# STATEMENT ON THE USE OF THE DENGUE VACCINE

Committee on Immunization
Pediatric Infectious Disease Society of the Philippines
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Dengue continues to be a leading cause of morbidity in the Philippines. The disease ranks ninth among the ten leading cause of morbidity (FHSIS 2013), with the majority of cases being reported in the 5-14 years age group (PIDSR 2014). A national dengue seroprevalence data is unavailable, except in two areas (Guadalupe, Cebu and San Pablo, Laguna), which showed 58% of children aged 2-4 years old, 75% of children aged 5-8 years, 89% of children aged 9-12 years old and 93% of children aged 13-14 years old, to be seropositive.[1]

There is no specific cure for the disease, thus efforts have been focused on early detection, optimal management and prevention through vector control. The development of vaccines against dengue has long been a priority because these interventions have been met with limited success.

A tetravalent live attenuated dengue vaccine manufactured by Sanofi Pasteur was licensed by the Philippine FDA last December 2015. The Department of Health then planned a program to vaccinate 9 year-old children enrolled in public schools in selected regions which reported the highest number of dengue cases (Regions III, IVA and NCR). The PIDSP interim recommendation was subsequently released on February 2016, to guide private practitioners on the use of the vaccine.

The PIDSP Committee on Immunization has reviewed available evidence on vaccine safety and efficacy (Sabchareon Lancet 2012, Capeding Lancet 2014, Villar NEJM 2015, Hadinegoro NEJM 2015). Based on this review, the committee has concluded the following:

1. The live attenuated tetravalent dengue vaccine appears to be safe for use in the pediatric age groups recommended (≥9 years).
2. Current evidence suggests that the vaccine provides better protection for older children ≥ 9 years, and for those who were already exposed and are positive for dengue antibodies.
3. Children below 9 years should not receive the vaccine because of safety signals of increased risk of hospitalization for dengue and for developing severe dengue. The risk for developing dengue following dengue vaccination is particularly greater in those 2 to 5 years old.
4. Vaccine efficacy against hospitalization for confirmed dengue more than 25 months after the last dose was 68% (58-76%) in those aged ≥ 9 years old and 44% ( 32-55% ) in those aged < 9 years old.[4]
5. Using data from the Capeding study (CYD14), vaccine efficacy against confirmed dengue in children aged 2 to 14 years old during the 25 month follow-up period for those who received 3 doses of the vaccine is 53%( 45-60% ) against symptomatic dengue and 67% (52-78% ) against hospitalized dengue ( Appendix 2: Tables 2-3).

The above conclusions are consistent with those of the WHO Strategic Advisory Group of Experts dated April 2016.

The Committee on Immunization hereby recommends the following:

1. The vaccine should be administered to children ≥ 9 years old as a Three-dose series given subcutaneously, following a 0-6-12 month schedule.
2. Children below 9 years should not receive the vaccine.
3. The vaccine should not be given at the same time as other vaccine because data on concomitant administration with other vaccines is not available at this time.
4. The need for booster doses is not well defined at this time.

As part of a public health program, the Committee on Immunization suggests the following:

1. Enhance the surveillance system that integrates epidemiological, entomological, environmental , clinical and laboratory data to include seroprevalence data.
2. Disseminate information, education and communication materials on dengue vaccination for healthcare workers and the public.
3. Provide enhanced training for healthcare workers on administering the vaccine, including cold chain management, the informed consent process as well as surveillance for Adverse Events Following Immunization (AEFIs).
4. Emphasize the importance of coordinated strategies for dengue control, including vector control, adequate case management, and community programs to prevent transmission of dengue virus.
5. Conduct a cost effectiveness study, utilizing local prevalence rates, facility utilization rates, and social costs, in order to justify and prioritize a long term dengue vaccination program.

**References:**

(1) L'Azou M. et al. Symptomatic Dengue in Children in 10 Asian and Latin American Countries. New England Journal Of Medicine 374; 12 March 24, 2016. pp 1155-1166.

(2) Capeding MR, Tran NH, Hadinegoro SRS, Ismail HI, et al. Clinical efficacy and safety of a novel 2 tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo controlled trial Lancet 2014; 384: 1358–65.

(3) Sabchareon A, Wallace D, Sirivichayakul C, Limkittikul K, Pornthep Chanthavanich, et. al. Protective 1 efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. Lancet 2012; 380: 1559–67.

(4) Villar L, Dayan GH, Arredondo-García JL, Rivera DL, Cunha R, et. al. Efficacy of a Tetravalent Dengue 3 Vaccine in Children in Latin America. N Engl J Med 2015;372:113-23.

(5) Hadinegoro, SR, Arredondo-García JL, Capeding MR, Deseda C, Chotpitayasunondh T, et. al. Efficacy 4 and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease. N Engl J Med 2015: 1-12.

(6) Summary of the April 2016 meeting of the Strategic Advisory Group of Experts on Immunization (SAGE) http://www.who.int/immunization/sage/en/index.html

## APPENDIX 1

### Definition of Severe Virologically-Confirmed Dengue and Dengue Hemorrhagic Fever

The Independent Data Monitoring Committee classified dengue cases as severe using the following criteria: virologically-confirmed dengue fever, i.e. temperature ≥38°C on ≥2 consecutive days and virological confirmation, and at least one of the following:

1. Platelet count ≤100x109/L *and* bleeding (tourniquet, petechiae or any bleeding) *and* plasma leakage (effusion on chest X-ray or clinically apparent ascites including imaging procedures or hematocrit >20% above baseline recovery level or standard for age if only one reading).
2. Shock (pulse pressure ≤20 mmHg in a child or adolescent, or hypotension [≤ 90 mmHg] with tachycardia, weak pulse and poor perfusion).
3. Bleeding requiring blood transfusion
4. Encephalopathy i.e., unconsciousness or poor conscious state (Glasgow Coma Scale (GCS) score) or convulsions not attributable to simple febrile convulsion or focal neurological signs.
5. Liver impairment (AST >1000 U/L or prothrombin time, international normalized ratio >1.5)
6. Impaired kidney function (serum creatinine ≥1.5 mg/dL)
7. Myocarditis, pericarditis or heart failure (clinical heart failure) supported by chest X-ray, echocardiography, electrocardiogram or cardiac enzymes where they were available

Every effort was made to identify and document any existing chronic co-morbidity, such as uncontrolled epilepsy, chronic liver disease, of existing cardiac disease or acute co-morbidity, such as acute hepatitis.

Severity of the dengue episodes was assessed using the following 1997 WHO criteria for defining dengue hemorrhagic fever (DHF), since clinicians are more familiar with this definition:

The following must be present:

1. Fever, or history of acute fever, lasting 2-7 days, occasionally biphasic.
2. Hemorrhagic tendencies, evidenced by at least one of the following:
    - a positive tourniquet test;
    - petechiae, ecchymoses or purpura;
    - bleeding from the mucosa, gastrointestinal tract, injection sites or other locations
    - hematemesis or melena
3. Thrombocytopenia (100,000 cells per $mm^3$ or less). • Evidence of plasma leakage due to increased vascular permeability, manifested by at least one of the following:
    - a rise in the hematocrit ≥20% above average for age, sex and population;
    - a drop in the hematocrit following volume-replacement treatment ≥20% of baseline;
    - signs of plasma leakage such as pleural effusion, ascites and hypoproteinemia.

*(Modified from: Supplement to: Hadinegoro SR, Arredondo-García JL, Capeding MR, et al. Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. N Engl J Med 2015;373:1195-206. DOI: 10.1056/NEJMoa1506223)*

## APPENDIX 2

### Efficacy of Recombinant Live Attenuated Tetravalent Dengue Vaccine (CYD-TVD)
### Summary of Evidence

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**Objectives**

The objectives of this report is to review the efficacy of recombinant tetravalent live attenuated dengue vaccine (CYD-TVD) from the available literature.

**Methods**

A systematic search for all literature using recombinant tetravalent live attenuated dengue vaccine was done. All available phase II and phase III studies were included. Two independent reviewers appraised the studies using the framework from the book "Painless EBM" by Dans, Dans and Silvestre (Chapter 2: How to appraise an article on therapy). The reviewers likewise independently appraised the results. The reviewers met to discuss consistency of the review and to resolve inconsistencies (if any). Relative risks (RR), relative risk reduction (RRR), absolute risk reduction (ARR) and numbers needed to treat (NTT) were computed along with their 95% confidence intervals using original sample sizes recruited (intention to treat (ITT) analysis). This was done with the intent not to overestimate magnitude of treatment effect.

**Summary of Included Studies**

Three primary studies and one summary study were included in this report. The main objective of all studies was to determine the efficacy and safety of a recombinant tetravalent dengue vaccine (CYD-TVD) among healthy children. One Phase 2b trial, CYD -57 by Sabchareon et al (2012)[1], involved 4002 children in Thailand, and two Phase 3 trials, CYD-14 by Capeding et al (2014)[2], and CYD-15 by Villar,et. al (2015)[3], included 10,275 Asian children and 20,869 Latin American children, respectively. A summary study by Hadinegoro, et al., attempted to integrate the efficacy analyses of the three primary studies and reported the long term follow-up safety data.[4]

Table 1 summarizes the study designs of the three trials. All studies were randomized controlled trials; the trials of Sabchareon and Capeding were observer-blind. Over 35,000 children were included, with age ranges of 4-11 years old and 2-14 years old for the study of Sabchareon and Capeding, respectively, while an older age group (9-16 years) was involved in the study by Villar et al. CYD-TDV was compared to normal saline in the studies of Capeding and Villar, while inactivated rabies vaccine was used as control in the study by Sabchaereon. The incidence of symptomatic virologically confirmed dengue was the primary outcome in all trials. Other outcomes measured include rates of hospitalization, severe dengue and severe adverse events (SAE), while death was reported only in study by Capeding.

Over-all, all the trials fulfilled the validity criteria according to the framework of Dans, Dans and Silvestre. Randomization, allocation concealment and similar baseline characteristics of the study population included in the studies were all present and / or adequately performed. Patients were (allegedly) blinded in the study by Villar. This is being questioned by the reviewers considering that it was mentioned in the study of Capeding that the physical characteristics of the vaccine are different from that of normal saline. The CYD-57 study had no mention of blinding of caregivers. All the subjects were analyzed in the original groups to which they were randomized in a 2:1 ratio for

treatment: control. Follow-up was complete in all studies. It should be mentioned that the trial methods were uniform across the different trials including the details of allocation concealment. This is not unexpected since all the trials followed a uniform protocol considering that they were all sponsored by the manufacturer of the vaccine.

**Table 1: Summary of study designs of three trials on the efficacy of recombinant live attenuated tetravalent dengue vaccine (CYD-TVD)**

| | Sabchareon 2012 CYD 57 | Capeding 2014 CYD 14 | Villar 2015 CYD 15 |
|---|---|---|---|
| Patients | 4-11 years old | 2-14 years old | 9-16 years old |
| Intervention | CYD-TDV versus inactivated vaccine | CYD-TDV vs saline | CYD-TDV vs saline |
| Primary Outcomes | Symptomatic virologically confirmed dengue | Symptomatic virologically confirmed dengue | Symptomatic virologically confirmed dengue |
| Other outcomes | Severe dengue<br>Severe adverse events | Hospitalization<br>Severe dengue<br>Severe adverse events<br>Death | Hospitalization<br>Severe dengue<br>Severe adverse events |
| Methods | Randomized controlled observer blind | Randomized placebo controlled observer blind | Randomized placebo controlled (allegedly) blind |
| Randomized | Yes<br>2:1 treatment: control | Yes<br>2:1 treatment: control | Yes<br>2:1 treatment: control |
| Allocation concealment | Interactive web response system | Interactive voice-response/web-response system | Interactive voice-response/web- response system |
| Baseline characteristics same | Yes | Yes | Yes |
| Patients blinded | No | No | Yes (allegedly) |
| Caregivers blind | No mention | Parents and caregivers unaware<br>Trial staff aware | Parents unaware<br>Injecting staff aware |
| Outcome assessor blind | Yes | Yes | Monitoring committee semi-blind |
| Intention to treat | ITT and per protocol analysis | ITT and per protocol analysis | ITT and per protocol analysis |
| Follow-up complete | Yes | Yes | Yes |

## Primary Outcome:

### Incidence of Virologically Confirmed Dengue [Table 2]

The study by Sabchareon involved 4002 children (2669 in the treatment group and 1333 in the control). Of these, 45 patients assigned to the treatment group and 32 controls developed virologically confirmed dengue more than 28 days after the third dose injection of the vaccine. The relative risk for development of virologically confirmed dengue was 0.702 (95% CI 0.441, 1.1). The number needed to treat was 140 patients. The results were not statistically significant.

In the study by Capeding involving 10,275 participants, 282 of the 6851 vaccine recipients and 299 of the 3424 placebo recipients developed virologically confirmed dengue. The relative risk for development of virologically confirmed dengue was statistically significant: 0.471 (95% CI 0.403-0.552). The clinical vaccine efficacy (relative risk reduction) was 0.529 (95% CI 0.448-0.597). The number needed to treat was 22 (95% CI 18, 28).

The study of Villar was the largest, involving 20,969 participants. Two hundred seventy seven (277) of 13920 developed virologically confirmed dengue in the vaccine group versus 385/6949 in the control group. The relative risk was 0.346 (95% CI 0.309, 0.418) and vaccine efficacy (RRR) was 64.1% (95% CI58.2, 69.1). These were likewise statistically significant. The number needed to treat was 29 (95% CI24,34). Of all the studies, the study of Capeding had the highest prevalence of dengue (8.7% in the control population).

*Table 2. Treatment effect of recombinant live attenuated tetravalent dengue vaccine (CYD-TVD) on occurrence of symptomatic Virologically Confirmed Dengue*

| | Sabchareon 2012 | Capeding 2014 | Villar 2015 |
|---|---|---|---|
| Risk in Treatment | 45/2669 (0.017) | 282/6851 (0.041) | 277/13920 (0.020) |
| Risk in Control | 32/1333 (0.024) | 299/3424 (0.087) | 385/6949 (0.05) |
| Relative Risk | 0.702 (95% CI .449, 1.1) | 0.471 (95% CI 0.403, 0.552) | 0.346 (95% CI 0.309, 0.418) |
| Relative Risk Reduction | 0.298 (95% CI -0.10, 0.551) | 0.529 (95% CI 0.448-0.597) | 0.641 (95% CI 0.582, 0.691) |
| Absolute Risk Reduction | 0.027 (95% CI -0.002, -0.008) | 0.046 (95% CI -0.036, 0.057) | 0.036 (95% CI 0.030, 0.042) |
| Number needed to treat | 140 (95% CI 56, -557) | 22 (95% CI 18, 28) | 29 (95% CI 24, 34) |

**Secondary Outcomes:**

**Hospitalization for Virologically Confirmed Dengue [Table 3]**

The study by Sabchareon provided no data on the treatment effect of the dengue vaccine on hospitalization for virologically confirmed dengue. On the other hand, results of the studies conducted by Capeding and Villar showed statistically significant risk reduction for hospitalization among the treatment groups.

In the study by Capeding, among 6851 patients randomized to the vaccine group, 40 patients were hospitalized for dengue versus 61/3424 patients in the control. The relative risk was 0.328 (95% CI 0.220, 0.487), with a vaccine efficacy (RRR) of 67.2% (95% CI 51.9-78.0). The NNT was 84 (95% CI 48, 133).

In the study of Villar, 277/13920 in the vaccine group were hospitalized versus 385/6949 in the control group. The relative risk for hospitalization was 0.197 (95% CI 0.133, 0.346). Vaccine efficacy (RRR) was 0.803 (95% CI 0.654, 0.887), and the NNT was 202 (95% CI 140, 311). Similar to the study of Capeding, the results were statistically significant.

*Table 3. Treatment Effect of recombinant live attenuated tetravalent dengue vaccine (CYD-TVD) for Hospitalization for Virologically Confirmed Dengue*

| | Sabchareon 2012 | Capeding 2014 | Villar 2015 |
|---|---|---|---|
| Risk in Treatment | No data | 40/6851 (0.006) | 277/13920 (0.001) |
| Risk in Control | No data | 61/3424 (0.018) | 385/6949 (0.006) |
| Relative Risk | No data | 0.328 (95% CI 0.220, 0.487) | 0.197 (95% CI 0.133, 0.346) |
| Relative Risk Reduction | No data | 0.672 (95% CI 0.519, 0.780) | 0.803 (95% CI 0.654, 0.887) |
| Absolute Risk Reduction | No data | 0.012 (95% CI 0.008, 0.017) | 0.005 (95% CI 0.003, 0.007) |
| Number needed to treat | No data | 84 (95% CI 48, 133) | 202 (140, 311) |

**Occurrence of Severe Dengue [Table 4]**

Vaccine efficacy for the outcome of severe dengue was not significant in the study of Sabchareon. Three out of 2669 patients in the treatment group versus 2 out of 1333 children in the control group developed severe dengue. The relative risk was 0.749 (95% CI 0.125, 4.487) and vaccine efficacy (RRR) was 0.251 (95% CI -3.478, 0.875).

The study of Capeding provide no data of severe Dengue as an outcome.

The study of Villar showed significant results. Twelve (12) patients developed severe dengue: 1 in the vaccine group versus11 in the control group. The relative risk was 0.045 (95% CI 0.006, 0.351). Vaccine efficacy (RRR) was 95.5% (95% CI 64.9, 99.4). The number needed to treat was 662 (95% CI 362, 1358).

*Table 4. Treatment effect of recombinant live attenuated tetravalent dengue vaccine (CYD-TVD) on occurrence of severe dengue*

| | Sabchareon 2012 | Capeding 2014 | Villar 2015 |
|---|---|---|---|
| Risk in Treatment | 3/2669 (0.001) | No data | 1/13920 (0.00) |
| Risk in Control | 2/1333 (0.002) | No data | 11/6949 (0.002) |
| Relative Risk | 0.749 (95% CI 0.125, 4.487) | No data | 0.045 (95% CI 0.006, 0.351) |
| Relative Risk Reduction | 0.251 (95% CI -3.478, 0.875) | No data | 0.955 (95% CI 0.649, 0.994) |
| Absolute Risk Reduction (ARR) | 0.001 (95% CI -0.002, 0.004) | No data | 0.002 (95% CI 0.001, 0.003) |
| Number needed to treat | 2658 (95% CI 227, -468) | No data | 662 (95% CI 362, 1358) |

**Severe Adverse Events [Table 5]**

Table 5 shows the safety of the dengue vaccine on the risk of severe adverse events (SAE). It should be noted that in all studies, the risk of adverse events was not increased in the vaccine groups versus the control groups. Only the study of Capeding, however, showed significant results. The risk of serious adverse events was 355/ 6851 children in the vaccine group versus 220/3424 in the control. The relative risk was 0.806 (95% CI 0.685, 0.949). Vaccine efficacy (RRR) was 19.4% (95% CI 5.1, 35.1). The NNT was 81 (95% CI 94, 340).

*Table 5. Treatment effect of recombinant live attenuated tetravalent dengue vaccine (CYD-TVD) on occurrence of severe adverse events*

| | Sabchareon 2012 | Capeding 2014 | Villar 2015 |
|---|---|---|---|
| Risk in Treatment | 315/2669 (0.118) | 355/6851 (0.052) | 81/13920 (0.006) |
| Risk in Control | 176/1333 (0.132) | 220/3424 (0.064) | 40/6949 (0.006) |
| Relative Risk | 0.894 (95% CI 0.752, 1.062) | 0.806 (95% CI 0.685, 0.949) | 1.011 (95% CI 0.691, 1.478) |
| Relative Risk Reduction | 0.106 (95% CI 0.062, 0.248) | 0.194 (95% CI 0.051, 0.351) | -0.011 (95% -0.307, 0.475) |
| Absolute Risk Reduction | 0.014 (95% CI-0.007, 0.037) | 0.012 (95% CI 0.003, 0.002) | 0.00 (95% CI -0.002, 0.002) |
| Number needed to treat | 72 (95% CI 27, -136) | 81 (95% CI 94, 340) | 15939 (95% CI 468, -435) |

**Death**

Only the study of Capeding reported death as an outcome. All four cases belonged to the treatment group (4/6851) and none occurred among 3424 in the control group. All deaths, however, were considered unrelated to the study intervention. No vaccine related deaths (eg. immediate hypersensitivity, allergic reactions, development of viscerotropic or neurotropic disease) were observed.

**Summary of Treatment Effect**

In summary, the occurrence of symptomatic virologically confirmed dengue, the primary outcome measured in the three studies on the use of recombinant tetravalent dengue vaccine, was significant in the studies of Capeding and Villar. Vaccine efficacy of 52.9% and 64.1%, respectively. The relative risks for hospitalization among the vaccinated groups in these two studies were significant at 0.328 (95% CI 0.220, 0.487) and 0.197 (95% CI 0.113, 0.346) respectively. In the study of Villar vaccine efficacy (RRR) for severe dengue was 95.5% (95% CI 64.9, 99.4). The safety of vaccine in the development of severe adverse events was demonstrated in all the studies. This was significantly lower among the vaccinatedgroup in the study of Capeding. The RRR was 19.5% (95% CI 5.1, 35.1). Only the study of Capeding reported deaths with all 4 cases belonging to the treatment group. The causes of death, however, were not vaccine related in nature.

**Summary Study**

A study by Hadigenogro, et. al. explored long term efficacy and safety from the 3-5 year follow-up of the participants from the above three studies. Similar to the primary studies, the outcome evaluated was virologically confirmed dengue among children given the tetravalent dengue vaccine versus placebo.Secondary outcomes measured included incidence of hospitalization for virologically confirmed dengue during follow-up in years 3-6. Over-all, the paper fulfilled validity criteria, with observed randomization and allocation concealment, similarity of baseline characteristics, analysis in the randomized group and complete follow-up. It should be understood, however, that this summary study did not systematically follow-up all the participants and relied mainly on the reports of events by the authors of the primary studies. The summary study, however, allowed sub-group analysis according to age group.

Overall, the summary study by Hadinegoro reported lower (but not significant) relative risks for hospitalization for dengue among all children. The relative risk of 0.84 (95% confidence interval 0.56, 1.24). However relative risk for hospitalization for dengue was higher (but not statistically significant) for those under age 9 with relative risk of 1.58 (95% CI 0.83-3.02) compared to those among aged 9 years old and older, with relative risk of 0.50 (95% CI 0.29-0.86).

This report will concentrate on the follow-up data of the Capeding study since this is the population that included participants from the Philippines and the prevalence of Dengue is closest to that of our practice setting. For the Capeding study, a total of 10,165 participants were included in this follow up study; 6,778 in the vaccine group versus 3,387 in the control group. Computations in this review used the data from table 1 (page 5) of the main publication. Table 6 summarizes the treatment effect of the dengue vaccine on the incidence of hospitalization for virologically confirmed dengue among the different age groups of the Capeding study (CYD14). The relative risk for virologically confirmed dengue in the 2-5 years is increased in the vaccine group versus that of the placebo. The relative risk for hospitalization was 7.45 (95% CI 0.986, 56.3) in this age group. This was the only age group where the risks were that towards harm with a tendency for statistical significance. For the older age groups, however, the relative risks for virologically confirmed dengue were decreased and towards benefit, with relative risk of 0.627 (95% CI 0.22-1.83) and 0.249 (95% CI 0.02-1.74) among the 6-11 year old and 12-14 year old groups, respectively. These were not statistically significant but the sample size may not have been powered for such a sub-group analysis.

*Table 6. Treatment effect of recombinant live attenuated tetravalent dengue vaccine (CYD-TVD) on hospitalization for virologically confirmed dengue among age-specific groups for the Capeding study (CYD14).*

| | 2- 5 years old | 6-11 years old | 12-14 years old |
|---|---|---|---|
| Relative Risk | 7.45<br>(95% CI 0.986, 56.3) | 0.627<br>(95% CI 0.248, 1.59) | 0.249<br>(95% CI 0.046,1.355) |
| Relative Risk Reduction | -6.45<br>(95% CI -0.014, 55.33) | 0.373<br>(95% CI -0.587, 0.752) | 0.751<br>(95% CI -0.355, 0.954) |
| Absolute Risk Reduction | -0.008<br>(95% CI 0.001, 0.014) | 0.002<br>(95% CI -0.002, 0.006) | 0.04<br>(95% CI -0.001, 0.012) |
| Number Needed to Treat | -126<br>(95% CI 72, 840) | 606<br>(163, -648) | 256<br>(95% CI 83, -1325) |

The supplemental appendix of the study of Hadigenogro also provided data for total hospitalization and hospitalization for severe dengue for the above three studies. For the study of Capeding (CYD 14), additional calculations are being presented based on the Table 7 (derived from Table S4 of the supplemental appendix).

Table 7. *Number of severe hospitalized virologically confirmed dengue cases among the patients given dengue vaccine and placebo from the three trials [from Table S4. Supplementary Appendix]*[5]

| Trial/Year | Vaccine group (number of severe dengue cases/ number of hospitalized cases) | Control group (number of severe dengue cases/ number of hospitalized cases) |
|---|---|---|
| CYD14/Year 3 | 11/27 | 1/13 |
| CYD15/Year 3 | 3/16 | 5/15 |
| CYD57/Year 3 | 4/22 | 0/11 |
| Total Year 3 | 18/65 | 6/39 |
| CYD57/Year 4 | 1/16 | 2/17 |
| Total | 19/81 | 8/56 |

From the above table, for the outcome of hospitalization on long term follow-up , 27/6778 versus 13/3387 were hospitalized. The RR was 1.038 (95% CI 0.54, 2.01), RRR was -0.38 (-0.464, 1.01), ARR -0.00 (-0.003, 0.003) and the NNT was -6884 (392, -352). These results were not statistically significant. For the outcome of hospitalization for severe dengue, 11/6778 versus 1/3387 were reported on long term follow-up. The RR was 5.50 (0.71, 42.6), RRR was -4.50 (-0.29, 41.56), ARR was -0.001 (0, 0.003) and the NNT was -754 (380, -4481). These results are towards harm although not statistically significant but definitely worth considering.

**Conclusions**

Results from published literature from primary trials show that the vaccine is efficacious and effective in the prevention of virologically confirmed Dengue of all degrees of severity up to 24 months of follow-up.

Vaccine efficacy, however was at best only 0.529 (95% CI 0.448-0.597) in the Capeding study and only 0.641 (95% CI 0.582, 0.691) in the Villar study.

Secondary outcomes show that the vaccine is likewise safe with the vaccine group not having an increase in the risk of serious adverse events compared to placebo.

The summary study of Hadigenogro allowed for sub-group analysis according to age using data from long term follow up. This showed that for the Capeding study, the younger age group had an increase in the risk for hospitalization for virologically confirmed dengue compared to controls. Further, the long term follow-up data suggested that the risk for hospitalization for dengue and hospitalization for severe dengue were towards harm.

**Conflicts of Interest**

The authors declare that they have no interests in any of the pharmaceutical companies that are into development, manufacturing and marketing of Dengue vaccines.

**References:**

1. Sabchareon A, Wallace D, Sirivichayakul C, Limkittikul K, Pornthep Chanthavanich, et. al. Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. *Lancet* 2012; 380: 1559–67.

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3. Villar L, Dayan GH, Arredondo-García JL, Rivera DL, Cunha R, et. al. Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America. N Engl J Med 2015;372:113-23.

4. Hadinegoro, SR, Arredondo-García JL, Capeding MR, Deseda C, Chotpitayasunondh T, et. al. Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease. N Engl J Med 2015: 1-12.

5. Supplementary Appendix. Supplement to Hadinegoro, SR, Arredondo-García JL, Capeding MR, Deseda C, Chotpitayasunondh T, et. al. Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease. N Engl J Med 2015; 373: 1195-206.

# FACT SHEET FOR PARENTS AND PATIENTS ON DENGUE VACCINATION

It is important to be aware of the following information if you decide to have your child immunized.

- Vaccination against dengue is recommended for children > 9 years old.
- Vaccination is not recommended for children below 9 years old because of an increased risk of severe dengue and hospitalization for dengue. There is an ongoing 5-year long-term follow-up of these vaccinated children.
- No vaccine is completely safe or completely effective; thus, vaccination does not give 100% protection nor is it 100% safe.
- The vaccine appears to be more effective against dengue in those who were already exposed and are positive for dengue antibodies.
- For children receiving three (3) doses of the dengue vaccine, the chances of getting symptomatic dengue, hospitalization and severe dengue is significantly reduced.
- The most common side effects after vaccination are fever, body weakness, headaches, and pain at the injection site. You should report any side effects following dengue immunization to your doctor.
- Recommendations regarding the vaccine schedule and need for boosters may change as more information come in from ongoing studies.
- Control of dengue is multifactorial. In addition to appropriate clinical case management and vaccination, mosquito control is also important in prevention of dengue.