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 (M01ZH09), or no comparison group (SAEs)**

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

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 detected[7] • In 2 NCOS with 97 participants no SAEs were reported			⊕⊕OO[8] LOW due to observational study design

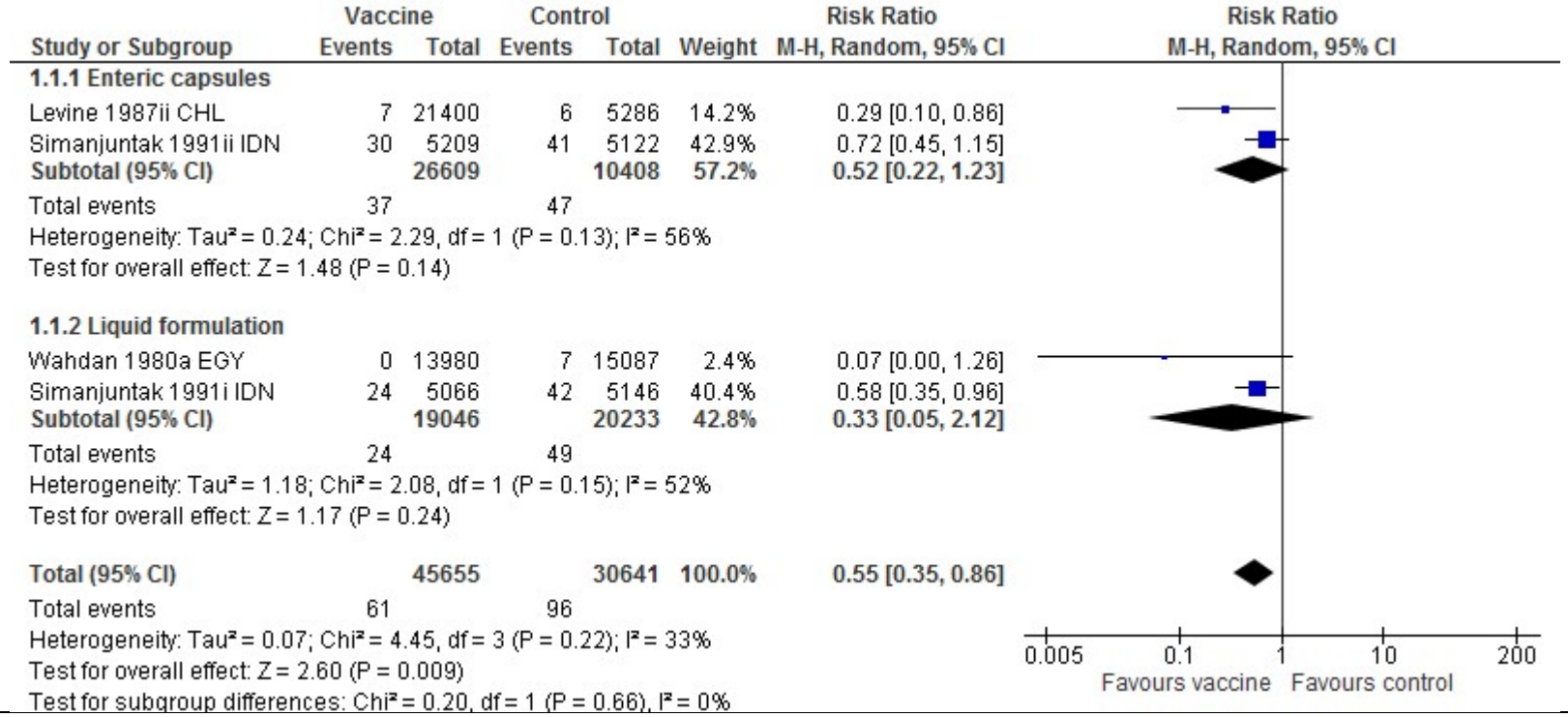
CI= confidence interval; NRCS= non-randomised comparative study; NCOS= non-comparative observational study; RCT= randomised controlled trial; RR= risk ratio

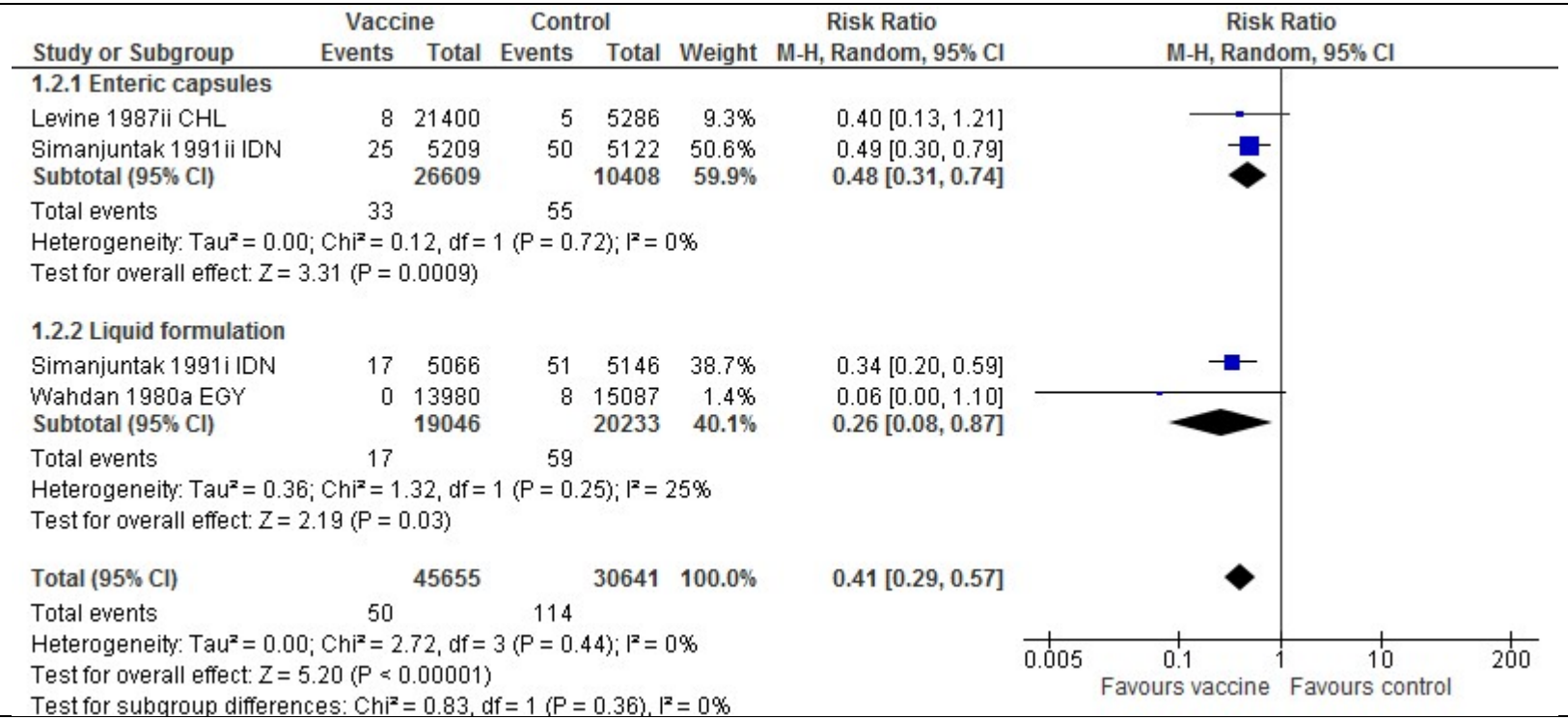
* Four additional cluster-randomized studies have evaluated efficacy for this vaccine but did not adjust for the effect of clustering and therefore were not included in the meta-analysis, see Additional table 1 in Anwar et al 2014. Failure to adjust for the potential effect of a cluster design is likely 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.

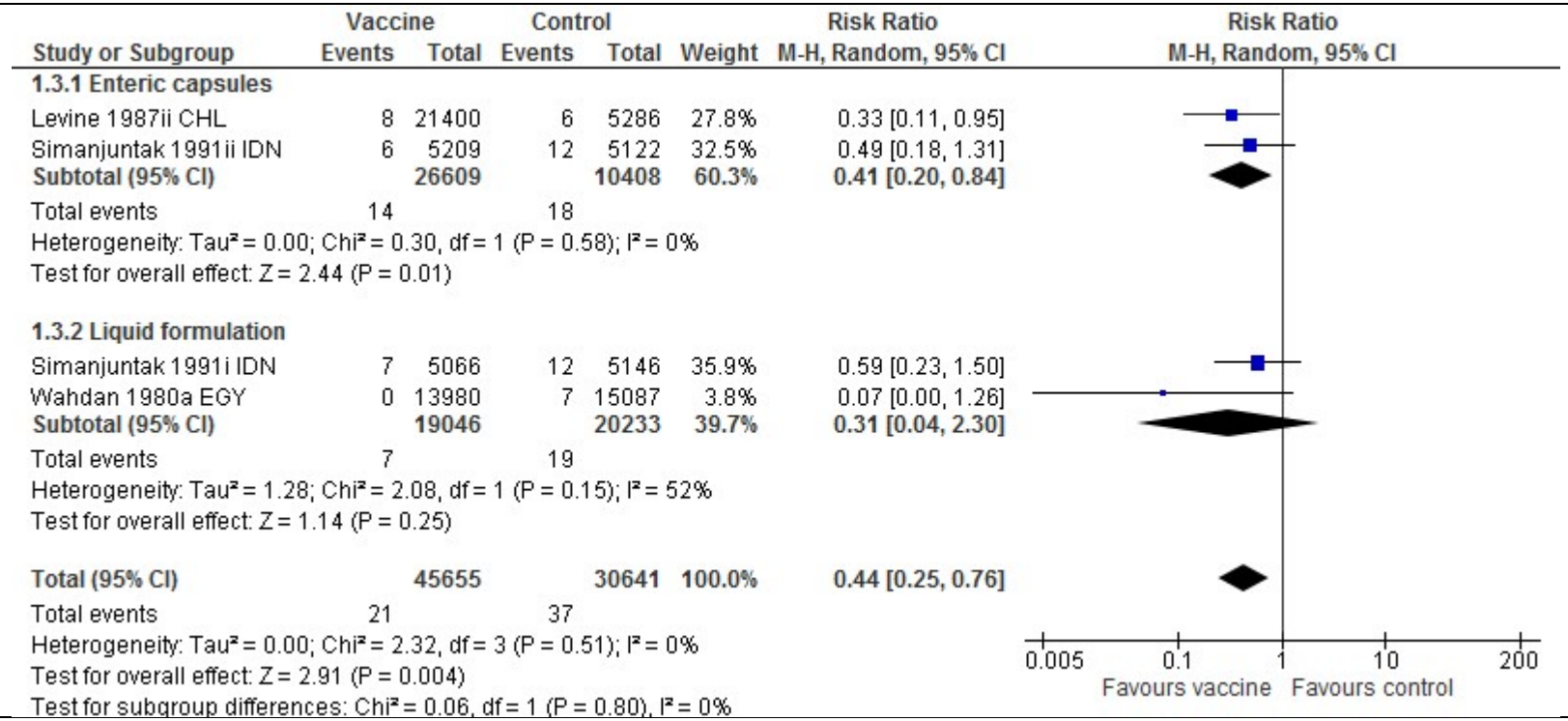
[1] The incidence of typhoid in a medium-risk setting is taken from the control group in a study from China (Yang 2001 CHN). The incidence of typhoid in a high-risk setting is taken from a study in India (Sur 2009 IND). This is consistent with the incidence levels described by a global epidemiological study (Crump 2004).
[2] Downgraded by one level for imprecision: Primary trial is not cluster adjusted. This estimate uses a small assumed intra-cluster correlation co-efficient of 0.0015.
[3] Downgraded by one level for inconsistency: moderate heterogeneity $I^2 = 50$
[4] Non-randomised comparative studies start at moderate certainty evidence.
[5] Downgraded by one level for indirectness: The vaccine has been evaluated in only one trial from one endemic setting (Zambia) in 27 participants.
[6] Downgraded by one level for imprecision: no events reported and very small sample size.
[7] One 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.
[8] Non-comparative observational studies start at low certainty evidence

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

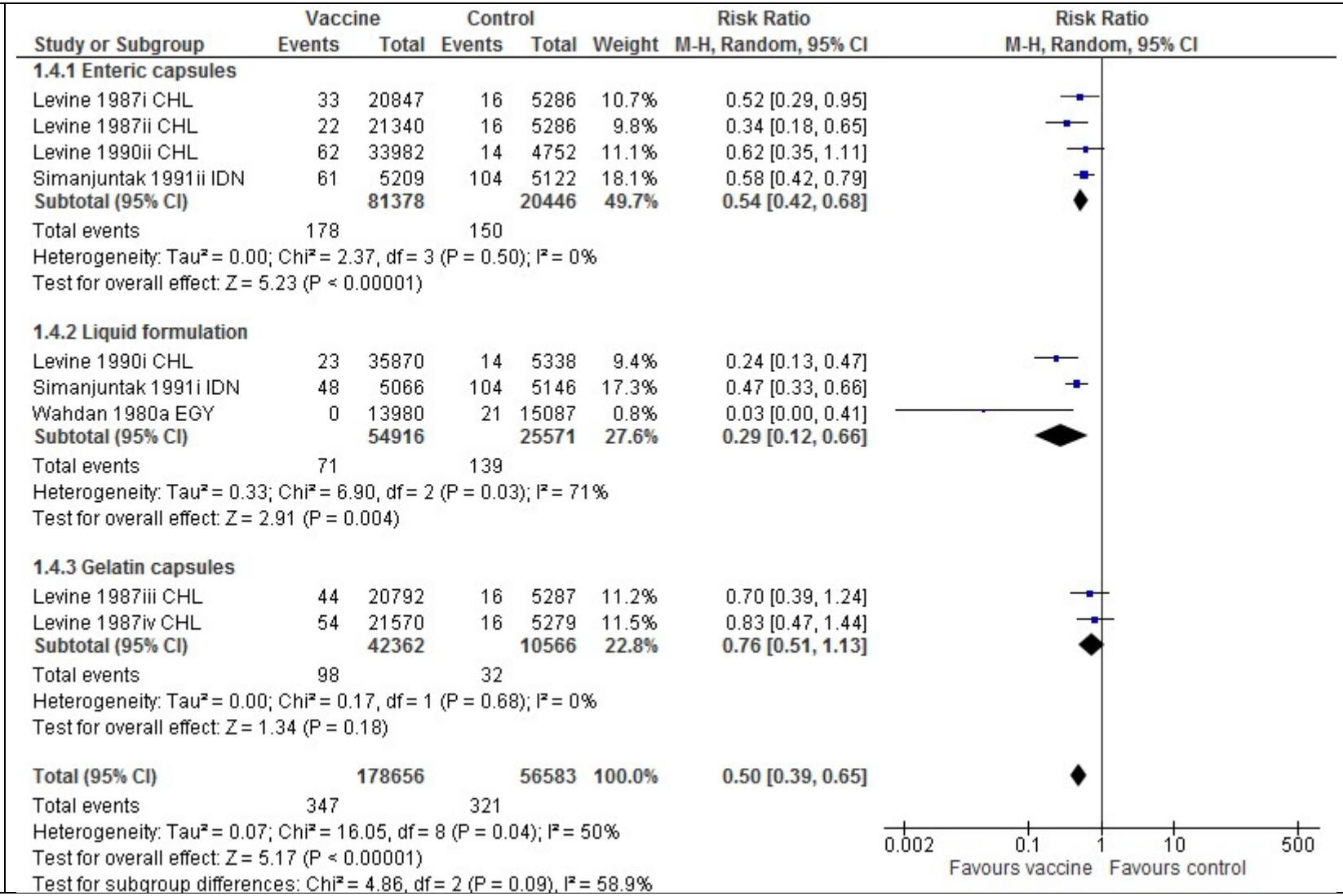
Patients: **3 to 44-year old children and adults**
***Setting*: Clinic in Indonesia**
Comparison: **Oral Ty21a vaccine (liquid or capsular formulation) versus placebo (3 doses 1 week apart)**

Outcome	Forest plot	Certainty of the evidence (GRADE)
Incidence of typhoid fever with 3 doses in children and adults (3-44 years) follow-up: Year 1		⊕⊕⊕O MODERATE

Incidence of typhoid fever with 3 doses in children and adults (3-44 years) follow-up: Year 2		⊕⊕⊕O MODERATE

Incidence of typhoid fever 3 doses in children and adults (3-44 years) follow-up: Year 3		⊕⊕⊕O MODERATE

Cumulative incidence of typhoid fever
3 doses in children and adults (3-44 years)
follow-up: 2.5 to 3 years



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MODERATE

See Appendix 3.1 for SAE results.