**Introduction**

The tetravalent dengue vaccine CYD-TDV (Dengvaxia®) is indicated for use in children aged 9 to 16 years and adults aged 16 years onwards for prevention of dengue infection, based on findings from two pivotal Phase III trials.*

*TDV was found to provide better seroprotection against confirmed dengue and severe dengue in subjects with prior dengue infection, whereas standard monovalent dengue vaccine (SDV) was associated with increased risk of dengue infection in seronegative participants following natural dengue exposure. 

With recommendations for vaccine reversion to identify those with SDV who could have offered protection,** Several randomized placebo-controlled, rapid-diagnostic tests (RDT) and IgG enzyme-linked immunosorbent assays (ELISA) were shown to be highly specific, while IgMs exhibited higher sensitivity than the RDTs in identifying prior dengue infection.

In this study, leveraging existing CYD-TDV Phase III data, we evaluated:

- Effectiveness of a test vaccine approach against symptomatic and hospitalised dengue disease, using multivariate analysis.
- Performance of existing serological tests in settings consistent with areas where CYD-TDV is licensed.

**Objectives**

**Primary objectives:**

- Assess vaccine efficacy (VE) for symptomatic virologically confirmed dengue (VCD) regardless of severity and viraemia in all test(-) subjects 2-16 years of age during Active Phase follow-up (Month 0 to Month 24).
- Assess VE against hospitalised VCD regardless of viraemia in all test(-) subjects 2-16 years of age over the entire 6 years of follow-up (0 to 72 months).
- Determine sensitivity, specificity of each assay in all subjects (14-16 age) 

**Sensitivity analyses included the following outcomes:**

- VE for symptomatic VCD (0-72 vs 0-25) – subjects by age strata. 
- VE for hospitalised VCD (0-72 vs 0-25) – subjects by age strata. 
- VE against severe VCD (0-72 vs 0-25) – virologically confirmed dengue.

**Methods**

*Study Design and Participants*

- **TDV Phase III trials:** Two randomised, placebo-controlled studies conducted in Latin American countries in 2,416-2,474 children (TDV+4) and 3,024-3,031 children (TDV-4) aged 2 years and 4 years, respectively.
- **The present analyses** were performed in the immunogenicity subsets, comprising a total of 3,381 seronegative subjects 2-16 years old from either study (TDV+4 and TDV-4) who had pre-dengue blood samples collected and analyzed (laboratory subset).

**Effectiveness Outcomes**

Efficacy analyses considered subjects randomized to receive CYD-TDV vs placebo group using pooled data from the immunogenicity subsets of CYD+4 and CYD-4.

- **VE:** defined as 1 (1 - Hazard Ratio (HR)), 95% c.i. were tested in test(-) subjects using a Cox regression model, using treatment group and study as fixed effects, with corresponding 95% confidence intervals calculated by the worst binomial method (Clopper-Pearson method).

**Results**

**Table 1. Characteristics of dengue-immunogenic used in this study.**

<table>
<thead>
<tr>
<th>Dengue-immunogenic</th>
<th>Dengvaxia 90% CI</th>
<th>Dengvaxia 95% CI</th>
</tr>
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<tbody>
<tr>
<td>Positive</td>
<td>0.0002 (0.0001, 0.0003)</td>
<td>0.0002 (0.0001, 0.0003)</td>
</tr>
<tr>
<td>Negative</td>
<td>0.9998 (0.9999, 1.0000)</td>
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**Table 2. Algorithms for classification of reference dengue seroconversion.**

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**Figure 1. CYD-TDV efficacy against symptomatic VCD up to 6 years in test(-) subjects 2-16 years of age.**

**Table 3. VE against symptomatic VCD in test(-) subjects by different age strata.**

<table>
<thead>
<tr>
<th>Age group</th>
<th>VE (90% CI)</th>
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<td>2-6 yrs</td>
<td>87.6 (76.7, 93.4)</td>
<td>88.3 (77.2, 92.4)</td>
</tr>
<tr>
<td>7-16 yrs</td>
<td>90.6 (85.4, 93.5)</td>
<td>91.9 (86.8, 94.6)</td>
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**Figure 2. CYD-TDV efficacy against hospitalised VCD up to 6 years in test(-) subjects 2-16 years of age.**

**Table 4. VE against hospitalized VCD in test(-) subjects by different age strata.**

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**Figure 3. Immune response sensitivity and specificity in all subjects 2-16 years of age.**

**Figure 4. CYD-TDV efficacy against hospitalised VCD up to 6 years in test(-) subjects 2-16 years of age.**

**Conclusions**

- The rate of severe VCD events in test(-) subjects with all assays (immunoassays) and virological tests was not evaluable, since CYD-TDV prevented most symptomatic outcomes.

- The impact of Zika exposure on test performance was not evaluable, since CYD-TDV was found to prevent most symptomatic outcomes.

**Limitations**

- **VE** for severe VCD was lower than for symptomatic disease.

- **Sensitivity of the ELISAs** was significantly higher than that for the RDTs, as a result, the lower bound of 95% CI was above the null for all but one test (OnSite IgG/IgM).

**References**