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# PSMID INTERIM GUIDE ON THE USE OF DENGUE VACCINE (Update, 6 December 2017)

## BACKGROUND

Dengue is endemic in the Philippines and vaccination is an important component of a comprehensive dengue prevention and control strategy, in conjunction with vector control, surveillance and management of cases. In December 2015, the Philippines was the first Asian country to register and approve the use of the first dengue vaccine, Dengvaxia. A pooled analysis of the CYD 14/15 trials of the dengue vaccine showed higher efficacy rates for seropositive patients aged ≥9 years (81.9%, 95% CI 67.2, 90) compared to seronegative patients (52.5%, 95% Ci 5.9-76.1).[1] According to the WHO Scientific Advisory Group of Experts on immunization, countries with dengue seroprevalence of ≥70% should be targeted for vaccination.[2] PSMID subsequently released a position statement based on the best available scientific knowledge at that time.[3]In its statement, PSMID noted safety signals in the clinical trials suggesting a potential risk of antibody-dependent enhancement (ADE) of breakthrough dengue infection when the vaccine is administered to seronegative individuals. The Society thus recommended additional studies, including long-term surveillance of vaccinated individuals, to validate this observation.

On the 29th November 2017, Sanofi Pasteur released news of additional safety and efficacy analyses of five years of clinical data on study participants in the vaccine trials in Asia and Latin America.The announcement stated continued protection against dengue among those who had prior dengue infection but recommended against vaccination of those without previous infection.[4]According to the interim conditional recommendation of WHO released last 30 November 2017, dengue vaccine should only be restricted to individuals with prior exposure to dengue.

In addition, WHO noted that subjects without prior exposure to dengue (seronegative) had higher risk of severe dengue and hospitalizations should they contract the disease after vaccination.[5]In the Dengvaxia trial, thecriteria used in classifying dengue fever among the participants of was based on the grading system of WHO 1997 classification. The Independent Data Monitoring Committee classified participants as having severe dengue using the criteria: virologically confirmed dengue with at least one of the following: platelet count $<100,000^{9}/L$ and bleeding and plasma leakage; shock; bleeding requiring blood transfusion; encephalopathy; liver impairment; impaired kidney function; myocarditis, pericarditis or heart failure.[6]

**PRACTICE**

At present, dengue fever is classified into three types: dengue without warning signs, dengue with warning signs, and severe dengue. Based on the WHO 2009 Dengue classification, severe dengue is now defined as having clinical manifestations of dengue plus any of the following: severe plasma leakage leading to shock, or fluid accumulation with respiratory distress, severe bleeding and severe organ impairment (either as having AST or ALT > 1000, presence of seizures or impaired consciousness, myocarditis or renal failure).[7]

Currently, there are no definitive tests that can determine the serostatus or past infection of dengue.In the dengue vaccine trial, dengue plaque reduction neutralization test (PNRT) was used to determine baseline serostatus of the participants.[6] Unfortunately, this is currently not available for commercial use. In the additional analyses carried out for the cohort of vaccinees followed up for six years, an NS1 antibody assay was used to determine the serostatus at baseline. Antibody tests such as dengue IgG and IgM are meant to detect current or recent past dengue infection but is not accurate enough to determine past infection. These tests can also have cross-reaction; thus, they can also be positive if a person is infected with any flavivirus such as chikungunya.

**INTERIM STATEMENT**

Based on the above information, PSMID asserts that:

- Dengue vaccine is safe and effective among those with prior exposure to dengue. Current evidence does not support giving dengue vaccine to individuals without past dengue infection.

- Vaccines are not without risk; we support the right of each individual to full disclosure prior to consent. Disclosure should include the epidemiology of the disease, probable outcomes once disease is contracted and available treatments, and the short- and long-term risks and benefits of vaccination.

- Long-term follow-up and independent review of efficacy and safety of drugs are important aspects of patient safety. PSMID supports mechanisms and initiatives that would determine the seroprevalence of dengue in representative samples across geographic areas and age groups, the target population for vaccination, the safety and cost-effectiveness of current and future dengue vaccines. A national registry of individuals who received at least one dose of Dengvaxia should be created. These individuals should be monitored regularly for occurrence of signs and symptoms compatible with dengue for at least 6 years.

They are encouraged to consult any physician once they have symptoms for proper management, work-up, and immediate notification to health authorities.

- For individuals who have yet to complete the 3 doses, they are encouraged to wait for further advisory from the Department of Health, pending review of the intention-to-treat analyses of the long-term efficacy of the vaccine.

- For those who intend to get vaccinated, a history of past dengue infection should be determined, and the option of serotesting prior to vaccination should be offered. Risks and benefits should be discussed prior to vaccination, as well as the risks of not being immunized.

- There is no simple solution to preventing dengue. Thus, to have a sustainable dengue control program, appropriate clinical management, laboratory surveillance and prevention efforts such as expansion of disease surveillance to include the communities and the private sector, vector control, and strengthening of epidemic response at all levels should always be emphasized.

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