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The Safety of Dengvaxia and Should Hospitalization be an Outcome for its Clinical Trial?

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The uncertainties on the efficacy and safety of Dengvaxia continue to haunt doctors, parents, and lawmakers alike in the Philippines. After the mass immunization of about 850,000 children with Dengvaxia, there has been a continuing report of deaths, unofficially 29 to date among those who received the vaccine between 2016-2017.

Countries in the Asia Pacific region, including the Philippines, were one of the sites for the Dengvaxia Clinical Trial. In 2014, the Efficacy Trial of Dengvaxia covering the period after completion of the 3 doses up to the 28th day was published by Capeding, et al. An overall efficacy rate of 56.5% was reported but it can be misleading since the efficacy rates for each serotype varied widely. The secondary analyses showed low (35%) and inconclusive efficacy against serotype 2, which is considered as a weak point of Dengvaxia® and is still under research *(Sauer J, et al, 2018).* The Number Needed to Vaccinate (NNV), based on the results regardless of Dengue serotype of 117 Dengue cases out of 6848 in the Vaccine group and 133 Dengue cases in 3424 under the Placebo group, is about 46. It means 46 individuals have to be vaccinated in order to avert 1 case of Dengue *(Capeding, 2014).*However, NNV for Dengue type 2 is 322.5 which is almost double the numbers you have to vaccinate to prevent 1 case of Dengue. In contrast, the NNV for the trivalent Influenza Vaccine for community-dwelling seniors is 40 *(Kolber M 2014),* and 1031- 3050 for childhood influenza with an efficacy of 50% for ages 6-23 months *(Lewis EN, 2007).* Although NNV has been used to assess the cost effectiveness of several vaccines, a systematic review on NNV have shown no definite threshold for a favorable NNV *(Hashima, 2014).*

What is disturbing however, are the reports of 4 death by Capeding in the Vaccine Group giving the probability of 1 death out of 1712 versus none in the Placebo group. One of the deaths was due to acute disseminated encephalomyelitis which occurred 7 days after vaccine administration, indicating a strong temporal relationship with Dengvaxia administration. The rest of the deaths were due to injuries and were adjudged as not related to Dengvaxia. I feel it is too soon to discount the possibility of a relationship between these deaths with the vaccine. Many years back cases of vehicular accidents and falls especially among the elderlies were actually due to benzodiazepine use (Pariente, 2008) which at first glance may not be considered as plausible.

Unfortunately, the Efficacy and Long Term Safety Study of Dengvaxia® in endemic regions involving participants who completed the 3 -doses of Dengvaxia up to 25th month post immunization cast more doubts and concerns upon the safety and efficacy of the vaccine.

The results of CDY 14 which is the Dengvaxia Trial in the Asia Pacific Region revealed an increased incidence of hospitalization and severe dengue in the vaccine group especially among those seronegative prior to the Dengvaxia administration *(Hadinegoro 2015).*

Twenty seven cases of hospitalization for Dengue out of 6778 (39.83%) were reported in the vaccine group and only 13/3887 (33.44%) for the placebo group. We calculated a NNV of (-) 6896 for the overall group , the negative value changing the NNV instead to the Number Needed to Harm (NNH), meaning that out of 6896 children vaccinated with Dengvaxia, 1 will be hospitalized. This negative NNV(-502), persisted for those belonging under age groups less than 9 years of age and more than 9 years old close to the 3rd year post immunization. Unlike NNT which is favorable if it carries a low value , a high NNH is more ideal.

Why use hospitalization to measure outcome? Paradoxically, vaccine trials target healthy individuals and are meant to prevent illnesses, not to treat an existing disease. If drug regulation has not changed, hospitalizations, like deaths, disability, and congenital anomalies, are considered severe adverse events and is a warning signal about the safety of the product being studied.

Perhaps, since Dengvaxia® does not confer cross-protection for other strains of Dengue, Sanofi had expected from the onset the higher possibility of a second dengue episode in endemic settings. The second episode will likely be more severe and naturally fatal based on the proposed mechanism of Sacket known as Antibody Dependent Enhancement phenomenon first described after the Dengue epidemic in Thailand and the Philippines. Clinically, the best Dengue vaccine is one that protects the child not only from a first infection but also attenuates or minimizes the severity of a second episode of Dengue which disappointingly Dengvaxia failed to demonstrate. Despite being endemic to the Philippines, there was very little protection given by Dengvaxia as a whole to children 9 years and older during which time seropositivity should be higher in a dengue endemic country.

Was it worth spending 3.5 billions for the Dengue vaccine, a cost which is equivalent to the entire dengue control program of the country? Dengue has killed 25,000 worldwide which is only 2.5% of the 500,000 reported cases of severe Dengue (WHO Fact Sheet updated 2017). These statistics are not remarkable compared to the 500,000 deaths worldwide from Influenza . Moreover, only 25% of Dengue is symptomatic while 75% are subclinical or resolves spontaneously without catastrophic outcomes. The case fatality rate is likewise low at 0.44% among those with symptomatic dengue infections.

Is the vaccine safe? Even the old vaccines such as MMR are known to be associated with some severe adverse reactions. For example, after decades of MMR use by 1.8 Million people and 3 million doses, the incidence of probable or indeterminate adverse events of MMR was calculated to be 5.3 /100,000 *(Patja 2012).* Only 1 death was recorded due to febrile seizure from MMR. In contrast, Dengvaxia with only 6851 exposed population already showed 4 deaths and higher risk for hospitalization by the third year post immunization.

The number of deaths and autopsy findings described by the forensic expert in the Public Attorney's Office as rapid and characterized by massive bleeding as well as enlargement of almost all internal organs are warning signals to not only provide intervention but also follow-up this cohort of Dengvaxia vaccinees to determine future adverse events. Presently, there is no room for Dengvaxia in the Philippines or perhaps anywhere else where the course of Dengue infection is similar to the country.

Logically, if we can set up a program that can screen the etiology of fever in a child at the community level and sift out the Dengue cases for confirmation and be able to administer timely, appropriate and aggressive management, the deaths averted will be significant. Children affected with dengue in the Philippines die because of late detection ergo late or no interventions. The vector mosquito is abundant and all serotypes of dengue are present in the Philippines. With the number of deaths reported after the mass immunization, I personally think there is no advantage for the vaccine over a sustained and reliable vector control coupled with early detection of Dengue infections.

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