WHAT HAPPENED IN THE PHILIPPINES WITH THE DENGUE VACCINE?

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DISCLOSURES AND DISCLAIMER

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

  Mundipharma, Merck (MSD), Cathay Drug Company, Abbott Diagnostics, Biomerieux, Westmont, Unilab, Cepheid, Macare, BSV, Astellas, Philcare Pharma
- The opinions expressed in this talk are the speaker's personal opinions and do not necessarily reflect the stand of UP Manila or any of the speaker's affiliated institutions

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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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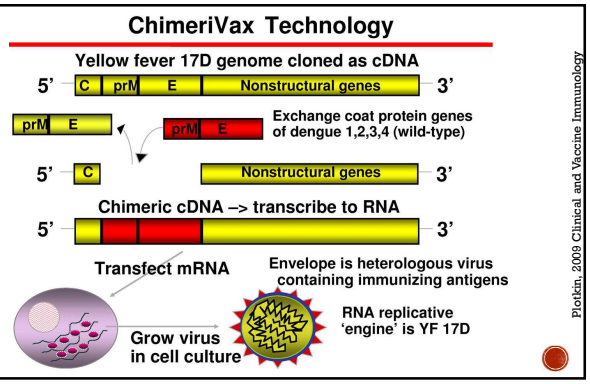

Plotkin, 2009 Clinical and Vaccine Immunology

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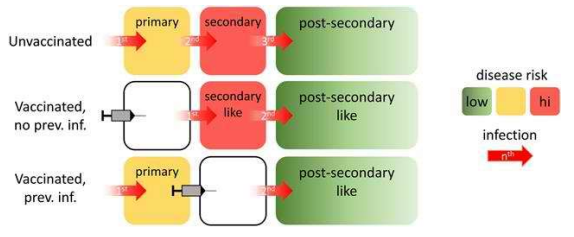

Flasche et al., 2016

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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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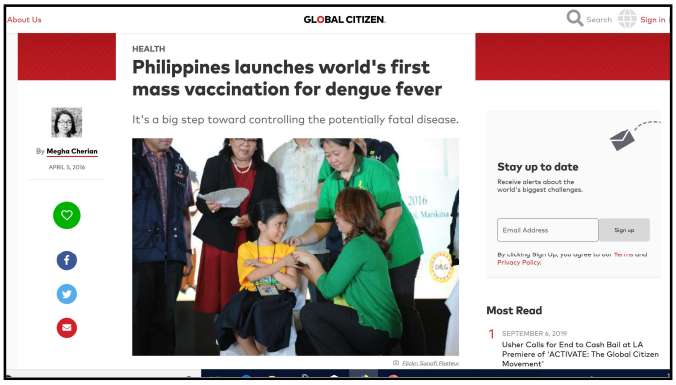

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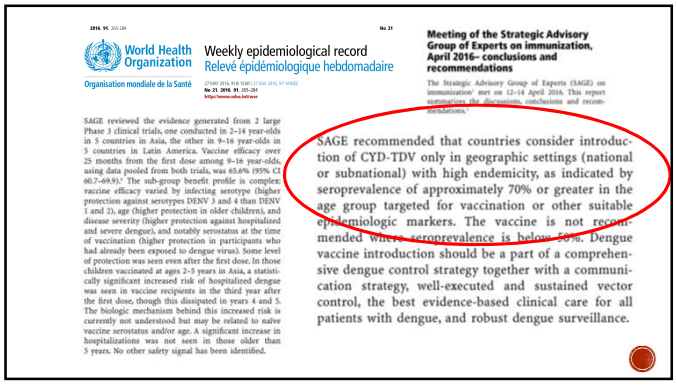

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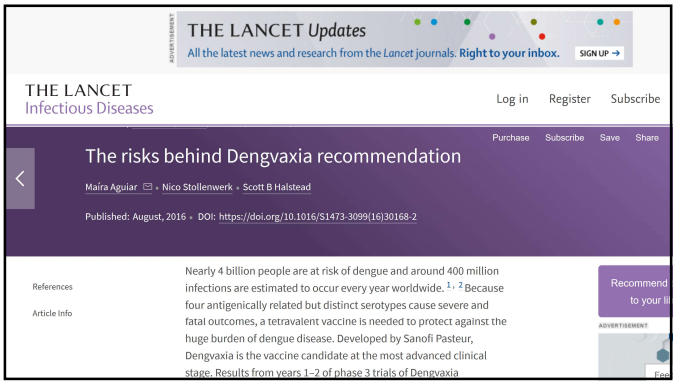

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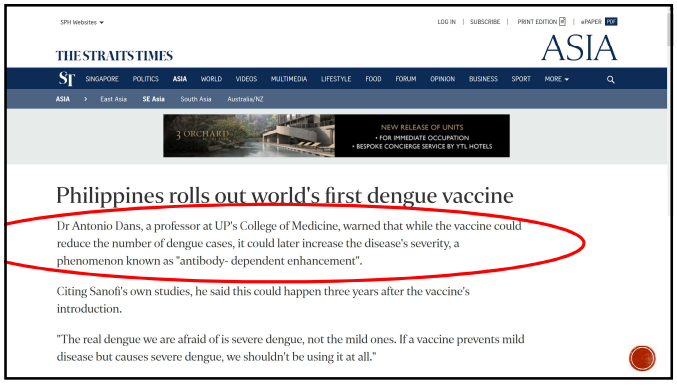

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MAJOR ISSUES RAISED (DANS, HALSTEAD, AGUIAR ETC.)

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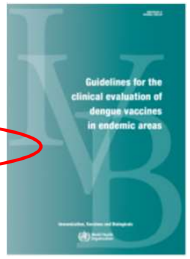
A suggested schedule to monitor the safety of a dengue vaccine includes the following.

- **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 control for three to five years in all vaccinees in endemic trial sites. 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 trials.
- **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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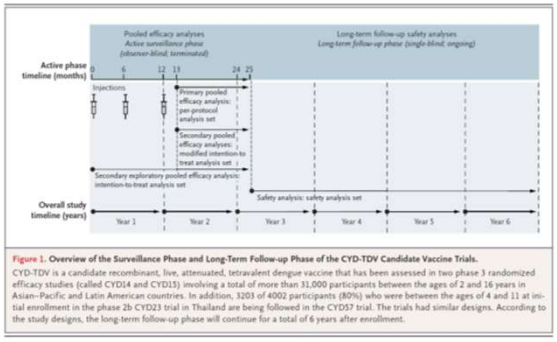

Figure 1. Overview of the Surveillance Phase and Long-Term Follow-up Phase of the CYD-TDV Candidate Vaccine Trials.

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 2b CYD23 trial in Thailand are being followed in the CYD57 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.

Hadinegoro SR, Arredondo-García JL, Capeding MR, et al. 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 Sep 24;373(13):1195-206.

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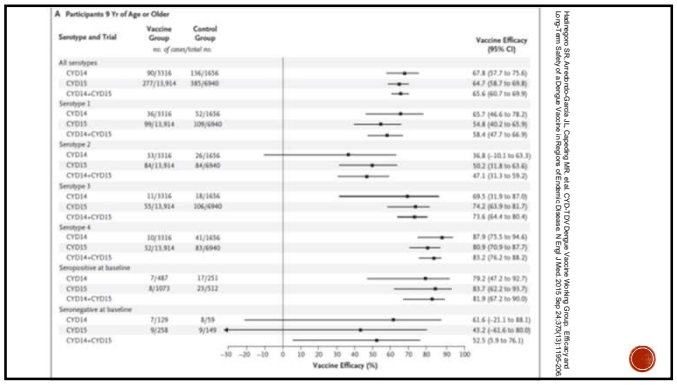

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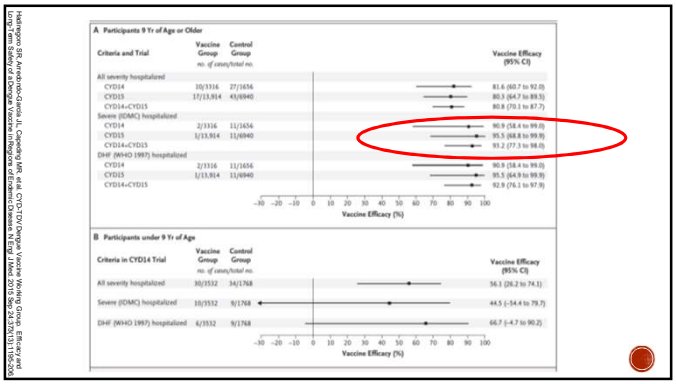

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AFTERMATH

- 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 infectionCompany 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

NATION 3,346 SHARES

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

By: Jhesset O. Enano - Reporter / @JhessetEnanoINQ Philippine Daily Inquirer / 12:49 PM December 02, 2017

Volunteers Against Crime and Corruption founding chair Dante Jimenez. INQUIRER FILE PHOTO

LATEST STORIES MOST READ

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PNOY's DENGVAXIA, 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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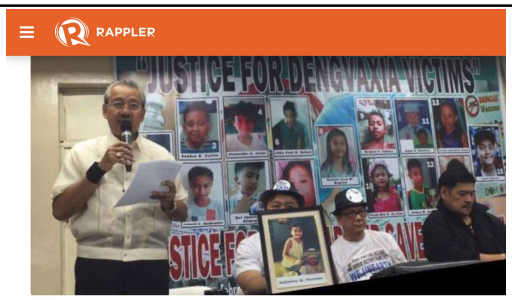

DENGVAXIA. PAO's forensics head Erwin Erfe says a 10-year-old vaccinated child was found with signs of the rare vaccine-related viscerotropic disease during a press conference on February 5, 2018. Photo by Lian Buan/Rappler

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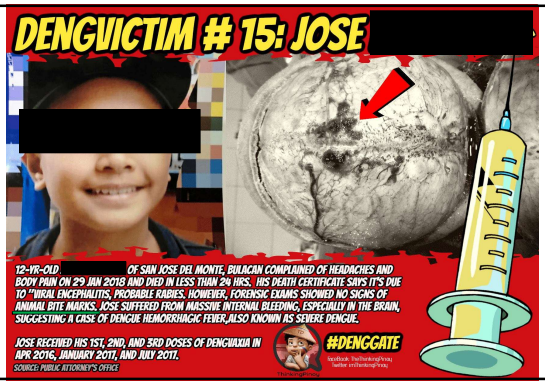

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WHAT IS VISCEROTROPISM?

- 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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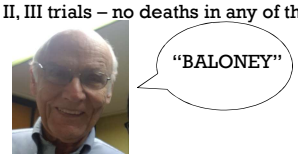
CAN CYD-TDV CAUSE VISCEROTROPISM?

- 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:



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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 x (4/1000 decrease in severe dengue) = 2,666 LESS cases of severe dengue
  - 20% seronegative: 166,600 x (2/1000 increase in severe dengue) = 333 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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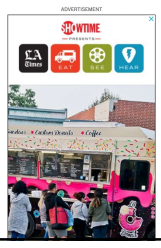
Los Angeles Times

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. (Noel Celis / 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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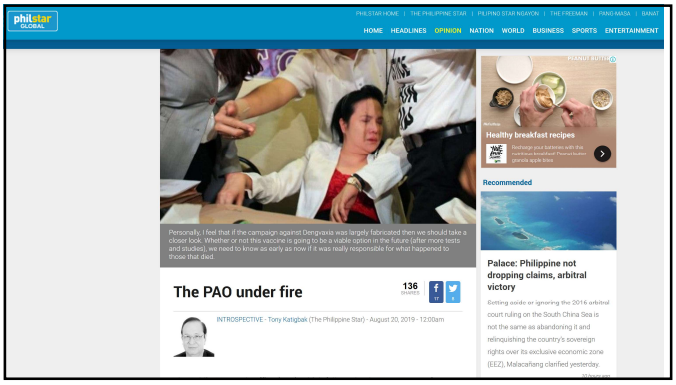

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FIGHTING BACK

- 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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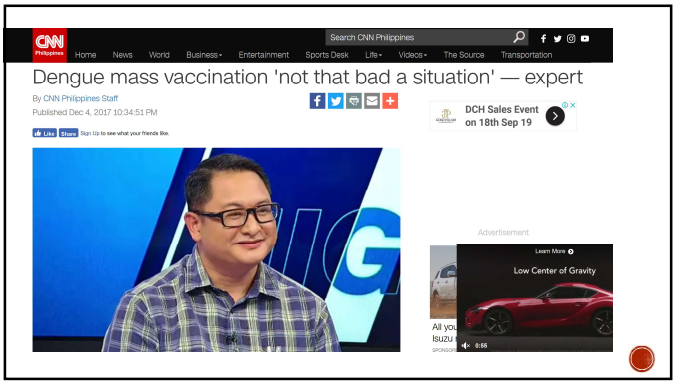

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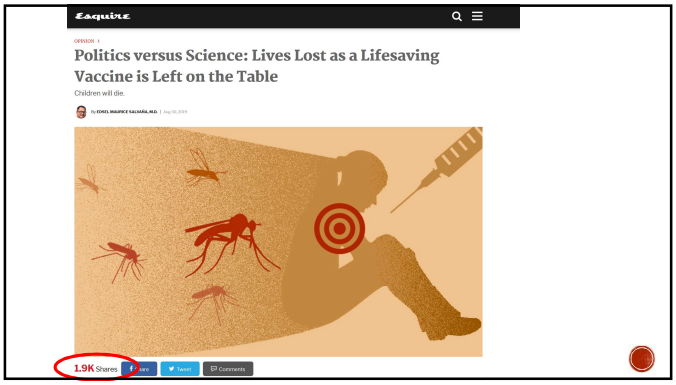

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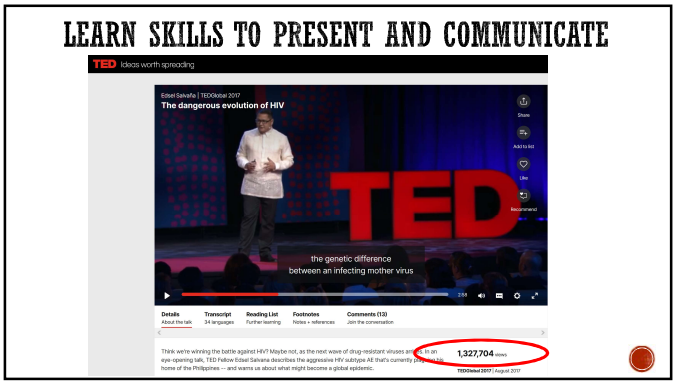

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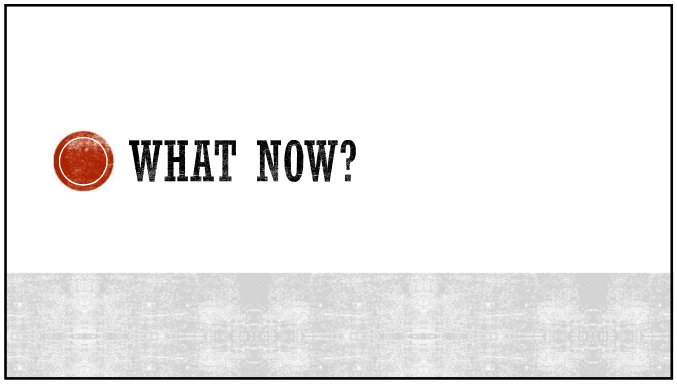

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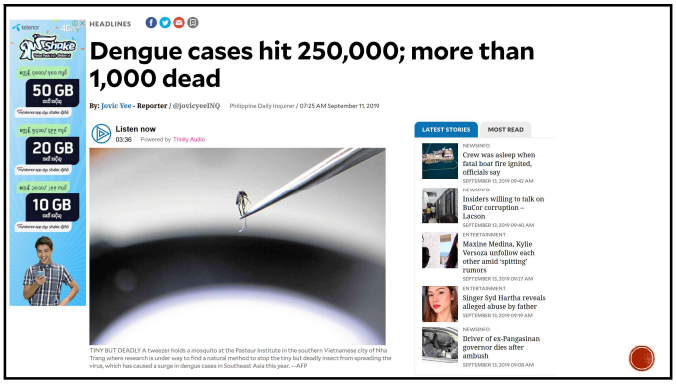

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IS DENGVAXIA STILL USEFUL?

- 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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