GRADE TABLE 3a: What is the risk of other serious adverse events (non-dengue) in **seropositive** individuals 9-16 years of age vaccinated with CYD-TDV?

Population: 9-16 year-old **seropositive** individuals living in dengue endemic areas
Intervention: 3 doses of CYD-TDV administered 6 months apart
Comparison: Placebo
Outcome: Serious adverse events (non-dengue)

What is the risk of other serious adverse events (non-dengue) in **seropositive** individuals 9-16 years of age vaccinated with CYD-TDV?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious[2]	0
		Imprecision	Serious[3]	-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			There is no evidence of an association between CYD-TDV and non-dengue serious adverse events in seropositive participants based on clinical trials.

[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 the Phase 3 trials conducted in 2-16 year-olds, the proportion of participants with serious adverse events (SAEs) and fatal AEs was similar between seropositive participants in the CYD and placebo group based on the immune subset. In CYD14, the proportion with an SAE was 11.7% and 10.1% in the CYD and placebo groups, respectively, and the proportion with a fatal SAE was 0% in both groups. In CYD15,

the proportion with an SAE was 11.4% and 12.9% in the CYD and placebo groups, respectively, and the proportion with a fatal SAE was 0.5% and 0.6% in the CYD and placebo groups, respectively.

[2]There are a limited number of trial participants beyond 16 years of age to assess the risk of serious adverse events in the 17-45 year population. For consideration of the risk of SAEs in the 17-45 year-old population based on extrapolation from the Phase 3 trials, the quality of the evidence would need to be further downgraded by 1 for indirectness.

[3]Even large Phase 3 clinical trials are limited in their ability to detect rare SAEs. The GRADE score was thus downgraded by 1 for imprecision.