GRADE TABLE 2b: What is the **duration of protection/risk** in **seronegative** individuals 9-16 years of age vaccinated with CYD-TDV?

Population: 9-16 year-old **seronegative** individuals living in dengue endemic areas
Intervention: 3 doses of CYD-TDV administered 6 months apart
Comparison: Placebo
Outcome: Virologically-confirmed dengue occurring > 12 months of completion of 3 doses

What is the duration of protection/risk in **negative** 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	Very serious[2]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		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 is associated with an increase in severe and hospitalized dengue in seronegative participants 9-16 years

[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. Active surveillance of participants lasted only until study month 25, after which surveillance was hospital-based. Thus, it is

not possible to evaluate the duration of protection against virologically-confirmed dengue of any severity. However, since severe outcomes are also of interest and importance from a public health perspective, the confidence is not downgraded.

Based on participants with serostatus derived from the new analyses, in seronegative participants aged 9-16, The HRs for hospitalized VCD and severe VCD in seronegative participants were 1.41 (95%CI: 0.74;2.68, p=0.29) and 2.44 (95%CI: 0.47;12.56, p=0.28), respectively, with point estimates >1 for all methods in pooled analyses. The effect suggested the effect could vary by age, although the confidence intervals for each estimate were wide and overlapped. The HR against hospitalized VCD amongst seronegative 9-16 year-olds was 0.836 (95%CI 0.227-3.081) during the active phase of study years 1 and 2, 2.892 (95%CI 0.679-12.315) during study year 3, 1.789 (95%CI 0.667-4.798) during study year 4, and 1.428 (95%CI 0.45-4.528) during study year 5 and beyond. Thus, the trend in the point estimate for HR in this age group is declining with time, although the confidence intervals all overlap.

[2]The study design of CYD14 and CYD15 included 25 months of active surveillance followed by hospital-based surveillance. Thus, duration of protection against VCD cannot be assessed. However, active surveillance is currently being reinstated. Data on hospitalized dengue has been collected throughout the trial period, though with different surveillance systems in the Active and Hospital Phases. With the limitations of this change in surveillance and that the CYD and placebo groups have different histories of dengue exposure at the start of later time intervals, it is one source of data available now to assess protection over the period of the trial.

The NS1 method 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. The false-negative rate (misclassifying serpositives as seronegatives) is low (4.7%), and would have limited effect in the interpretation of the data.