

WHAT HAPPENED IN THE PHILIPPINES WITH THE DENGUE VACCINE?

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- Received speaker's honorarium and/or consultation fees from:
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OBJECTIVES

- To discuss the circumstances surrounding the controversial launch of the Dengvaxia mass vaccination in the Philippines
- To understand the consequences of poor science communication regarding Dengvaxia on the public and the national vaccination program.

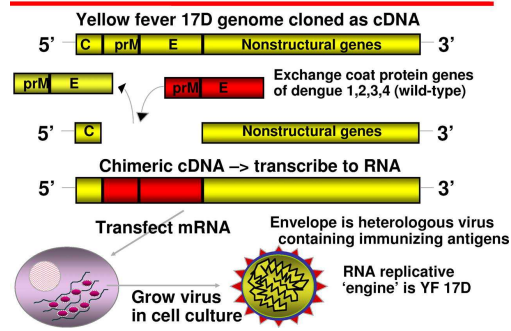
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DENGUE VACCINE

- Only currently approved vaccine is Sanofi CYD-TDV
- CYD-TDV: Chimeric Yellow Fever Dengue – Tetravalent Dengue Vaccine

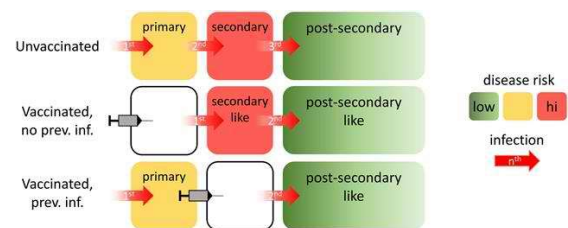
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ChimeriVax Technology



Plotkin. 2009 Clinical and Vaccine Immunology

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Flasche et al., 2018

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THE BEGINNING

- DOH announces mass vaccination program for dengue in 2016 (an election year)
- Justification is high rates of dengue (170k cases/year; 700 deaths)
- Philippines: 100M people, all dengue serotypes present

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HEALTH
Philippines launches world's first mass vaccination for dengue fever

It's a big step toward controlling the potentially fatal disease.

By **Megha Charlan**
APRIL 5, 2016

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2016, 95, 502-504
World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

Meeting of the Strategic Advisory Group of Experts on immunization, April 2016 - conclusions and recommendations

The Strategic Advisory Group of Experts (SAGE) on immunization met on 12-14 April 2016. This report summarizes the discussions, conclusions and recommendations.

SAGE reviewed the evidence generated from 2 large Phase 3 clinical trials, one conducted in 2-14 year-olds in 5 countries in Asia, the other in 9-16 year-olds in 3 countries in Latin America. Vaccine efficacy over 25 months from the first dose among 9-16 year-olds, using data pooled from both trials, was 65.6% (95% CI 60.7-69.9). The sub-group benefit profile is complete vaccine efficacy varied by infecting serotype (higher protection against serotypes DENV 3 and 4 than DENV 1 and 2), age (higher protection in older children), and disease severity (higher protection against hospitalized and severe dengue), and notably serostatus at the time of vaccination (higher protection in participants who had already been exposed to dengue virus). Some level of protection was seen even after the first dose. In those children vaccinated at ages 2-5 years in Asia, a statistically significant increased risk of hospitalized dengue was seen in vaccine recipients in the third year after the first dose, though this disappeared in years 4 and 5. The biologic mechanism behind this increased risk is currently not understood but may be related to naive vaccine serostatus and/or age. A significant increase in hospitalizations was not seen in those older than 5 years. No other safety signal has been identified.

SAGE recommended that countries consider introduction of CYD-TDV only in geographic settings (national or subnational) with high endemicity, as indicated by seroprevalence of approximately 70% or greater in the age group targeted for vaccination or other suitable epidemiologic markers. The vaccine is not recommended where seroprevalence is below 50%. Dengue vaccine introduction should be a part of a comprehensive dengue control strategy together with a communication strategy, well-executed and sustained vector control, the best evidence-based clinical care for all patients with dengue, and robust dengue surveillance.

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The risks behind Dengvaxia recommendation

Maíra Aguiar · Nico Stollenwerk · Scott B Halstead

Published: August, 2016 · DOI: [https://doi.org/10.1016/S1473-3099\(16\)30168-2](https://doi.org/10.1016/S1473-3099(16)30168-2)

References Article Info

Nearly 4 billion people are at risk of dengue and around 400 million infections are estimated to occur every year worldwide.^{1, 2} Because four antigenically related but distinct serotypes cause severe and fatal outcomes, a tetravalent vaccine is needed to protect against the huge burden of dengue disease. Developed by Sanofi Pasteur, Dengvaxia is the vaccine candidate at the most advanced clinical stage. Results from years 1-2 of phase 3 trials of Dengvaxia

Recommend to your list

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THE STRAITS TIMES

ASIA

PHILIPPINES

Philippines rolls out world's first dengue vaccine

Dr Antonio Dans, a professor at UP's College of Medicine, warned that while the vaccine could reduce the number of dengue cases, it could later increase the disease's severity, a phenomenon known as "antibody-dependent enhancement".

Citing Sanofi's own studies, he said this could happen three years after the vaccine's introduction.

"The real dengue we are afraid of is severe dengue, not the mild ones. If a vaccine prevents mild disease but causes severe dengue, we shouldn't be using it at all."

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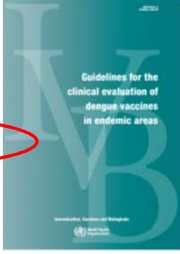
MAJOR ISSUES RAISED (DANS, HALSTEAD, AGUIAR ETC.)

- Safety signal already there among seronegatives – serotesting proposed
- Phase 3 technically not finished (Phase IIIa and Phase IIIb) – only Year 3 of safety analysis at time of approval
- Post-hoc analysis of 9-year old cutoff
- Is it ethical to continue control group even when efficacy has been demonstrated?

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A suggested schedule to monitor the safety of a dengue vaccine includes the following.

- Pre-licensure short term, Phases 1 to 3: Monitoring days 1–21 of clinical reactions after vaccination and wild dengue exposures in endemic country trial sites.
- Pre-licensure long term, Phases 2 and 3: Monitoring of SAEs for six months or more after the last vaccination, and the relative risk of dengue disease versus unvaccinated controls for five years in all vaccinees in endemic areas. **A Phase 3 trial can be stopped after one year to assess efficacy, and then be continued for 2–4 more years to assess elements of long-term safety, even beyond licensure. The safety monitoring plan is an important component of the clinical protocol and must be finalized before starting the Phase 3 trial.**
- Post licensure: The safety schedule should be designed to extend the certainty of conclusions drawn from the dataset or to identify safety signals related to rare events. The schedule includes extended follow-up of the participants enrolled in Phase 3 and Phase 4 trials, as well as national/regional epidemiological surveillance for presumptive dengue after licensure.



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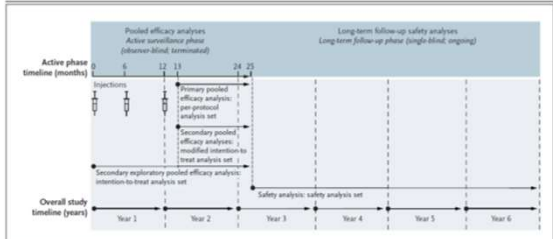
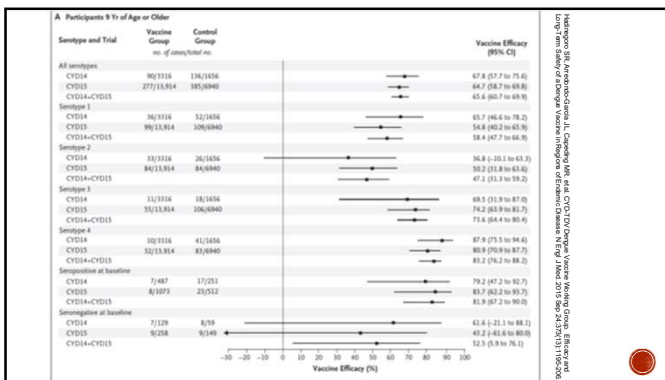


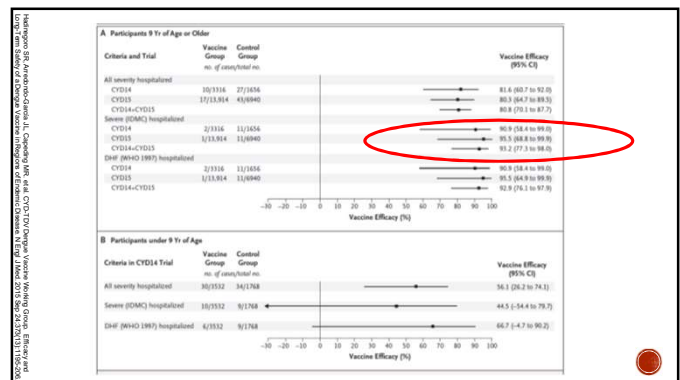
Figure 1. Overview of the Surveillance Phase and Long-Term Follow-up Phase of the CYD-TDV Candidate Vaccine Trials. CYD-TDV is a candidate recombinant, live, attenuated, tetravalent dengue vaccine that has been assessed in two phase 3 randomized efficacy studies (called CYD14 and CYD15) involving a total of more than 31,000 participants between the ages of 2 and 16 years in Asian-Pacific and Latin American countries. In addition, 3203 of 4002 participants (80%) who were between the ages of 4 and 11 at initial enrollment in the phase 3b-CYD15 trial in Thailand are being followed in the CYD17 trial. The trials had similar designs. According to the study designs, the long-term follow-up phase will continue for a total of 6 years after enrollment.

Hadjigeron SR, Amedondo-Garcia JL, Capeding MR, et al. CYD-TDV Dengue Vaccine Working Group. *Estimating Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease.* *N Engl J Med.* 2015; Sep 24;373(13):1196-206

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AFTERMATH


- Proceeded with mass vaccination program
- Administration candidate lost
- New administration (Duterte) continued program, total vaccinated about 830,000 (some estimates lower or higher)

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AND THEN:

- A **NEW** analysis using stored sera found loss of effectiveness and increased risk of severe dengue (WHO 1997 criteria) in seronegatives.
- STILL** effective in seropositives
- Sanofi released this information November 2017 **WITHOUT RELEASING ACTUAL DATA ON RISK**

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SANOFI  **Press Release**
 Source: Sanofi (EURONEXT: SAN) (NYSE: SNY)

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.

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 **Antonio Dans** is 😞 feeling sad with Tony Leachon and 24 others.
 November 30, 2017 · 🌐

Read this news alert from Sanofi. 📰

Our heart bleeds for more than 600,000 Filipino children who received dengue vaccine without assessment for prior infection. Sanofi, WHO, DOH - what happens to them now???

MEDIAROOM.SANOFI.COM
Sanofi updates information on dengue vaccine | Sanofi
 New analysis of long-term Dengvaxia® data found differences in vaccine performance based on prior dengue infection Company will ask regulators to...

👍👎🗨️ 487 311 Comments 1.1K Shares

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WHAT HAPPENED NEXT?

- Dr. Antonio Dans' social media post goes viral, picked up by media and the Public Attorney's Office
- Result: widespread panic (at least in the Philippines)
- Mass vaccination suspended
- Vaccine CPR suspended (noncompliance of PMS – Sanofi disputes)

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SECTIONS Thursday, April 26, 2018 INQUIRER.NET TODAY'S PAPER 🔍

VACC: Controversial anti-dengue program is worse than any heinous crime

By: **Jesset O. Emano - Reporter** / @jessetEmanoINQ @Inquirer Daily Inquirer / 12:49 PM December 02, 2017




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PNOY'S DENGAXIA, A Ticking Time Bomb, possible GENOCIDE?

BY: ARCHLIGHT MEDIA / ON: DECEMBER 3, 2017 / IN: BREAKING NEWS, PH, POPULAR / WITH: 0 COMMENTS

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FINALLY, (BELATEDLY), FACTS:

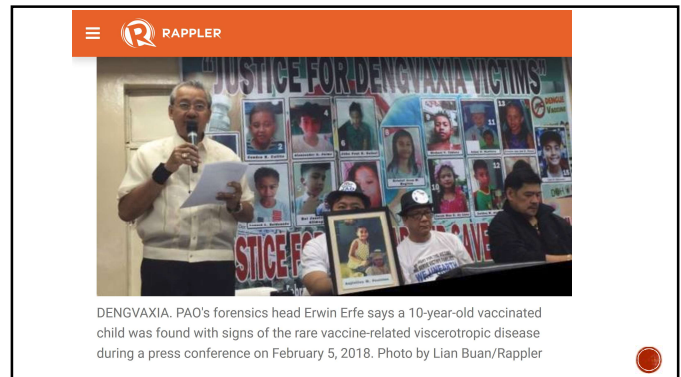
- Risk of severe dengue in seronegatives increases by 2/1000; from 2/1000 to 4/1000
- Almost **same as risk of unvaccinated seropositive:** 4.8/1000
- Risk of severe dengue in seropositive decreases by 4/1000; from 4.8/1000 to less than 1/1000
- **No DEATHS in cohort of 35,000 patients from phase 3's**

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BY THEN, IT WAS **TOO LATE**

- Dense explanations of risk did little to assuage the panic
- Political vendettas started to come out
- Autopsies done by non-pathologist – suggested “enlarged organs” forming a pattern of alleged “viscerotropism”

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DENGVAXIA. PAO's forensics head Erwin Erfe says a 10-year-old vaccinated child was found with signs of the rare vaccine-related viscerotropic disease during a press conference on February 5, 2018. Photo by Lian Buan/Rappler

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WHAT IS VISCEROTROPISM?

- Known side effect of Yellow Fever Vaccine 17D (>500 million doses given)
- Extremely rare, 1 in 250,000 YF vaccine doses
- 50% mortality
- Usually occurs within 2 to 5 days of vaccination
- Recovery of virus (PCR, culture, tissue staining for antigen) from tissues makes the diagnosis

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CAN CYD-TDV CAUSE VISCEROTROPISM?

- Theoretical risk since it is from a YF backbone
- However, no virulence genes present (replaced with DENV)
- Possibly reversion if mixed with YF (not present in the Philippines)
- No cases in Phase I, II, III trials – no deaths in any of these either
- Short answer:



“BALONEY”

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SO WHAT KILLED THESE KIDS?

▪ **NOT viscerotropism**

- Natural causes – expect 400 deaths in this cohort by National Census mortality data per year
- Other causes found in most deaths by PGH Panel which included a FORENSIC PATHOLOGIST – including lupus, appendicitis, sepsis
- Vaccine failure – even in seropositives, some may still die of dengue since it does not prevent 100% of severe dengue – PGH panel also pointed this out

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WHAT TO EXPECT WITH THE COHORT

- If we do calculations based on limited data, this is the overall public health effect:

833,000 recipients (>9 years old)

80% seropositive: $666,400 \times (4/1000 \text{ decrease in severe dengue}) = 2,666 \text{ LESS cases of severe dengue}$

20% seronegative: $166,600 \times (2/1000 \text{ increase in severe dengue}) = 333 \text{ MORE cases of severe dengue}$

OVERALL EFFECT: 2,333 LESS cases of severe dengue

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ANALYSIS: THE GOOD, THE BAD AND THE UGLY

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THE "GOOD"

- Dengue vaccine framework needs to be more robust
- Safety signals are real, especially with seronegatives – need serotesting
- Mass vaccination premature - stopped
- Aguiar, Halstead, Dans were right in flagging concerns

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THE "BAD"

- Poor risk communication by Sanofi and WHO
- Poor science communication in social media and mainstream media
- DOH caught in a conflict of interest, affected other vaccination programs – FDA under DOH
- Removal from market of a useful vaccine for a specific population (seropositives)

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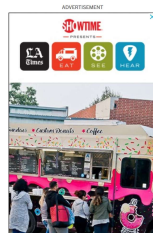
Los Angeles Times

WORLD & NATION

Philippine measles outbreak fed by distrust of vaccines – rooted in vaccination scandal



A Philippine Red Cross worker administers a measles vaccine in Manila. (Neal Cole / AFP/Getty Images)

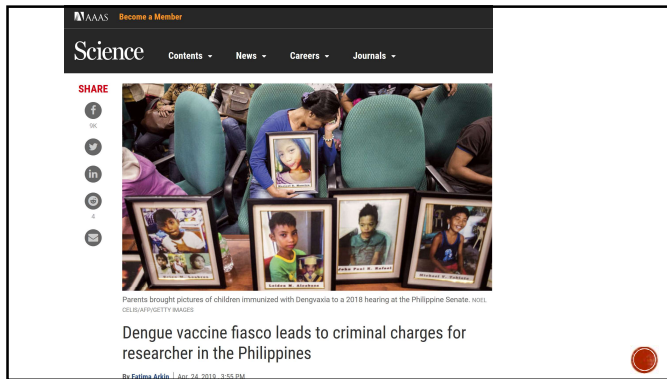


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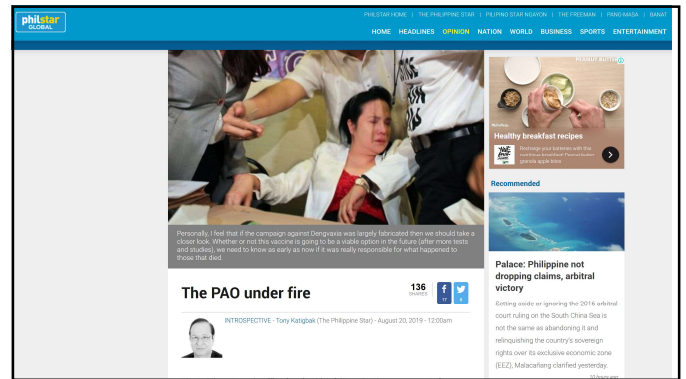
THE "UGLY"

- Possible use of mass vaccination program as a campaign tool is unconscionable
- Deliberate implication of theoretical severe side effects (some by MDs) is unacceptable
- Manufacture of autopsy results is criminal
- Politicians with vendettas attacking scientists in Congress and grandstanding

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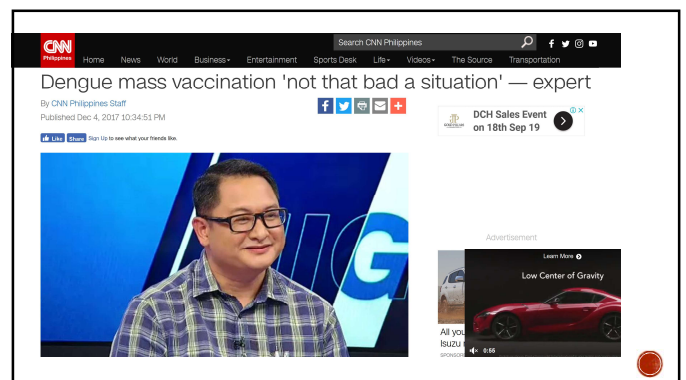


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FIGHTING BACK

- Scientists/Physicians/Vaccinologists need to engage in mainstream media and social media
- Highlight benefits of vaccines, not just combat perceived risk
- Stand up for science

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RAPPLER

PHILIPPINES

'Panic' over Dengvaxia harms other vital vaccination programs, health experts say

58 doctors & experts, in a statement, slam the 'unsubstantiated' claims being made against Dengvaxia and DOH officials that is causing parents to slowly lose faith in other government health programs

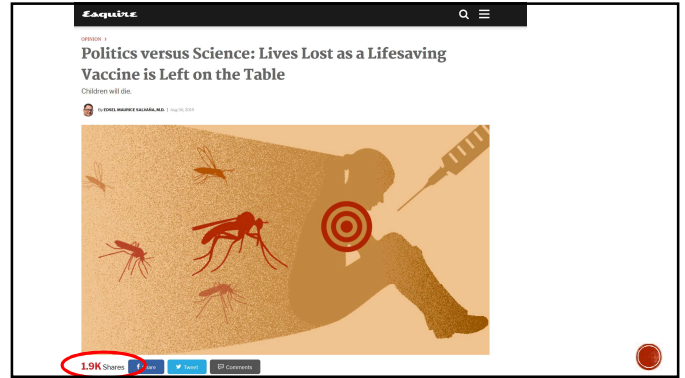
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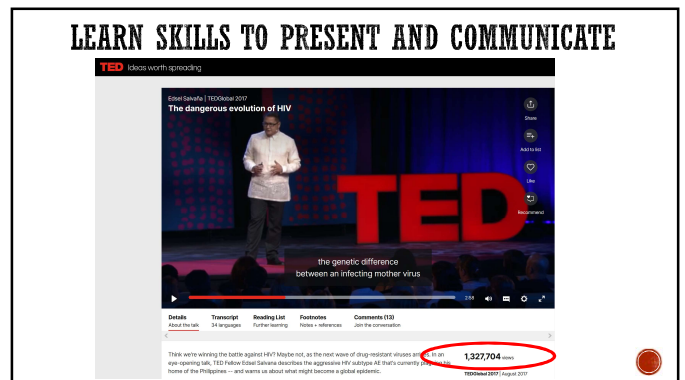
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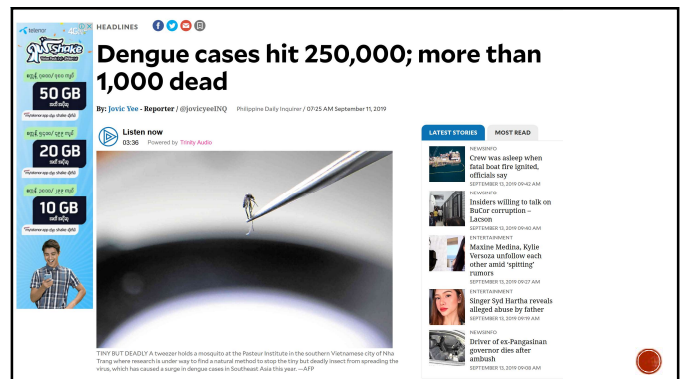
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IS DENGVAXIA STILL USEFUL?

- Yes, especially for seropositives – 93% decreased risk of severe dengue
- Need to develop reliable test that can diagnose prior dengue infection – only 1 out of 4 dengue infections are symptomatic – ongoing
- We tried to get funding for anti-NS1 testing for mass vaccination cohort – parents rejected it since they were convinced vaccine was harmful regardless of serostatus



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SUMMARY

- Philippine Dengvaxia Fiasco was politically tainted, fueled by science miscommunication AND pseudoscientific propaganda causing widespread panic
- Vaccine programs HAVE BEEN hurt by the panic, and political agendas plus lousy media interpretations of science CONTINUE to confuse the issue
- Doctors need to ENGAGE, and be reliable sources of information
- Vaccines remain one of the most important public health inventions of all time, we must FIGHT BACK to preserve VACCINE TRUST



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THANK YOU!



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