Summary of Findings 3.1: Typhoid Ty21a vaccine versus placebo or control vaccine in children and adults

Patients: 3 to 44-year old children and adults (efficacy) / 3 to 60-year old children and adults (SAEs)

Setting: Clinic in Indonesia, Chile, Egypt (efficacy) / Chile, Indonesia, Italy, the Netherlands, UK, USA, Zambia (SAEs)

Comparison: Oral Ty21a vaccine (liquid or capsular formulation) versus placebo (3 doses 1 week apart) (efficacy) / Oral Ty21a vaccine (liquid or capsular formulation) (1 to 3 doses) versus placebo, no treatment, control vaccine (Dukoral Rotarix; ACAM2017), typhoid candidate vaccine (Mo1ZH09), or no comparison group (SAEs)

Outcome		Absolut	e effect	Relative effect (95% CI)	Certainty of the evidence (GRADE)	
	Plain language summary	Placebo/control vaccine	Ту21а	Nº of participants & studies		
Incidence of typhoid fever		Moderate risk1				
	3 doses oral Ty21a vaccine compared with placebo probably reduces the incidence of typhoid fever in	4 per 10,000	2.2 per 10,000 (1.4 to 3.4)	RR 0.55 (0.35 to 0.86)	⊕⊕⊕O MODERATE ²	
3 doses in children and adults (3-44 years)	children and adults in the first year after	High risk ¹		76,296 participants in 3 RCTs*		
follow-up: Year 1	vaccination	51 per 10,000	28.1 per 10,000 (17.9 to 43.9)	— KCI3*	due to imprecision	
Incidence of typhoid		Moderate risk1				
Incidence of typhoid fever	3 doses oral Ty21a vaccine compared with placebo probably reduces the incidence of typhoid fever in	4 per 10,000	1.6 per 10,000 (1.2 to 2.3)	RR 0.41 (0.29 to 0.57)	⊕⊕⊕O MODERATE ²	
3 doses in children and adults (3-44 years)	children and adults in the second year after	High risk ¹		76,296 participants in 3 RCTs*		
follow-up: Year 2	vaccination	51 per 10,000	20.9 per 10,000 (14.8 to 29.1)	NC13	due to imprecision	
Incidence of typhoid	3 doses oral Ty21a vaccine compared with placebo probably reduces the incidence of typhoid fever in children and adults in the third year after	Moderate risk1			⊕⊕⊕O MODERATE² due to imprecision	
Incidence of typhoid fever		4 per 10,000	1.8 per 10,000 (1 to 3)	RR 0.44 (0.25 to 0.76) 76,296 participants in 3		
3 doses in children and adults (3-44 years)		High risk ¹		RCTs*		
follow-up: Year 3	vaccination	51 per 10,000	22.4 per 10,000 (12.8 to 38.8)	KC13*		
Cumulative incidence	3 doses oral Ty21a vaccine compared with placebo probably reduces the incidence of typhoid fever in children and adults over 2.5 to 3 years of follow-up	Moderate risk1			⊕⊕⊕O MODERATE ³	
of typhoid fever		4 per 10,000	2 per 10,000 1.6 to 2.6	RR 0.50 (0.39 to 0.65)		
3 doses in children and adults (3-44 years)		High risk ¹		235,239 participants in 4 RCTs*		
follow-up: 2.5 to 3 years	crilidien and addits over 2.5 to 3 years of follow-op	51 per 10,000	25.5 per 10,000 (19.9 to 33)	RCIS"	due to inconsistency	
Serious adverse events (RCTs) 1 to 3 doses in children	Evidence from RCTs: SAEs due to Ty21a are very rare in children and adults. Ty21a results in little or no difference in	o/28,269 (placebo/no treatment)	0/56,165	RR not estimable** 84,434 participants in 5 RCTs	⊕⊕⊕⊕ HIGH	
and adults follow-up: not reported	SAEs compared with placebo or typhoid candidate vaccine in children and adults.	o/76 (control vaccine)	0/111	RR not estimable** 187 participants in 2 trials		

					64
Serious adverse events (NRCS) 3 doses in adults follow-up: not reported	Evidence from non-randomised comparative studies: We are uncertain about the effect of Ty21a vaccine compared with control vaccine (dukoral) on SAEs in adults; certainty of evidence was very low.	0/14	0/13	RR not estimable** 27 participants in 1 NRCS	⊕OOO ^{4,5,6} VERY LOW due to non-randomised comparison, indirectness, and imprecision
Serious adverse events (NCOS) 1 to 3 doses in children and adults follow-up: up to 6 months	Evidence from non-comparative observational studies: SAEs due to Ty21a vaccine may be very rare in children and adults at up to 6 months' follow-up.	 19 SAEs were reported in US national surveillance 1990-2002; a rate of 0.34 per 100,000 doses was detected⁷ In 2 NCOS with 97 participants no SAEs were reported 			⊕⊕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

^{*} Four additional cluster-randomized studies have evaluated efficacy for this vaccine but did not adjust for the effect of clustering and therefore were not included in the meta-analysis, see

Additional table 1 in Anwar et al 2014. Failure to adjust for the potential effect of a cluster design is likely to lead to overestimation of the treatment effect. In addition, results on third year and on overall cumulative incidence of typhoid fever are available in the Cochrane Review.

** Effect could not be estimated because no events were reported.

¹The 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).

²Downgraded by one level for imprecision: Primary trial is not cluster adjusted. This estimate uses a small assumed intra-cluster correlation co-efficient of 0.0015.

³Downgraded by one level for inconsistency: moderate heterogeneity $l^2 = 50$

⁴Non-randomised comparative studies start at moderate certainty evidence.

⁵Downgraded by one level for indirectness: The vaccine has been evaluated in only one trial from one endemic setting (Zambia) in 27 participants.

⁶Downgraded by one level for imprecision: no events reported and very small sample size.

⁷One case of gastroenteritis-like illness and pruritic rash @ 18 days was attributed to Ty21a vaccine, the remaining SAEs were assessed by trialists not to be related to Ty21a vaccine.

⁸Non-comparative observational studies start at low certainty evidence

Forest plot 3.1: Typhoid Ty21a vaccine versus placebo in children and adults – efficacy outcomes

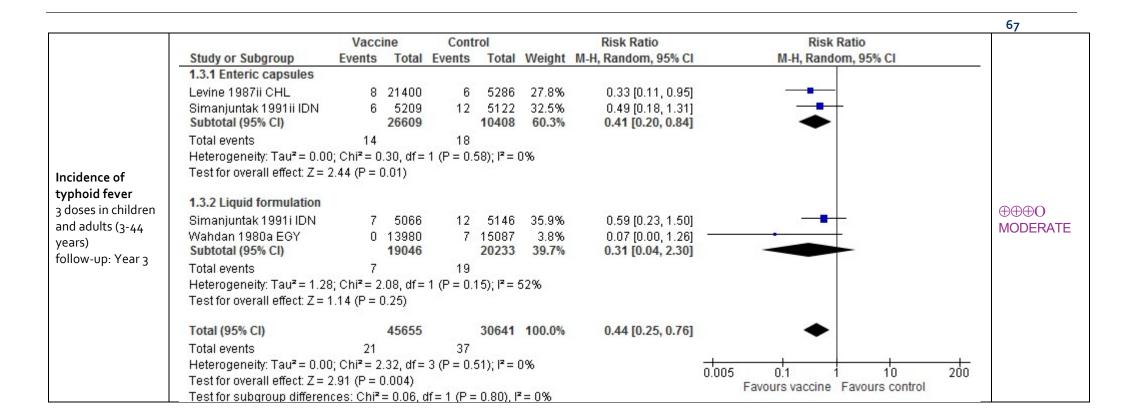
Patients: 3 to 44-year old children and adults

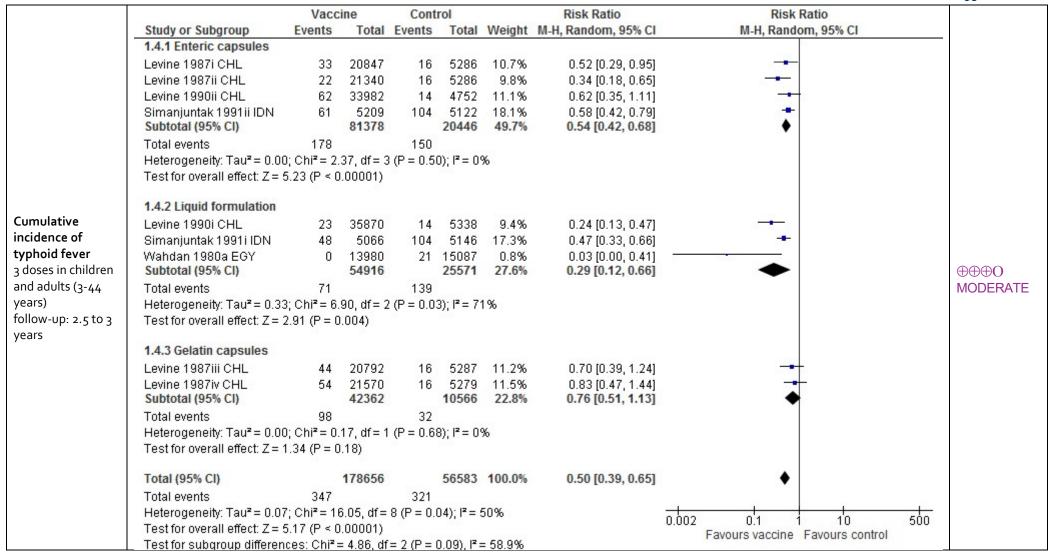
Setting: Clinic in Indonesia

Comparison: Oral Ty21a vaccine (liquid or capsular formulation) versus placebo (3 doses 1 week apart)

Outcome	Forest plot								Certainty of the evidence (GRADE)	
		Vacci	ne	Cont	rol		Risk Ratio	Risk Ratio		
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI		
	1.1.1 Enteric capsules									
	Levine 1987ii CHL	7	21400	6	5286	14.2%	0.29 [0.10, 0.86]			
	Simanjuntak 1991ii IDN Subtotal (95% CI)	30	5209 26609	41	5122 10408	42.9% 57.2 %				
	Total events	37		47						
	Heterogeneity: Tau ² = 0.24	4; Chi ² = 2.	29, df=	1 (P = 0.1)	$(3); I^2 = 5$	56%				
Incidence of	Test for overall effect: Z =	1.48 (P = 0)	1.14)							
typhoid fever										
with 3 doses in	1.1.2 Liquid formulation								$\oplus \oplus \oplus O$	
children and adults	Wahdan 1980a EGY	0	13980	7	15087	2.4%	0.07 [0.00, 1.26]		MODERATE	
(3-44 years)	Simanjuntak 1991i IDN	24	5066	42		40.4%	0.58 [0.35, 0.96]		MODEIVATE	
follow-up: Year 1	Subtotal (95% CI)		19046		20233	42.8%	0.33 [0.05, 2.12]			
	Total events	24		49						
	Heterogeneity: Tau ² = 1.18; Chi ² = 2.08, df = 1 (P = 0.15); I ² = 52%									
	Test for overall effect: Z=	1.17 (P = 0	1.24)							
	Total (95% CI)		45655		30641	100.0%	0.55 [0.35, 0.86]	•		
	Total events	61		96						
	Heterogeneity: Tau ² = 0.01	200								
	Test for overall effect: Z =			161	2008			0.005 0.1 1 10 2 Favours vaccine Favours control	:00	
	Test for subgroup differen		20000000	If = 1 (P =	ravours vaccine ravours control					

		Vaccine	е	Cont	rol		Risk Ratio	Risk Ratio			
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	_		
	1.2.1 Enteric capsules										
	Levine 1987ii CHL	8 2	1400	5	5286	9.3%	0.40 [0.13, 1.21]				
	Simanjuntak 1991ii IDN		5209	50	5122	50.6%	0.49 [0.30, 0.79]	+			
	Subtotal (95% CI)		26609		10408	59.9%	0.48 [0.31, 0.74]	•			
	Total events	33		55							
	Heterogeneity: Tau² = 0.00			1 (P = 0.7)	72); $I^2 = 0$	0%					
Incidence of	Test for overall effect: $Z = 3$	3.31 (P = 0.0	0009)								
typhoid fever	4.2.2.Limid formulation										
with 3 doses in	1.2.2 Liquid formulation	1000		2020	020002	1404100	10101110111 315011	_	$\oplus \oplus \oplus O$		
children and adults	Simanjuntak 1991i IDN		5066	51	5146	38.7%	0.34 [0.20, 0.59]		MODERATE		
(3-44 years)	Wahdan 1980a EGY	- / 3	3980 9046	8	15087 20233	1.4% 40.1%	0.06 [0.00, 1.10]				
follow-up: Year 2	Subtotal (95% CI)	17	9040	59	20233	40.170	0.26 [0.08, 0.87]				
	Total events		2 df=) EN: 13 — 1	250					
	Heterogeneity: Tau² = 0.36; Chi² = 1.32, df = 1 (P = 0.25); l² = 25% Test for overall effect: Z = 2.19 (P = 0.03)										
	restroi overali ellect. Z = 2	2.13 (1 - 0.0	33)								
	Total (95% CI)	4	5655		30641	100.0%	0.41 [0.29, 0.57]	•			
	Total events	50		114							
	Heterogeneity: Tau ² = 0.00); Chi ² = 2.7	2. df=	9232211 10121	(44) ; $ ^2 = 0$		-1tt				
	Test for overall effect: Z = 5	[20] [12] [13] [14] [15] [15] [15] [15] [15] [15] [15] [15						0.005 0.1 1 10 200			
	Test for subgroup differences: $Chi^2 = 0.83$, $df = 1$ (P = 0.36), $I^2 = 0\%$							Favours vaccine Favours control			





See Appendix 3.1 for SAE results.