



# Why the change in label?

**Bad Science → Bad Policy**

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## DENGVAXIA™ NIGHTMARE

People clamor:

**DID ANYONE REALLY CARE ABOUT  
PEOPLE'S HEALTH?**

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# Dengvaxia

- 🌐 A new innovator/novel vaccine – a recombinant, live, attenuated, tetravalent Dengue vaccine (CYD-TDV)
- 🌐 Made out of a combination of yellow fever and dengue fever but in weakened form
- 🌐 In 5,000 vaccinated people, 17-18 dengue cases may be prevented
- 🌐 Adverse events after immunization, may include four: serious allergic reaction, viscerotropism/neurotropism, waning effectiveness, and enhanced dengue symptoms



**Why there was a need for  
Sanofi to change its label?**

## Sanofi updates information on dengue vaccine

- \* New analysis of long-term Dengvaxia® data found differences in vaccine performance based on prior dengue infection
- \* Company will ask regulators to update product label to reflect new information

**PARIS, FRANCE – November 29, 2017** – Sanofi will ask health authorities to update information provided to physicians and patients on its dengue vaccine Dengvaxia® in countries where it is approved. The request is based on a new analysis of long-term clinical trial data, which found differences in vaccine performance based on prior dengue infection.

Based on up to six years of clinical data, the new analysis evaluated long-term safety and efficacy of Dengvaxia in people who had been infected with dengue prior to vaccination and those who had not. The analysis confirmed that Dengvaxia provides persistent protective benefit against dengue fever in those who had prior infection. **For those not previously infected by dengue virus, however, the analysis found that in the longer term, more cases of severe disease could occur following vaccination upon a subsequent dengue infection.**

## Proposed Label Update

Based on the new analysis, Sanofi will propose that national regulatory agencies update the prescribing information, known as the label in many countries, requesting that healthcare professionals assess the likelihood of prior dengue infection in an individual before vaccinating. Vaccination should only be recommended when the potential benefits outweigh the potential risks (in countries with high burden of dengue disease). For individuals who have not been previously infected by dengue virus, vaccination should not be recommended.

# Review of a licensed dengue vaccine: Inappropriate subgroup analyses and selective reporting may cause harm in vaccination programs by Dans, et.al. (JCE)

[http://www.jclinepi.com/arti.../S0895-4356\(17\)30972-1/fulltext](http://www.jclinepi.com/arti.../S0895-4356(17)30972-1/fulltext)

The review considered the Asian Dengvaxia study as bad science (errors in the design, analysis, and interpretation of scientific studies). Why?

1. Sanofi claimed absolute safety prematurely (in children aged 9 or more) after only 3 years of follow-up, when they committed to 6 years (when evidence of harm begin to manifest) follow-up study.
  - The dengue mass vaccination program and the Phase 3 (A-B) Clinical Trials being done by Dra. Capeding (RITM) funded by Sanofi were both ongoing at the same time, thus, led to confusion.

2. Even on the 3rd year of follow-up, there was evidence that it might be unsafe to vaccinate children who had no signs of past dengue infection due to anti-body dependent enhancement. These signals were hidden within the study of Sanofi because of inappropriate analyses and selective reporting, where debates among the scientific/medical community arose.

Debatables:

- a) New data or old data?
- b) Anti-body dependent enhancement (ADE), theory by Dr. Scott Halstead

# Other issues on the science

- 🌐 Baseline risk was low.
- 🌐 Sample population in the clinical trial was 31,000 but the government decided to inoculate 800,000 school-age children.
- 🌐 Not an age issue but rather an issue of serotype (seropositive and seronegative).
- 🌐 Extended study should be done for the dengue vaccine as per WHO Technical Guidelines

# **Impact of Sanofi's Announcement**

# Impact

- 🌐 It created confusion, particularly on the definition of 'severe dengue'
- 🌐 'Severe Dengue' Sanofi's Protocol Definition
  1. Platelet count  $\leq 100 \times 10^9/L$ , bleeding and plasma leakage (effusion or ascites or HCT  $> 20\%$ )
  2. Shock
  3. Bleeding requiring blood transfusion
  4. Encephalopathy or convulsions or focal neuro signs
  5. Liver impairment (AST  $> 1,000$  u/L or protime  $> 1.5$ )
  6. Impaired kidney function (Creat  $\geq 1.5$  mg/dL)
  7. Myocarditis, pericarditis or heart failure

# Other classification, 1997 (milder to severe)

-  DHF 1 Tourniquet, easy bruising
-  DHF 2 Bleeding from nose and gums
-  DHF 3 Low blood pressure
-  DHF 4 Profound shock

# Impact

- 🌐 After a week, Sanofi seemed to downplay its announcement and claimed that Dengvaxia did not cause ‘severe dengue’ in the sense used by WHO, whose definition includes only patients who develop shock, impaired consciousness, severe bleeding, heart, lung or liver failure.
- 🌐 Sanofi’s trial used ‘hospitalization’ as its marker, with most of the patients admitted due to minor bleeding. No deaths were reported in the study.

# Impact

- 🌐 Due to confusion and alarm, parents and their children were now worried, hysterical and panicky; grew anxious about the plight of their children.
- 🌐 Undue burden in the health system because of the authorities' chose to ignore the safety/warning signs, thus, delayed and inappropriate action.

# Implication for the vaccination program

- 🌐 People's loss of trust and confidence in the vaccination program, other healthcare services and the entire DoH.
- 🌐 Opportunity to redeem and rectify the situation with good science (this time); the world is looking at the Philippines on how the investigation and panel of experts' studies will turn out. (Dr. Aguilar, UP-PGH)

# Implication for the vaccination program

- 🌐 Science has been compromised, however, this can also be an opportunity for people to learn to appreciate, while at the same time question science.
- 🌐 Opens a platform to discuss the science between the experts and the people.
- 🌐 Opportunity to revisit processes and protocols in deciding and assessing science.

**Thank You!**