**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)

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<td>2 RCT&lt;sup&gt;1&lt;/sup&gt;</td>
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**Factors decreasing confidence**
- Limitation in study design: None serious<sup>2</sup>, 0
- Inconsistency: None serious, 0
- Indirectness: None serious<sup>3</sup>, 0
- Imprecision: None serious<sup>4</sup>, -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

**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.

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<sup>1</sup> 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.

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.

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, with the lower bound of the 95%CI crossing 0 for the multiple imputation method and NS1 method.

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.