Summary of Findings 2.1: Typhoid Vi-polysaccharide vaccine versus placebo or control vaccine in children and adults – efficacy outcomes

Patients: **2 to 19 year old children and adolescents, and adults up to 55 years (efficacy) / children (>2 years) and adults (≤82 years) (SAEs)**
***Setting*: Clinic or home setting in China, India, Nepal, Pakistan and South Africa (efficacy) / East- and South east Asia, Europe, Cuba, South Africa, and the USA (SAEs)**
Comparison: **Capsular polysaccharide of *S typhi*, Vi vaccine (single dose intramuscular injection) versus placebo, pneumococcal vaccine, hepatitis A vaccine or meningococcal vaccine (efficacy) / ViPS vaccine versus placebo, control vaccine (meningococcal, hepatitis A), candidate typhoid vaccine (Vi-CRM_{197}), or no comparison group (SAEs)**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Control	ViPS		
Incidence of typhoid fever in children and adults follow-up: Year 1	1 dose ViPS vaccine compared with placebo reduces the incidence of typhoid fever in children and adults in the first year after vaccination	Moderate risk[1]		RR 0.31 (0.26 to 0.37) 99,797 participants in 3 RCTs	⊕⊕⊕⊕ HIGH
		4 per 10,000	1.2 per 10,000 (1.0 to 1.5)		
		High risk[1]			
		51 per 10,000	15.8 per 10,000 (13.3 to 18.9)		
Incidence of typhoid fever in children and adults follow-up: Year 2	1 dose ViPS vaccine compared with placebo probably reduces the incidence of typhoid fever in children and adults in the second year after vaccination	Moderate risk[1]		RR 0.41 (0.31 to 0.55) 194,969 participants in 4 RCTs	⊕⊕⊕O MODERATE[2] due to inconsistency
		4 per 10,000	1.6 per 10,000 (1.2 to 2.2)		
		High risk[1]			
		51 per 10,000	20.9 per 10,000 (15.8 to 28.1)		
Incidence of typhoid fever in children and adults follow-up: Year 3	1 dose ViPS vaccine compared with placebo probably reduces the incidence of typhoid fever in children and adults in the third year after vaccination	Moderate risk[1]		RR 0.50 (0.32 to 0.78) 11,384 participants in 1 RCT	⊕⊕⊕O MODERATE[3] due to indirectness
		4 per 10,000	2 per 10,000 (1.2 to 2.2)		
		High risk[1]			
		51 per 10,000	25.5 per 10,000 (15.8 to 28.1)		
Cumulative incidence of typhoid fever in children and adults follow-up: 2.5 to 3 years	1 dose ViPS vaccine compared with placebo probably reduces the incidence of typhoid fever in children and adults over 2.5 to 3 years after vaccination	Moderate risk[1]		RR 0.45 (0.30 to 0.70) 11,384 participants in 1 RCT	⊕⊕⊕O MODERATE[3] due to indirectness
		4 per 10,000	1.8 per 10,000 (1.2 to 2.2)		
		High risk[1]			
		51 per 10,000	23 per 10,000 (15.8 to 28.1)		
Serious adverse events (RCTs) in children and adults follow-up: up to 6 months	Evidence from RCTs: SAEs due to ViPS vaccine are very rare in children and adults. There may be little or no difference in SAE rate for ViPS compared with placebo, control vaccines, or typhoid candidate vaccine in children and adults at up to 6 months follow-up.	60 per 10,000 (placebo)	12 per 10,000 (0.6 to 248)[a]	RR 0.20 (0.01 to 4.14) 132,301 participants in 5 RCTs	⊕⊕⊕⊕ HIGH[4]
		0.85 per 10,000 (control vaccines)	1.63 per 10,000 (0.4 to 6.54)[b]	RR 1.91 (0.48 to 7.66) 203,936 participants in 9 RCTs	
		114 per 10,000 (typhoid candidate vaccine)	41 per 10,000 (8 to 207)[c]	RR 9.58 (0.47 to 195.64) 204 participants in 2 RCTs	

Serious adverse events (NRCS) in children and adults follow-up: 3 days	Evidence from non-randomised comparative studies: We are uncertain about the effect of ViPS vaccine compared with control vaccine (meningococcal) on serious adverse events in adults; certainty of evidence was very low.	0/94	0/411	RR not estimable** 505 participants in 1 NRCS	⊕OOO[5,6,7] VERY LOW due to non-randomised comparison, imprecision, and inconsistency
Serious adverse events (NCOS) in children and adults follow-up: up to 6 months	Evidence from non-comparative observational studies: SAEs due to ViPS vaccine may be very rare in children and adults at up to 6 months follow-up.	• 24 SAEs were reported in US national surveillance 1990-2002; a rate of 0.59 per 100,000 doses were detected[d] • No SAEs were reported in Cuban national surveillance 1999-2008 • in 16 NCOS with 264,739 participants 6 SAEs were reported[e]			⊕⊕OO[8] LOW due to observational study design

CI= confidence interval; NRCS= non-randomised comparative study; NCOS= non-comparative observational study; RCT= randomised controlled trial; RR= risk ratio; ViPS= Vi capsular polysaccharide typhoid vaccine
** Effect could not be estimated because no events were reported

[1] The incidence of typhoid in a medium-risk setting is taken from the control group in a study from China (Yang 2001 CHN).The incidence of typhoid in a high-risk setting is taken from a study in India (Sur 2009 IND). This is consistent with the incidence levels described by a global epidemiological study (Crump 2004).

[2] Downgraded by 1 for inconsistency: The magnitude of the protective effect varied between trials from 34% to 69% (I^2 = 72%). The reasons for this are not clear; one potential factor may be the different age groups included in the trials, with Khan 2012 PAK suggesting lower protective effect in children < 5 years of age.

[3] Downgraded by 1 for indirectness: evaluated by only one study in one setting (South Africa)

[4] Although 95% CIs were very wide due to few events, we did not downgrade for imprecision because sample size was very large.

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

[6] Downgraded by 1 for imprecision: very low (zero) event rate.

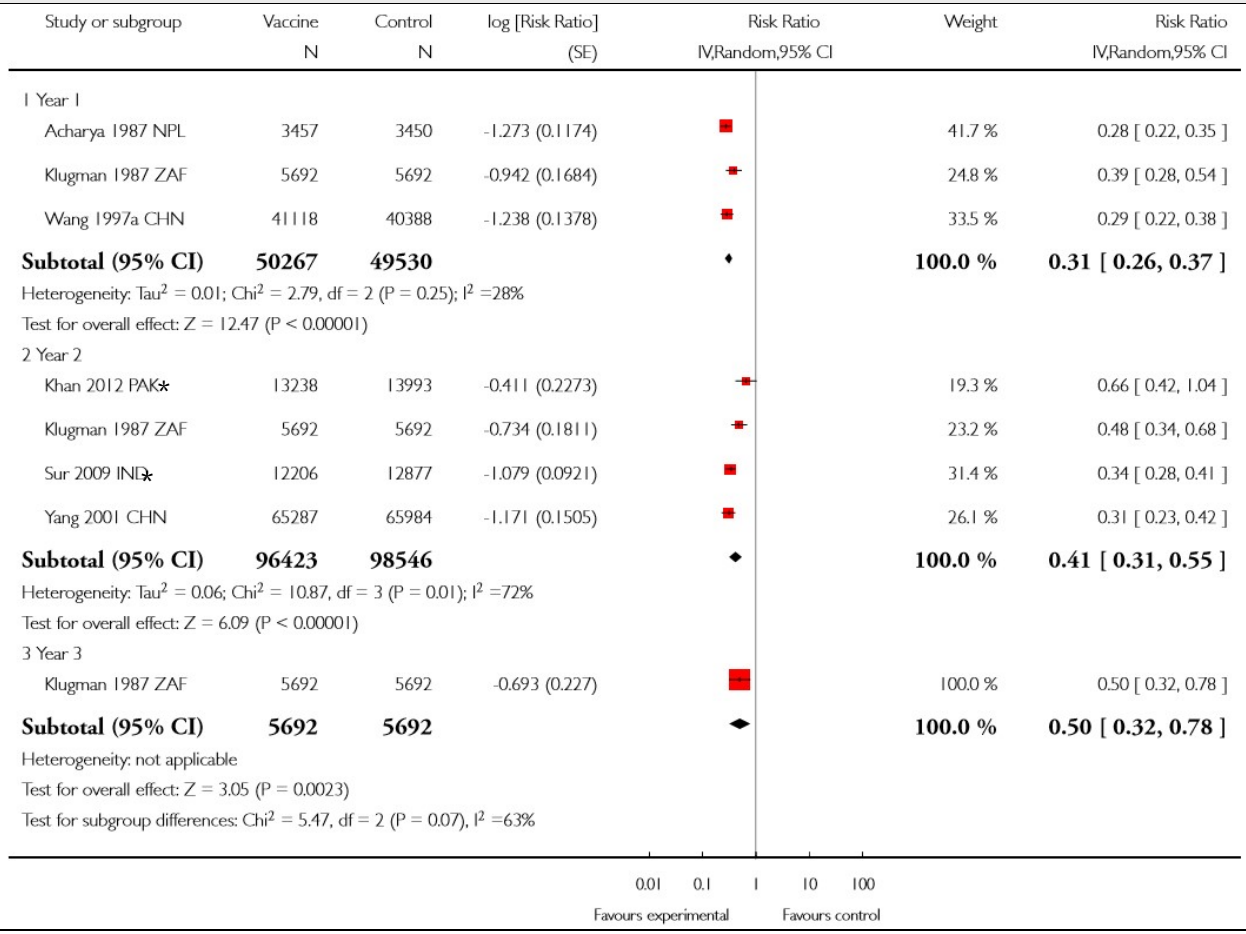
[7] Downgraded by 1 for indirectness: evaluated by only one study in one setting (China).

[8] Non-comparative observational studies start at low certainty evidence.

[a] No SAEs in ViPS group. [b] 13 SAEs were reported for ViPS groups in two studies, none were assessed by trialists to be related to ViPS.(deaths: cardiovascular, diabetes, burns, malaria, poisoning, tuberculosis, and upper gastrointestinal bleeding; hospitalisations: 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) [c] Two SAEs were reported for ViPS group in one study, none were assessed by trialists to be related to ViPS (hospitalisations: 1 pneumothorax and 1 ankle fracture). [d] 24 SAEs were reported for ViPS, one SAE was assessed by trialists to be related to ViPS re-challenge (generalised pruritis and throat tightening), the remaining 23 were assessed by trialists not to be related to ViPS. See Begier 2004 USA in Table A2.1.4 for full details. [e] Six SAEs were reported for ViPS, one SAE was assessed by trialists to possibly be related to ViPS (generalized urticaria with pruritus), the remaining five were assessed by trialists not to be related to ViPS. See Marcus 2007 USA in Table A2.1.4 for full details.

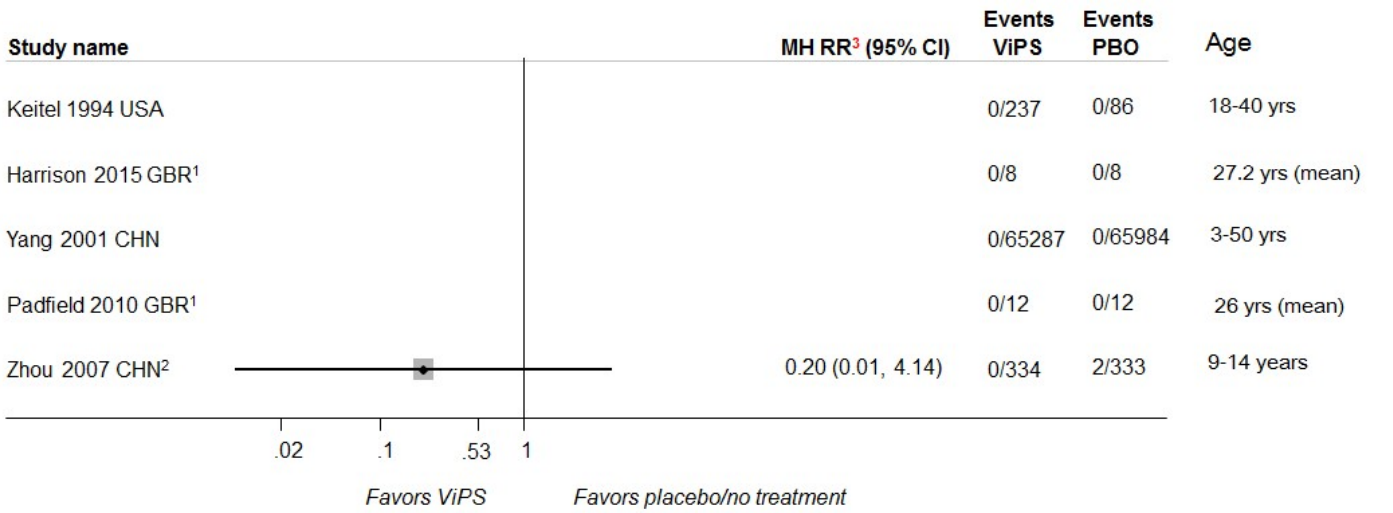
Forest plot 2.1: Typhoid Vi-polysaccharide vaccine versus placebo or control vaccine in children and adults – efficacy outcomes

Patients: **2 to 19 year old children and adolescents, and adults up to 55 years (efficacy) / children (>2 years) and adults (≤82 years) (SAEs)**
***Setting*: Clinic or home setting in China, India, Nepal, Pakistan and South Africa (efficacy) / East- and South east Asia, Europe, Cuba, South Africa, and the USA (SAEs)**
Comparison: **Capsular polysaccharide of *S typhi*, Vi vaccine (single dose intramuscular injection) versus placebo, pneumococcal vaccine, hepatitis A vaccine or meningococcal vaccine (efficacy) / ViPS vaccine versus placebo, control vaccine (meningococcal, hepatitis A), candidate typhoid vaccine (Vi-CRM$_{197}$), or no comparison group (SAEs)**

Outcome	Forest plot	Certainty of the evidence (GRADE)
Incidence of typhoid fever in children and adults follow up: 1, 2, and 3 years		⊕⊕⊕⊕ HIGH ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE

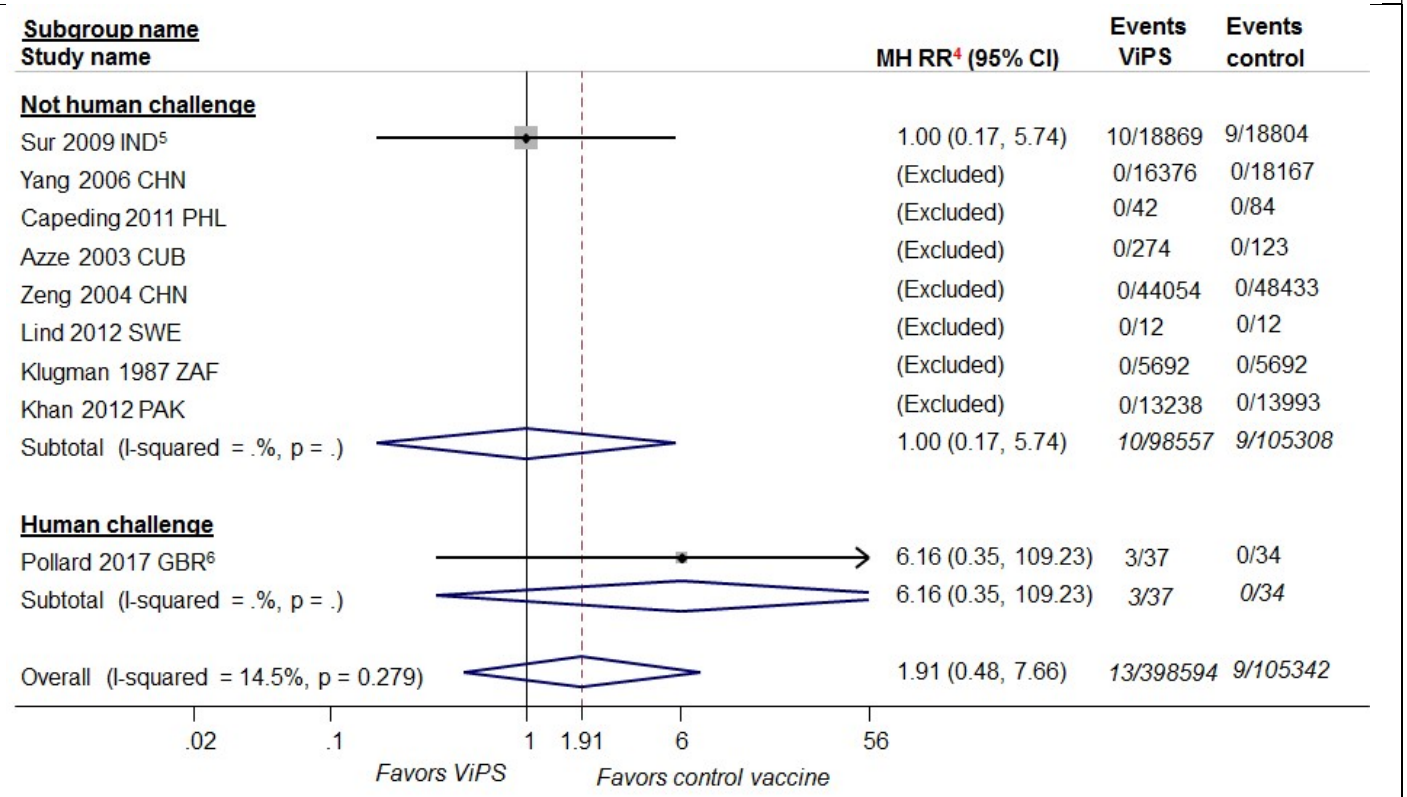
Serious adverse events (compared with placebo/no treatment)

in children and adults
follow-up: up to 1 month

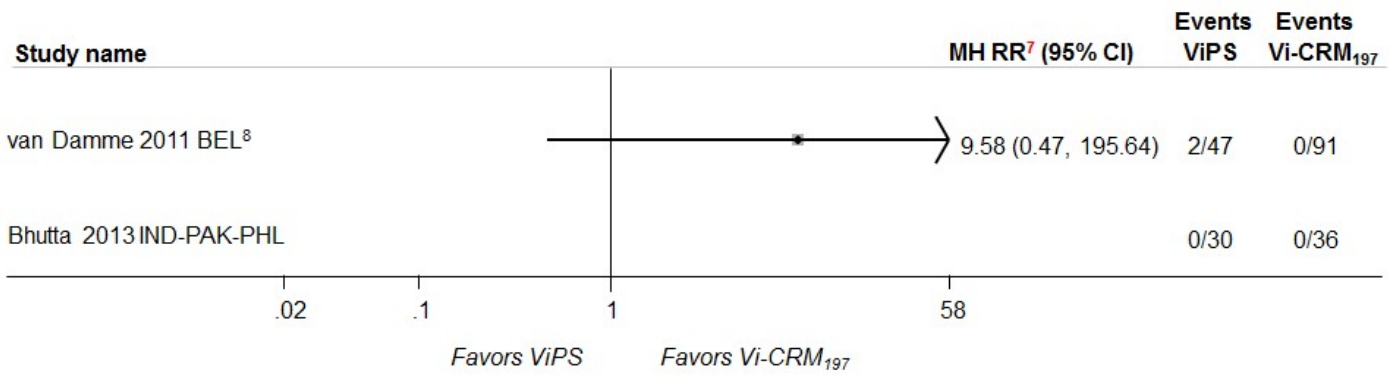


Serious adverse events (compared with control vaccine)

in children and adults
follow-up: up to 1 month



⊕⊕⊕⊕
HIGH

Serious adverse events (compared with candidate typhoid vaccine) in adults follow-up: up to 6 months		

*Cluster trial. Meta-analysis using generic inverse variance method was used to enable pooling adjusted cluster-RCTs with individual-RCTs.

[1]RCT Crossover ViPS versus placebo. ViPS used to elicit inflammatory response in neurophysiological (Harrison 2015) and vascular (Padfield 2010) study.

[2]RCT ViPS booster versus placebo booster, follow-up: 1 month. Two SAEs in placebo arm: 2 hospitalisations – 1 bronchitis, 1 breathing difficulties. Study also included non-randomised parallel arm: primary ViPS vaccination in non-immunised children (n = 331, with no SAEs).

[3]A 0.5 continuity correction was added to all cells of the 2x2 table. Results are the same also when the reciprocal of the opposite treatment arm size was added to all cells of the 2x2 table as a continuity correction.

[4]The reciprocal of the opposite treatment arm size was added to all cells of the 2x2 table as a continuity correction.

[5]Cluster-RCT ViPS versus hepatitis A vaccine in children and adults ≥2 years old, follow-up: 1 month. All 19 SAEs were deaths, none were assessed by trialists to be related to vaccination. (Causes reported as cardiovascular, diabetes, burns, malaria, poisoning, tuberculosis, and upper gastrointestinal bleeding.) ICC equal to 0.01.

[6]Human challenge RCT ViPS versus meningococcal vaccine in adults (18-60 years old), follow-up: 1 week. All 3 SAEs were hospitalisations, none were assessed by trialists to be related to vaccination (Causes reported as 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)

[7]0.5 continuity correction was added to all cells of the 2x2 table

[8]RCT ViPS versus Vi-CRM197 in adults (aged 18-40 years), follow-up: 1 month. Both SAEs were hospitalisations: 1 pneumothorax and 1 ankle fracture.

See Appendix 2.1 for all SAE results.