GRADE TABLE 1b: What is the efficacy of 3 doses of CYD-TDV in preventing clinical dengue in **seronegative** individuals 9-16 years of age in the first year following vaccination?

Population: 9-16 year-olds living in dengue endemic areas **seronegative** at vaccination
Intervention: 3 doses of CYD-TDV administered 6 months apart
Comparison: Placebo
Outcome: Virologically-confirmed dengue occurring < 25 months of completion of the first dose (13 months post dose 3)

What is the efficacy of 3 doses of CYD-TDV in preventing clinical dengue in **seronegative** individuals 9-16 years of age in the 25 months following the first vaccination?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	None serious[2]	0
		Inconsistency	None serious	0
		Indirectness	None serious[3]	0
		Imprecision	None serious[4]	-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 quality of evidence			3
Summary of Findings	Statement on quality of evidence			Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of effect on health outcome.
	Conclusion			CYD-TDV demonstrates consistently positive (>0) point estimates of vaccine efficacy against virologically-confirmed dengue in the first 25 months after the first vaccination among trial participants 9-16 years of age who were **seronegative** at the time of vaccination.

[1] CYD-TDV has been evaluated in two parallel Phase 3 clinical trials, known as CYD14 and CYD15. CYD14 was conducted in 5 countries in Asia (Indonesia, Malaysia, Philippines, Thailand, and Vietnam), with 5,234 participants

aged 9-14 years at first vaccination (10,275 participants in the full trial population aged 2-14 years). CYD15 was conducted in 5 countries in Latin America (Brazil, Colombia, Honduras, Mexico, and Puerto Rico (US)), with 20,869 participants aged 9-16 years at first vaccination. In each of these trials, participants were randomized to vaccine and placebo in a 2:1 ratio. Because the physical appearance of the vaccine and placebo was different, unmasked trial staff were responsible only for preparation and administration of injections and were not involved in the follow-up of trial participants. For the ascertainment of trial endpoints the trials were observer-masked. All serology testing was also performed in a blinded manner. Based on the immune subset, vaccine efficacy amongst seronegatives was 35.5% (95%CI -27.0-66.6) in CYD14, 43.2% (95%CI -61.6-80.0) in CYD15, 38.1% (95%CI -3.4-62.9) in the two trials pooled, and 52.5% (95%CI 5.9-76.1) in the two trials pooled with the age limited to 9-16 years. There were few seronegatives in the immune subset, making it hard to estimate vaccine efficacy with precision. The confidence is downgraded in the category of imprecision, although it does reflect a flaw in the study design.

Data based on the new analysis provides variable point estimates for seronegatives. In 9-16 year-olds, vaccine efficacy is estimated at 39% (95%CI -1-63) using the multiple imputation method, 45% (95%CI 26-58) using the TMLE method, and 18% (95%CI -18-43) using the NS1 method.

[2] The methods used for re-analysis of the Phase 3 trial data are based on assays and statistical methods that are associated with misclassification of serostatus at baseline, which vary by assay. The false-negative rate (misclassifying seropositives as seronegatives) is low, and for this analysis there is to be limited bias due to misclassification.

[3]Based on the best assay for serostatus in the immune subset, the confidence intervals are very wide. All cross zero except when the analysis is limited to 9-16 year-olds. The imprecision remains for most new analyses, wit the lower bound of the 95%CI crossing 0 for the multiple imputation method and NS1 method.

[4] Vaccine efficacy has been assessed only the 9-16 year population within the indicated age range of 9-45 or 9-60 years. SAGE recommendations focus on the 9-16 year-old population, which is more relevant for high endemicity settings. Licensure has been granted by regulatory authorities in the 17+ population based on immunological bridging, although there is no accepted correlate of protection. The confidence in the estimate of effect for the 17-45 **seronegative** population would be downgraded by 1 for indirectness.