(English translation, for accuracy please refer to the original document published on PIDST Website)

Guidance for the use of Dengvaxia™

By the Pediatric Infectious Diseases Society of Thailand and

the Infectious Diseases Association of Thailand

26th December 2017

……

The dengue vaccine, or Dengvaxia™, developed by Sanofi Pasteur, is a live vaccine containing a chimerix virus of 17D Yellow Fever (YF) backbone of which the prM and envelope gene were replaced by the corresponding gene of each of the 4 dengue virus serotypes (DENV1-4). The recombinant virus is cultured in vero cells. It has been licenced in Thailand since January 2017 and is recommended for use in children and adults between the ages of 9 and 45 years. Dengvaxia™ is a safe vaccine, but has limited efficacy with a 65% rate of protection against dengue infection. This means that those who have been vaccinated may still become infected with the dengue virus.

On the 29th of November 2017, Sanofi Pasteur announced new clinical trial information on adverse effects of the vaccine, leading to a confusion on how to appropriately use the vaccine in practice. The Pediatric Infectious Diseases Society of Thailand (PIDST) and the Infectious Diseases Society of Thailand (IDST) issued an initial recommendation on the 7th December 2017 on the use of Dengvaxia™. The World Health Organization (WHO) later issued the recommendation on the 22nd December 2017. From this, the PIDST and the IDST have summarized the relevant data and update the recommendations as following:

1. What is the new information about the Dengvaxia™ vaccine that has been available since 2017?

There are two phase 3 studies: CYD14 study in 10,000 children aged 2-16 years conducted across 5 Asian countries, and CYD15 study in 20,000 children aged 9-16 years conducted in 5 Latin American Countries. Four-thousand of the total 30,000 participants in these two clinical trials combined were tested for serological evidence of prior dengue infection before vaccination using the 50% plaque reduction neutralization assay (PRNT50). Among the tested cases, the vaccine provided 82% protection against dengue infection in 9-16 year-old children with serological evidence of prior dengue infection, whereas in those with no serological evidence of prior infection, this figure dropped to 52%.

To study the effects of prior dengue infection on dengue vaccination further, Sanofi Pasteur conducted another study by randomly selecting 3,300 blood samples at month 13 (after which the 3-dose dengue vaccination course was completed) that were taken from all the subjects participating in phase 3 studies (CYD14 and CYD15) and phase 2b (CYD23/57) clinical trials, and included the samples from all participants that became infected with dengue during the clinical trial. All samples were tested for anti-NS1 antibody, a novel method of testing for dengue infection developed by the University of Pittsburgh, USA. As Dengvaxia™ contains a chimeric yellow fever backbone, it does not contain the NS-1 antigen of the dengue virus and so a positive result ($\geq$ 9 EU/ml) signifies evidence of natural dengue infection. **When anti-NS1 antibody results were compared to PRNT50 results, a false negative (misclassify dengue exposed samples as seronegative by the assay) rate of only 5% was noted, but with a 30% rates of false positive results.**

(English translation, for accuracy please refer to the original document published on PIDST Website)

The multiple imputation analysis was also performed on month 13 anti-NS1 antibody data with adjustments for other factors to predict whether participants had previously been infected with the dengue virus before vaccination. It found similar outcomes on the efficacy of Dengvaxia™ in protection against hospitalized virologically confirmed dengue (VCD) and severe dengue in volunteers aged 9-16 years with prior dengue infection when compare with the efficacy analysis using PRNT50 alone. However, volunteers without prior dengue infection were 1.4 times more likely to be hospitalized for dengue infection (HR=1.412, 95%CI=0.743-2.682, *p*=0.287) and 2.4 times more likely to develop severe dengue infection (includes all grades of dengue hemorrhagic fever and all forms of severe dengue) (HR=2.435 95%CI=0.472-12.559, *p*=0.283) compared to placebo. All the severe dengue were dengue hemorrhagic fever (DHF) grades 1 and 2, none had shock or severe bleeding. There were no deaths, and all cases made a full recovery. Those without prior dengue infection who received Dengvaxia™ were more likely to be hospitalized for dengue after month 30 of vaccination compared to those who received placebo.

2. **In patients hospitalized VCD, are individual without prior dengue infection who received Dengvaxia™ more likely to develop more severe disease than those who received placebo?**

From analysis of data from all 3 phase-3 studies totaling more than 30,000 volunteers, it was found that those hospitalized with dengue infection during the trial had similar disease severities regardless of their history of dengue vaccination. From the analysis using data from anti-NS1 antibody testing, there were very few hospitalization subjects and there was no differences in disease severity between the two groups.

3. **Is the level of risk for hospitalization with VCD contributed from Dengvaxia™ worth the potential benefits of the vaccine?**

The overall risk/benefit ratio of Dengvaxia™ has been calculated as follows:

- For every 1000 people with prior dengue infection (seropositive) who receive the vaccine, 15 people will be protected from hospitalization for dengue infection and 4 people will be protected from severe dengue (encompassing DHF grades 1-4 and other forms of severe dengue infection) over a period of 5 years.
- For every 1000 without prior dengue infection (seronegative) people who receive the vaccine, 5 people will be at increased risk for hospitalization for dengue infection and 2 people will be at increased risk for severe dengue (encompassing DHF grades 1-4 and other forms of severe dengue infection) over a period of 5 years.
- From this new analysis, the risk of severe dengue that can be estimated in 5 years following vaccination are as follows:
    - **Seropositive vaccinated individuals have a risk of < 1.0 per 1000 persons vaccinated**
    - **Seropositive unvaccinated individuals have a risk of 4.8 per 1000 persons not vaccinated**
    - **Seronegative vaccinated individuals have a risk of 4.0 per 1000 persons vaccinated**

- **Seronegative unvaccinated individuals have a risk of 1.7 per 1000 persons not vaccinated**

4. **Should immune status against dengue of individuals be tested prior to vaccination?**

From all studies aforementioned, both PRNT50 (which is a standard test, with a positive titer considered to be ≥1:10 against at least 1 dengue serotype) and anti-NS1 antibody (a newly developed test) are tests not available in general routine practice. The diagnostic tests that are generally available utilize ELISA, or rapid tests using immunochromatography technique, have inadequate sensitivity for detecting low titers from remote infections. A positive ELISA or rapid test may be supportive evidence for prior dengue infection, however, a negative result does not rule out previous infections. Additionally, there is no data as of yet on how the results of these tests correlate with those measured using PRNT50. It should also be noted that ELISA can also produce false positive tests in other Flavivirus infections. In the absence of appropriate testing, serological testing for evidence of prior dengue infection before vaccination is therefore not recommended in routine practice. If ELISA or rapid tests are to be done, their limitations should be prior discussed. The history of illness from dengue infection should always be asked to help assess the benefit and risk from the vaccine.

5. If serological testing is not performed prior to vaccination, how can the risk following vaccination be assessed? Should vaccination be recommended or not?

From published data on phase 3 clinical trials overall without consideration of serostatus before vaccination (as serological testing was not performed in the majority of the volunteers) in children ages between 9-16 years, dengue vaccination can reduce rates of symptomatic VCD by 65.6% (95% CI: 60.7–69.9), reduces hospitalization for VCD by 80.5% (95% CI: 70.1-87.7), and reduces rates of severe dengue (using IDMC definition) by 93.2% (95% CI: 77.3-98.0). The 5-year follow-up data found rates of hospitalization and severe dengue in the vaccinated group to be consistently lower than those of the unvaccinated group.

The recent additional analysis have uncovered potential risks in sub-group without prior dengue infection following vaccination. The likelihood of seronegativity in children in areas with high incidence of dengue or in adults is low, as most would have been infected. It is recommended that the risks and benefits of the dengue vaccine is discussed prior to their decision on whether to receive the vaccine. For example, in areas of high seroprevalence such as in Ratchaburi province, seropositive rate for dengue (reported from the phase 3 trial) was 80% using the PRNT50 method in 9-year-old children. If 1000 children in Ratchaburi Province were vaccinated without serological testing and followed-up for 5 years, there will likely be a total of 800 children who will seropositive, equating to a total of approximately 12 cases of hospitalizations from dengue prevented; and 200 children who are likely seronegative, equating to an increase of 1 case of hospitalization due to dengue. Although the calculated benefits of the population in such setting are much higher than the risks, the individuals receiving the vaccine must be aware of and accept the potential risks following vaccination. In a population where high rates of seroprevalence is likely, particularly in Thai adults where seropositivity rates were found to be over 90% in all studies utilizing PRNT50 methods, the potential benefits is much higher than the risk. However, in

areas with low dengue seroprevalence, benefits are relatively lower and therefore dengue vaccination is not recommended in such settings.

The available seroprevalence studies in Thailand have not yet achieved nationwide coverage. Studies on seroprevalence utilizing ELISA IgG/IgM methods may underestimate true seroprevalence, whilst very few available studies used PRNT50. For example, in a study in medical personnel at the Queen Sirikit National Institute of Child Health (QSNICH) in Bangkok between the ages of 21-30 years, 92% were found to be PRNT50 positive. In comparison, in a study in Bangkok and Chonburi provinces in individuals between 17-29 years old, only 64% were found to be ELISA IgG positive. Older populations are more likely to be seropositive. Currently, the Thai Ministry of Public Health and the Thai National Vaccines Institute are conducting a large dengue seroprevalence study covering various age groups nationwide, with the results expected to be announced in the near future.

The seroprevalence of dengue infection could be indirectly estimated based on the incidence of dengue illness reported from various areas. This information is available through the Thai Bureau of Vector Borne Diseases website. It must be noted that this is the indirect information to reflect the seroprevalence and subjected to the effectiveness of the reporting system in different areas.

6. In individuals who have already received one or two doses of the dengue vaccine, should their course be completed?

Those with incomplete dengue vaccination courses should be queried about their personal history of dengue infections or illness. If they have previously had dengue infection, it is recommended that the course is completed. However, if they have not or are unsure, they should be given additional information regarding the potential risks as described above before the decision is made on whether to continue their vaccination course. Currently, no data is available on the benefits and risks of dengue vaccination in those received incomplete vaccination courses.

7. Are there any further recommendations that the WHO have issued which is different to the above?

The Global Advisory Committee on Vaccine Safety issued its recommendation statement on Dengvaxia™ on the 7th December 2017, which can be found at http://www.who.int/vaccine_safety/committee/GACVS-StatementonDengvaxia-CYD-TDV/en/. Its contents are no different to the recommendations discussed above. They clearly state that the dengue vaccine that has been in use has been administered in areas of high seroprevalence, where the proportion of individuals who are seronegative and might have the risk from dengue vaccination is approximately less than 1%, of whom severe diseases can mostly be avoid with appropriate care. Therefore, those who have received vaccination should continue to avoid mosquito bites, and should immediately seek medical attention if dengue like illness occurs. It is not recommended to give vaccination in those without prior dengue infection at this time, and no recommendation for those who received incomplete vaccination as there is insufficient data.

The WHO issued another recommendations for medical practice on the 22nd December 2017, which can be found at

http://www.who.int/immunization/diseases/dengue/q_and_a_dengue_vaccine_dengvaxia_use/en/. Its contents are consistent with its statement on the 7th December 2017 in explaining the increased rates of severe dengue in those without prior dengue infection which was hypothesized that vaccination in this population is the silent primary infection, which in turn increases the risk of severe dengue infection from subsequent natural secondary infection. This risk resolves after the individuals acquire a natural dengue infection.

The WHO places emphasis on the prevention of mosquito bites and seeking of appropriate medical attention if dengue illness is suspected, regardless of individual vaccination status.

8. Does the WHO recommend serological testing prior to vaccination? What are their recommendations on dengue vaccination?

The WHO state that currently there are no appropriate test kits available for routine practice. The use of ELISA IgG testing may be an option, but could also produce false positive results from cross reactivity with the Zika and Japanese Encephalitis viruses, in addition to the disadvantage of substantial laboratory processing times. No rapid tests have yet been validated for the determination of serostatus in clinical practice. History previous dengue infections can help to predict the serostatus, however, it is well known that not all dengue infections are symptomatic. In summary, WHO does not have any clear guidance on whether serology testing should be performed prior to dengue vaccination and what tests to use, citing the need for further studies.

The WHO states that it ***"Acknowledges that in high seroprevalence settings, the vaccine can have significant population-level benefits. However, until a full review has been conducted, WHO recommends vaccination only in individuals with a documented past dengue infection, either by a diagnostic test or by a documented medical history of past dengue illness."***

9. What does the WHO recommend for the management of those with an incomplete dengue vaccination course with an uncertain history of previous dengue infection?

The WHO states that ***"there is no evidence to determine the risk and benefit of completion or suspension of the series in those who have received only one or two doses. However, in documented high seroprevalence settings, where vaccination has started but the schedule has not yet been completed, there is likely to be an overall benefit to the population if individuals complete the schedule, hereby assuring protection of seropositive individuals who make up the majority of the vaccinated population."*** The decision to vaccinate therefore depends on the situation of each individual.

10. Has Dengvaxia™ caused other severe side effects other than those already mentioned?

Based on reports both of phase 1-3 clinical trials and post-marketing surveillance following the administration of over 1 million doses across the Philippines and Brazil in addition to over ten-thousand doses in Thailand, no severe or unexpected side effects have been seen. The Philippines reported 3 deaths following vaccination, which was reviewed by local experts and were determined to be unrelated

to the vaccinations; the causes of death were cardiovascular disease, leukemia and pontine hemorrhage.

Preventive measures of dengue infection are the combinations of prevention of mosquito bites, mosquito control, removal of mosquito breeding sites, and vaccination. Dengvaxia® does not provide complete protection even following complete vaccination. It is therefore prudent that if dengue illness is suspected, immediate medical attention is sought regardless of vaccination status.

11. Should written consent be required to receive this vaccine?

Detailed information should be provided prior to vaccination. Medical staff should document that they have provided information of the vaccine, but the request for written consent to receive vaccination is not necessary.

References

1. **Sabchareon A, Wallace D, Sirivichayakul C, et al. Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai school children: A randomised, controlled phase 2b trial. Lancet 2012;380:1559-67.**
2. **Capeding MR, Tran NH, Hadinegoro SR, et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomized, observer-masked, placebo-controlled trial. Lancet 2014;384: 1358-65.**
3. **Villar L, Dayan GH, Arredondo-García JL, et al. Efficacy of a tetravalent dengue vaccine in children in Latin America. N Engl J Med 2015; 372:113-23.**
4. **L'Azou M, Moureau A, Sarti E, et al. Symptomatic dengue in children in 10 Asian and Latin American countries. N Engl J Med 2016;374:1155-66.**
5. **Vandepitte WP, Chaweethamawat A, Yoksan S. The seroprevalence of neutralizing antibody against dengue virus in healthcare workers. In: Proceedings of the Joint International Tropical Medicine Meeting, Bangkok, Thailand, December 6-8, 2017.**
6. **Udomchaisakul P, Tepsumethanon, Uraiwong K, et al. Dengue IgG seroprevalence among healthy adults in Thailand. In: Proceedings of the 7th Asian Congress of Pediatric Infectious Diseases, Beijing, China, October 12-15, 2014.**