕OOO VERY LOW
	Vi-TT vs control vaccine: only 1 study (Pollard 2017 GBR) included for this comparison. Tabulated in Appendix 1.2 (A.1.2.4)	
SAEs (NRCS)	Vi-TT: only 1 study (Mohan 2015 IND) included. Tabulated in Appendix 1.2 (A.1.2.5)	⊕OOO VERY LOW

[A] = 18-60 yrs, *human challenge study, unpublished data

Summary of Findings 1.4: Vi-TT typhoid conjugate vaccines versus typhoid Vi-polysaccaride vaccine (ViPS) in children and adults [18]

Patients: 2 to 60-year old children and adults
Setting: India, United Kingdom
Comparison: Vi-TT typhoid conjugate vaccine (Typbar-TCV®, 1 dose) versus typhoid ViPS vaccine (Typhim Vi® or Typbar®, 1 dose)

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		ViPS	Vi-TT		
Incidence of typhoid fever in adults follow-up: <1 month	We do not know about the effect of 1 dose Typbar-TCV on the incidence of typhoid fever in adults compared with ViPS typhoid vaccine at <1 month follow-up because the certainty of the evidence is very low.	200 per 1000	54 per 1000 (12 to 242)	RR 0.27 (0.06 to 1.21) 72 participants in 1 RCT	⊕OOO VERY LOW[1,2] due to serious indirectness and imprecision
Ratio of GMTs in adults follow up: 0-<1 month	We do not know about the effect of 1 dose Typbar-TCV on GMTs in adults compared with ViPS typhoid vaccine at <1 month follow-up because the certainty of the evidence is very low.	Mean: 140.5 EU	Mean: 579.7 EU	Ratio 4.12 (2.38 to 7.14) 74 participants in 1 RCT	⊕OOO VERY LOW[1,2] due to serious indirectness and imprecision
Ratio of GMTs in children and adults follow up: 1-<2 months	There probably is higher GMTs with 1 dose Typbar-TCV typhoid conjugate vaccine compared with ViPS typhoid vaccine at 1 to <2 months' follow-up in children and adults.	Mean: 411 EU/mL	Mean: 1293 EU/mL	Ratio 3.15 (2.70 to 3.61) 637 participants in 1 RCT	⊕⊕⊕O MODERATE[3] due to indirectness
Ratio of GMTs in children and adults follow up: 1-<2 years	There probably is higher GMTs with 1 dose Typbar-TCV typhoid conjugate vaccine compared with ViPS typhoid vaccine at 1 to <2 years' follow-up in children and adults.	Mean: 45.8 EU/mL	Mean: 81.7 EU/mL	Ratio 1.78 (1.53 to 2.08) 440 participants in 1 RCT	⊕⊕⊕O MODERATE[3] due to indirectness
Seroconversion in adults follow up: 0-<1 month	We do not know about the effect of 1 dose Typbar-TCV on seroconversion rate in adults compared with ViPS typhoid vaccine at <1 month follow-up because the certainty of the evidence is very low.	886 per 1000	1000 per 1000 (877 to 1000)	RR 1.13 (0.99 to 1.28) 72 participants in 1 RCT	⊕OOO VERY LOW[1,2] due to serious indirectness and imprecision
Seroconversion in children and adults follow up: 1-<2 months	There probably is a slightly better seroconversion rate for 1 dose Typbar-TCV typhoid conjugate vaccine compared with ViPS typhoid vaccine at 1-<2 months follow-up in children and adults.	931 per 1000	968 per 1000 (940 to 1000)	RR 1.04 (1.01 to 1.08) 637 participants in 1 RCT	⊕⊕⊕O MODERATE[3] due to indirectness
Seroprotection in children and adults follow up: 1-<2 years	There probably is a better seroconversion rate for 1 dose Typbar-TCV typhoid conjugate vaccine compared with ViPS typhoid vaccine at 1-<2 years follow-up in children and adults.	533 per 1000	741 per 1000 (640 to 863)	RR 1.39 (1.20 to 1.62) 440 participants in 1 RCT	⊕⊕⊕O MODERATE[3] due to indirectness

SAEs (RCTs) in children and adults follow up: up to 3 months	Evidence from RCTs: There probably is little or no difference in SAE rate for 1 dose Typbar-TCV typhoid conjugate vaccine compared with ViPS typhoid vaccine in children and adults at up to 3 months follow-up.	114 per 10,000 [a]	4.1 per 10,000 (8 to 207)[b]	RR 0.36 (0.07 to 1.82) 732 participants in 2 RCTs	⊕⊕⊕◯ MODERATE[4] due to imprecision
SAEs (NRCS) in children ≥2 years follow up: 2 days	Evidence from non-randomised comparative studies: We do not know about the effect of 1 or 2 doses Pedatyph typhoid conjugate vaccine compared with ViPS typhoid vaccine on SAEs; certainty of evidence was very low.	0 / 37	0 / 169	RR not estimable* 206 participants in 1 non-randomised comparative study	⊕◯◯◯ VERY LOW[5,6,7] due to no randomisation, indirectness, and imprecision

CI= confidence interval; EU= enzyme-linked immunosorbent assay (ELISA) unit; GMT= Geometric mean titre; NRCS= non-randomised comparative study; RCT= randomised controlled trial; RR= risk ratio; ViPS= typhoid Vi-polysaccharide vaccine; Vi-TT= typhoid Vi antigen coupled to tetanus toxin carrier protein

* Effect could not be estimated because no events were reported

[1] Downgraded two levels for serious indirectness: evaluated by only one trial in adults in the UK; human challenge study design uses high levels of bacterial inoculum and controls timing of infection relative to vaccination.

[2] Downgraded one level for imprecision: small sample size.

[3] Downgraded one level for indirectness: evaluated by only one trial in 8 sites in India.

[4] Downgraded one level for imprecision: wide 95% CI that include both no effect and benefit for ViPS.

[5] Non-randomised comparative studies start at moderate certainty evidence.

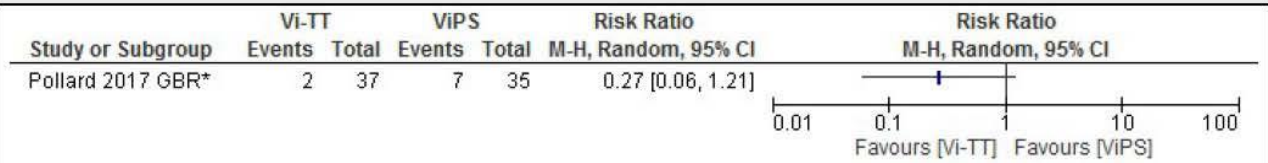
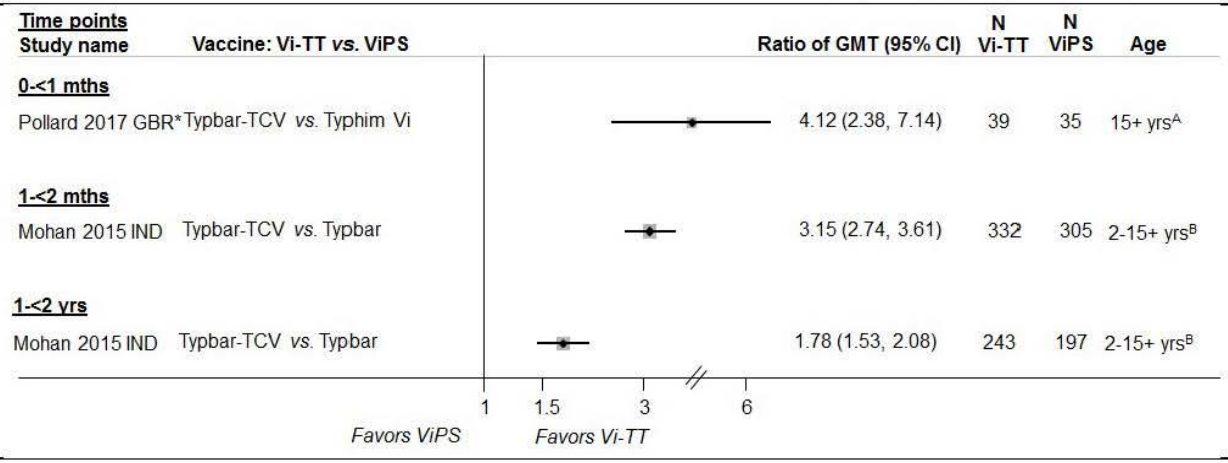
[6] Downgraded one level for indirectness: evaluated by only one trial in 3 sites in India.

[7] Downgraded one level for imprecision: no events were reported.

[a] Four hospitalisations in ViPS groups, none assessed to be related to vaccine: polyarthropathy following typhoid challenge and antibiotic use, requiring ongoing rheumatological input; urinary retention secondary to vaginal ulceration; semi-elective tonsillectomy for investigation of tonsilar lesion; febrile convulsions in a 3-year-old, resolved.
[b] One hospitalisation in Vi-TT group: per-rectum bleeding and altered bowel habit, diagnosed with inflammatory bowel disease. Not related to vaccination - onset of symptoms occurred prior to vaccination

Forest plots 1.4: Vi-TT typhoid conjugate vaccines versus typhoid Vi-polysaccaride vaccine (ViPS) in children and adults

Patients: 2 to 60-year old children and adults
Setting: India, United Kingdom
Comparison: Vi-TT typhoid conjugate vaccine (Typbar-TCV®, 1 dose) versus typhoid ViPS vaccine (Typhim Vi® or Typbar®, 1 dose)

Outcome	Forest plot	Certainty of the evidence (GRADE)
Incidence of typhoid fever with 1 dose Typbar-TCV in adults follow up: <1 month		⊕OOO VERY LOW
Ratio of GMTs with 1 dose Typbar-TCV in children and adults follow up: 0 months to <2 years		⊕OOO VERY LOW ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE

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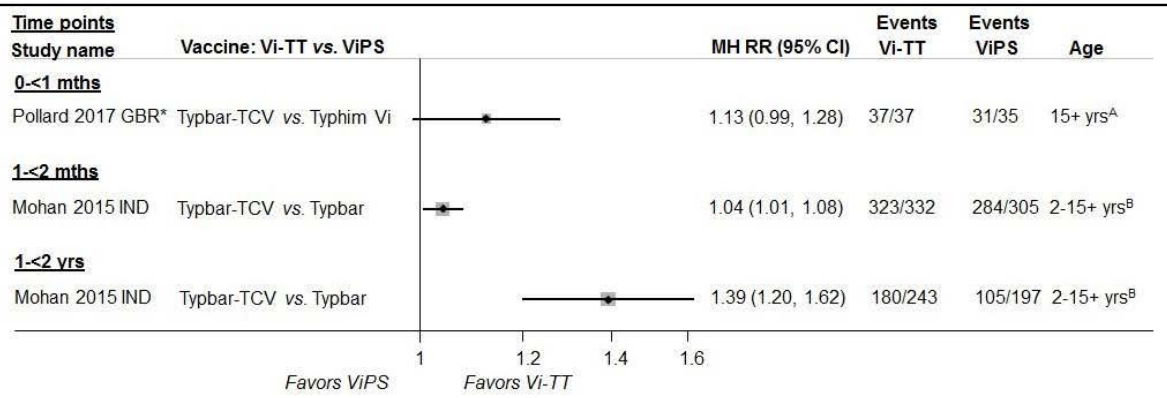
with 1 dose Typbar-TCV in children and adults

follow up: 0 months to <2 years</td>
<td> 
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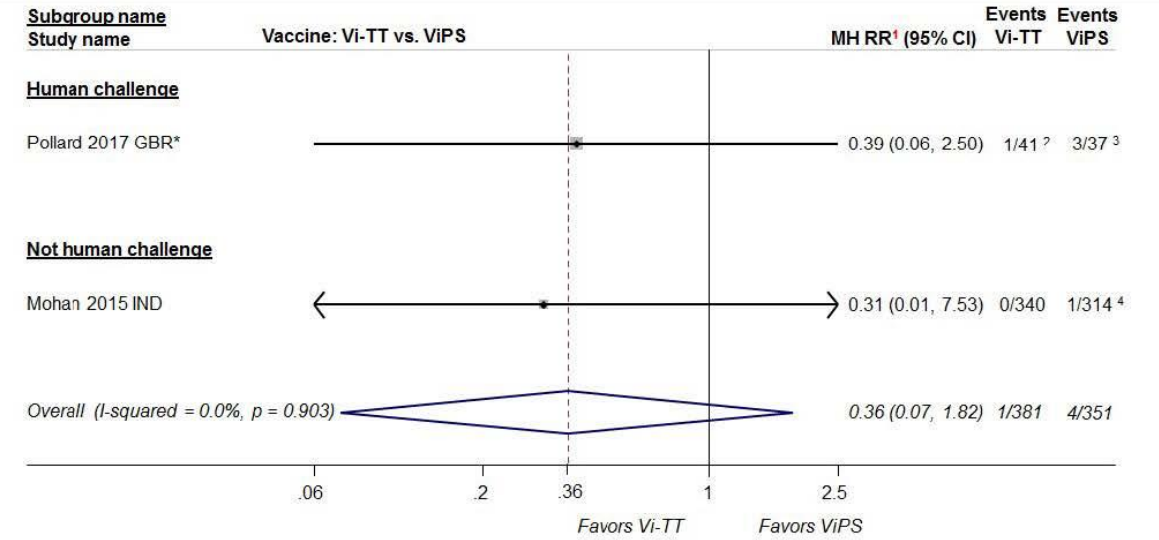
with 1 dose Typbar-TCV in children and adults

follow-up: 3 months</td>
<td> 
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<td>Vi-TT vs ViPS NRCS: only 1 study (Garg 2014 IND) included for this comparison. Tabulated in Appendix 1.2 (A.1.2.5)</td>
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[A] = 18-60 yrs; [B] = 2-45 yrs * Human challenge study, unpublished data

[1] A 0.5 continuity correction was added to all cells of the 2x2 table

[2] 1 hospitalisation for per-rectum bleeding and altered bowel habit. Diagnosed with inflammatory bowel disease. Not related to vaccination - onset of symptoms occurred prior to vaccination

[3] 3 Hospitalisations, none assessed to be related to vaccine. Polyarthropathy following typhoid challenge and antibiotic use, requiring ongoing rheumatological input. Hospitalisation for urinary retention secondary to vaginal ulceration. Hospitalisation for semi-elective tonsillectomy for investigation of tonsilar lesion.

[4] 1 Hospitalisation for febrile convulsions in a 3-year-old, resolved and assessed to be unrelated to vaccination.

Summary of Findings 1.6: Booster versus no booster Vi-TT in infants, children and adults

Patients: **infants, children and adults**
Setting**: India**
Comparison: **Booster dose of Typbar-TCV at 720 days after one initial dose, versus no booster (one initial dose of Typbar-TCV only)**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		No booster	Vi-TT booster		
Incidence of typhoid fever	No studies were identified for this outcome.				
Ratio of GMTs (aged 2-45 years) follow up: 42 days after booster dose (approx. 762 days after 1st dose) versus 720 days after 1st dose	We do not know about the effect of a booster dose of Typbar-TCV on GMTs in children and adults because the certainty of evidence is very low.	Mean: 81.7 EU/mL	Mean: 1685.3 EU/mL	Ratio 20.63 (19.05 to 22.03) 183 participants in 1 non-random cohort*	⨁◯◯◯ VERY LOW[1,2] due to risk of bias and indirectness
Ratio of GMTs (aged 6-23 months) follow up: 42 days after booster dose (approx. 762 days after 1st dose) versus 720 days after 1st dose	We do not know about the effect of a booster dose of Typbar-TCV on GMTs in infants because the certainty of evidence is very low.	Mean: 48.7 EU/mL	Mean: 1721.9 EU/mL	Ratio 35.36 (32.18 to 38.84) 193 participants in 1 open-label trial**	⨁◯◯◯ VERY LOW[1,2] due to risk of bias and indirectness
Seroconversion	No studies were identified for this outcome.				
SAEs	No studies were identified for this outcome.				

CI= confidence interval; EU= enzyme-linked immunosorbent assay (ELISA) unit; GMT= Geometric mean titre; RCT=randomised controlled trial; RR= risk ratio

*Three-hundred and forty participants aged 2 to 45 years received one dose of Typbar-TCV in a single arm of an RCT, and a non-random sample of 183 of these participants went on to receive a booster dose at 720 days. The comparison is between 243 of the 340 participants who received one dose with serum samples available at 720 days, and 175 of the 183 participants who received the initial dose plus a booster, with serum samples available at approximately 762 days. All 175 participants analysed in the booster dose group are also included within the non-booster dose groups. Correlation equal to 0 (no adjustment for matching), and 0.5 and 0.75 were applied; correlation to 0.5 shown in summary of findings table.

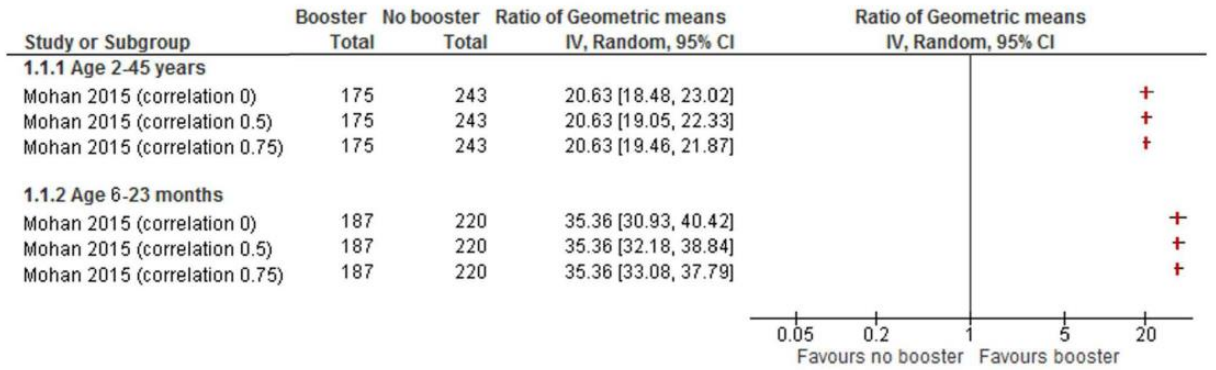
**Three-hundred and twenty-seven participants aged 6 to 23 months received one dose of Typbar-TCV in an open-label trial, and a non-random sample of 193 of these participants went on to receive a booster dose at 720 days. The comparison is between 220 of the 327 participants who received one dose with serum samples available at 720 days, and 187 of the 193 participants who received the initial dose plus a booster, with serum samples available at approximately 762 days. All 187 participants analysed in the booster dose group are also included within the non-booster dose groups. Correlation equal to 0 (no adjustment for matching), and 0.5 and 0.75 were applied; correlation to 0.5 shown in summary of findings table.

[1] Downgraded two levels for risk of bias: non-randomised comparison: analysis of the same sample participants before and after booster dose; age is a serious confounder, not controlled across groups.

[2] Downgraded one level for indirectness: evaluated by only one trial in India.

Forest plots 1.6: Booster versus no booster Vi-TT in infants, children and adults

Patients: **infants, children and adults**
***Setting*:** **India**
Comparison: **Booster dose of Typbar-TCV at 720 days after one initial dose, versus no booster (one initial dose of Typbar-TCV only)**

Outcome	Forest plot	Certainty of the evidence (GRADE)
Incidence of typhoid fever	No studies were identified for this outcome.	
Ratio of GMTs follow up: 1 month after booster dose versus 6 months after 3rd dose		⊕OOO VERY LOW
Seroconversion	No studies were identified for this outcome.	
SAEs	No studies were identified for this outcome.	

Summary of findings 1.8: 1 dose versus 2 doses Vi-TT typhoid conjugate vaccine in children

Patients: **children (mean age: 4.5 years)**
***Setting*: India**
Comparison: **1 dose versus 2 doses (2 month interval) Vi-TT (Peda Typh^{TM}) typhoid conjugate vaccine**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		2 doses Vi-TT	1 dose Vi-TT		
Incidence of typhoid fever	No studies were identified for this outcome.				
Ratio of GMTs in 2 to <5 year olds follow up: 2-<5 years	We do not know about the effect of 1 dose compared with 2 doses PedaTyph typhoid conjugated vaccine on ratio of GMTs at 2 to <5 years follow-up in children; evidence is of very low certainty.	Mean: 17 µg/mL	Mean: 14 µg/mL	Ratio 0.82 (0.25 to 2.68) 40 participants in 1 RCT	⊕OOO VERY LOW[1,2,3] due to risk of bias, indirectness, and imprecision
Seroconversion	No studies were identified for this outcome.				
SAEs (RCTs) in infants and children (≤5 years) follow up: up to 7 days	Evidence from RCTs We do not know about the effect of 2 doses compared with 1 dose PedaTyph typhoid conjugated vaccine on SAEs in children; evidence is of very low certainty.	0/200	0/200	RR not estimable** 400 participants in one RCT	⊕⊕OO VERY LOW[2,4,5] due to risk of bias, indirectness, and imprecision

CI= confidence interval; GMT= Geometric mean titre; RCT= randomised controlled trial; RR= risk ratio; Vi-TT= typhoid Vi antigen coupled to tetanus toxin carrier protein

[1] Downgraded one level for risk of bias: high risk of performance and attrition bias, and non-random comparison (a non-random subsample of children from an RCT were included in follow-up).

[2] Downgraded one level for indirectness: evaluated by only one trial in children in one setting (India).

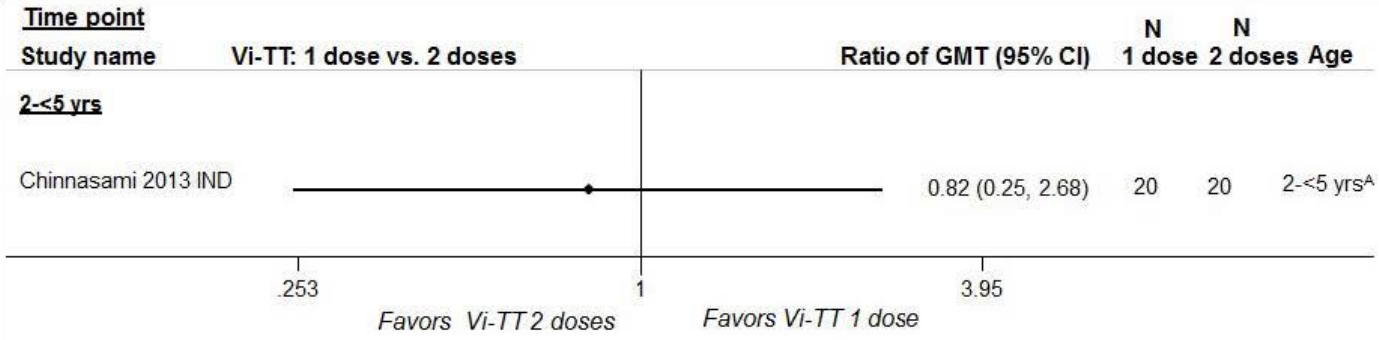
[3] Downgraded one level for imprecision: small sample size.

[4] Downgraded one level for risk of bias: high risk of performance and detection bias, and unclear randomisation methods.

[5] Downgraded one level for imprecision: no events were reported among relatively few participants, effect could not be estimated.

Forest plots 1.8: 1 dose versus 2 doses Vi-TT typhoid conjugate vaccine in children

Patients: **children (mean age: 4.5 years)**
***Setting*:** **India**
Comparison: **1 dose versus 2 doses (2 month interval) Vi-TT (Peda Typh™) typhoid conjugate vaccine**

Outcome	Forest plot	Certainty of the evidence (GRADE)
Incidence of typhoid fever	No studies were identified for this outcome.	
Ratio of GMTs follow up: 2 to <5 years		⊕OOO VERY LOW
Seroconversion	No studies were identified for this outcome.	
SAEs	1 versus 2 doses Vi-TT: only 1 study (Chinnasami 2013 IND) included for this comparison. Tabulated in Appendix 1.2 (A.1.2.6)	⊕OOO VERY LOW

[A]= range not reported; mean age 4.5 years at 30 months follow-up.