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

Population: 9-16 year-olds living in dengue endemic areas **seropositive** 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 **seropositive** individuals 9-16 years of age in the 25 months following the first vaccination?				
			Rating	Adjustment to rating
Quity	No. of studies/starting rating		2 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious[2]	0
		Indirectness	None serious[3]	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[4]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			4
Summary of Findings	Statement on quality of evidence			Evidence supports a high level of confidence that the true effect lies close to that of the estimate of effect on health outcome.
	Conclusion			CYD-TDV demonstrates statistically significant 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 **seropositive** 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 seropositives was 74.3% (95%CI 53.2-86.3) in CYD14, 83.7% (95%CI 62.2-93.7) in CYD15, 78.2% (65.4-86.3%) in the two trials pooled, and 81% (95%CI 67.2-90.0) in the two trials pooled with the age limited to 9-16 years. Data based on the new analysis affirms high vaccine efficacy in seropositives with point estimates ranging from 71-75%, depending on the method, and tight confidence intervals.

[2] With the new analyses, there is an indication of variability by age, depending on the analysis. At the extreme, vaccine efficacy in seropositives aged 9-16 years based on the multiple imputations analysis was 76% (95%CI 64-84), while seropositives aged 2-8 years it was 57% (95% CI 38-70). For other analyses, the difference in estimates by age was less pronounced. Because the vaccine is not currently licensed in the 2-8 year-old population, the confidence is not downgraded.

[3] 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 younger 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 **seropositive** population may be downgraded by 1 for indirectness.

[4]A large effect is noted (VE point estimate of 74.3%-83.7%, depending on the analysis) although currently the score is not eligible for upgrade at the maximum score.