GRADE TABLE 3b: What is the risk of other serious adverse events (non-dengue) 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: Serious adverse events (non-dengue)

<table>
<thead>
<tr>
<th>Rating</th>
<th>Adjustment to rating</th>
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<tbody>
<tr>
<td>2 RCT</td>
<td>4</td>
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</tbody>
</table>

Factors decreasing confidence
- Limitation in study design: None serious 0
- Inconsistency: None serious 0
- Indirectness: None serious 2
- Imprecision: Serious 3
- 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.

Summary of Findings
Conclusion: There is no evidence of an association between CYD-TDV and non-dengue serious adverse events in seronegative 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 seronegative participants in the CYD and placebo group based on the immune subset. In CYD14, the proportion with an SAE was 11.5% and 14% 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 11.2% and 10.7% in the CYD and placebo groups, respectively, and the proportion with a fatal SAE was 0% in both groups.

²There 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.

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