RESPONSE FROM THE PEDIATRIC INFECTIOUS DISEASE SOCIETY OF THE PHILIPPPINES REGARDING CURRENT ISSUES ON THE USE OF THE DENGUE VACCINE
12 December 2017

In December 2015, the Philippines licensed the first dengue vaccine, a recombinant live attenuated tetravalent dengue vaccine or CYD-TDV (Dengvaxia®) developed by Sanofi Pasteur. The vaccine became available for use in both the private sector and under the government vaccination program. In response to requests from private clinicians for guidance on use of the vaccine, the Pediatric Infectious Disease Society of the Philippines released its statement on the use of the dengue vaccine in May 20, 2016.[1] The recommendations included in this first statement were based on an independent review of the evidence available at that time regarding the efficacy and safety of the vaccine. [2] Results of the long term follow-up data that were included in the review [3] documented an increase in the risk for severe and hospitalized dengue in those aged 2-5 years old. For the age group ≥9 years, there was higher efficacy among participants who were seropositive at baseline compared to those who were seronegative. Subsequently, the World Health Organization and its advisory group on global policies and strategies for vaccines and immunization, the Strategic Advisory Group of Experts (SAGE), acknowledged that although there was evidence of elevated risk of hospitalized dengue in the 2–5-year age group, there was insufficient data to determine whether seronegative individuals aged ≥9 years who received the dengue vaccine may at a later time be at higher risk for severe or hospitalized dengue than those who did not receive the vaccine. [4] The WHO, together with regulatory authorities, scientists and experts in the field, called for continued research and surveillance to determine the effects of the dengue vaccine in vaccinated individuals 9 years of age and older, particularly those who were seronegative at baseline.

A recent announcement from Sanofi provided an update on the safety and efficacy of its live attenuated dengue vaccine, CYD-TDV (Dengvaxia ®). [5] In a new analysis of 6 years of clinical data, it was shown that for vaccinated individuals aged ≥9 years, the vaccine provides persistent protective benefit against dengue infection in those who had prior infection. However, for those who have not been previously infected by dengue virus (i.e. seronegatives), more cases of severe disease could occur, should there be a subsequent dengue infection.

Because of this finding, the manufacturer now states that “health care professionals should assess the likelihood of prior dengue infection before vaccinating”, and that vaccination should not be recommended for seronegative individuals. This will entail a change in the prescribing information of the vaccine; this proposed label update has been submitted to

the national regulatory authorities of countries where the vaccine is licensed, including the Philippines.

The manufacturer's announcement raises several points of concern for the clinician. These include:

1. How is "severe" disease defined in the clinical trials that assessed the efficacy and safety of the dengue vaccine?
2. How can serologic status be reliably determined?
3. Should partially vaccinated patients continue to receive the remaining doses?
4. What can we do for patients who have already received the vaccine?

HOW IS SEVERE DISEASE DEFINED IN THE CLINICAL TRIALS THAT ASSESSED THE EFFICACY AND SAFETY OF THE DENGUE VACCINE?

In the context of the clinical trials conducted for the licensure of the live attenuated dengue vaccine CYD-TDV, a participant was classified as having "severe" disease when he had fever of at least 2 days, virologically confirmed disease and at least one of the following criteria: [3]

- Platelet count ≤100x10^9 /L and bleeding (positive tourniquet test, 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)
- Shock (pulse pressure ≤20 mmHg in a child or adolescent, or hypotension [≤ 90 mmHg] with tachycardia, weak pulse and poor perfusion).
- Bleeding requiring blood transfusion
- 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.
- Liver impairment (AST >1000 U/L or prothrombin time, international normalized ratio >1.5)
- Impaired kidney function (serum creatinine ≥1.5 mg/dL)
- Myocarditis, pericarditis or heart failure (clinical heart failure) supported by chest X ray, echocardiography, electrocardiogram or cardiac enzymes where they were available

As such, a participant who was diagnosed to have virologically confirmed dengue and presented with clinical signs and symptoms compatible with any DHF grade (1 through 4) could be classified as having "severe" disease. The criteria used to assess the severity of virologically confirmed dengue cases was set by an Independent Data Monitoring Committee (IDMC) to ensure consistency in classification during the trial.

From the CYD 14 clinical trial which enrolled over 10,000 participants aged 2-14 years, results of the year 3 follow-up for safety showed that out of 6778 children vaccinated with the CYD-TDV vaccine, 27 were hospitalized for dengue, of which 11 were severe dengue as defined by the protocol. In contrast, among the 3387 children who were not vaccinated, 13 were hospitalized for dengue of which 1 was reported to be severe. Among those who were vaccinated and developed severe dengue, 8 were < 9 years of age and only 3 were ≥ 9 years of age. Although the dengue cases were not analyzed according to their baseline serostatus, none of the patients developed dengue shock syndrome nor died. [6]

HOW CAN SEROLOGIC STATUS BE RELIABLY DETERMINED?

Currently available rapid serologic tests are only intended to establish the diagnosis of dengue in a febrile patient. They have not been used to document prior exposure to dengue, and are limited by their moderate sensitivity (20.5-77.8%) and specificity (86.7-90.6%). [7]

In the re-analysis of their data, Sanofi utilized a new laboratory test --- an in-house anti-dengue NS1 assay --- to establish serologic status prior to vaccination, after these patients had already completed their 3-dose vaccination series. This test is not commercially available.

Since a reliable serologic test is not readily available locally, it is recommended that only children with documented prior dengue infection can be vaccinated after an informed discussion.

It is further recommended that rapid, accurate and readily available tests for seropositivity be developed to answer the need to establish serostatus prior to vaccination.

SHOULD PARTIALLY VACCINATED PATIENTS CONTINUE TO RECEIVE THE REMAINING DOSES?

For those without prior documented history of dengue infection, there is insufficient information to provide a definitive recommendation for those who have been partially immunized (defined as receipt of 1or 2 doses). It is not known whether the risk of disease is higher or lower in this group, compared to those who have received the complete series. Until more information becomes available, it is prudent to defer further doses.

In those who have documented past history of dengue infection or in those known to be seropositive for dengue, vaccination can be continued after an informed discussion. However, as the vaccine is currently suspended for marketing, sales and distribution, the series can be resumed once the new product label has been approved by PhilFDA.

WHAT CAN WE DO FOR PATIENTS WHO HAVE ALREADY RECEIVED THE VACCINE?

For patients with or without a prior history of dengue who have received any number of doses of the dengue vaccine, patient education should be strengthened together with efforts to encourage healthcare seeking behavior. Information on the risks and benefits of the vaccine, other interventions for prevention, the signs and symptoms of dengue, and the need for timely consult should be given so that adverse events, if any, can be managed and documented.

Any adverse event, including severe dengue that develops after vaccination should be reported simultaneously to PhilFDA and the manufacturer and should follow the procedures for reporting adverse events following any other vaccine (See Appendix A).

The management of vaccinated patients, should they develop disease, is similar to the current standard of care.

This announcement is also a reminder that dengue vaccination is only a part of a comprehensive dengue control strategy, which includes vector control measures, evidence-based best practices for clinical care for all patients with dengue illness, and strong dengue surveillance. [8]

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3. 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.
4. World Health Organization. Background paper on Dengue Vaccines prepared by SAGE working group on Dengue vaccines and WHO secretariat. Geneva, 17 March 2016; accessed from http://www.who.int/immunization/sage/meetings/2016/april/1_Background_Paper_Dengue_Vaccines_2016_03_17.pdf).

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6. Hadinegoro SR, Arredondo-García JL, Capeding MR, et al. For the CYD-TDV Dengue Vaccine Working Group. Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. N Engl J Med 2015; 373:1195-1206.
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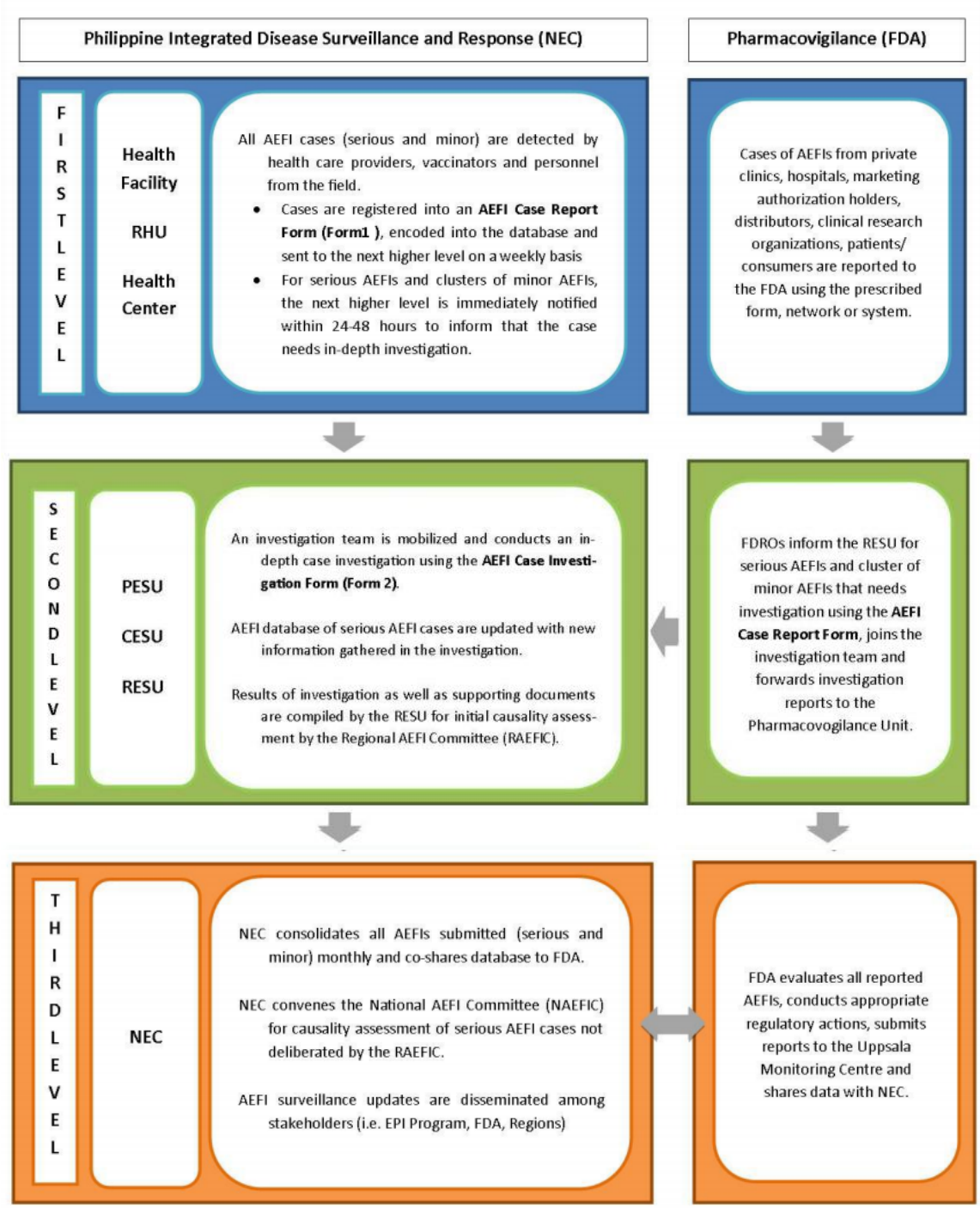
APPENDIX A. AEFI SURVEILLANCE FLOW



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