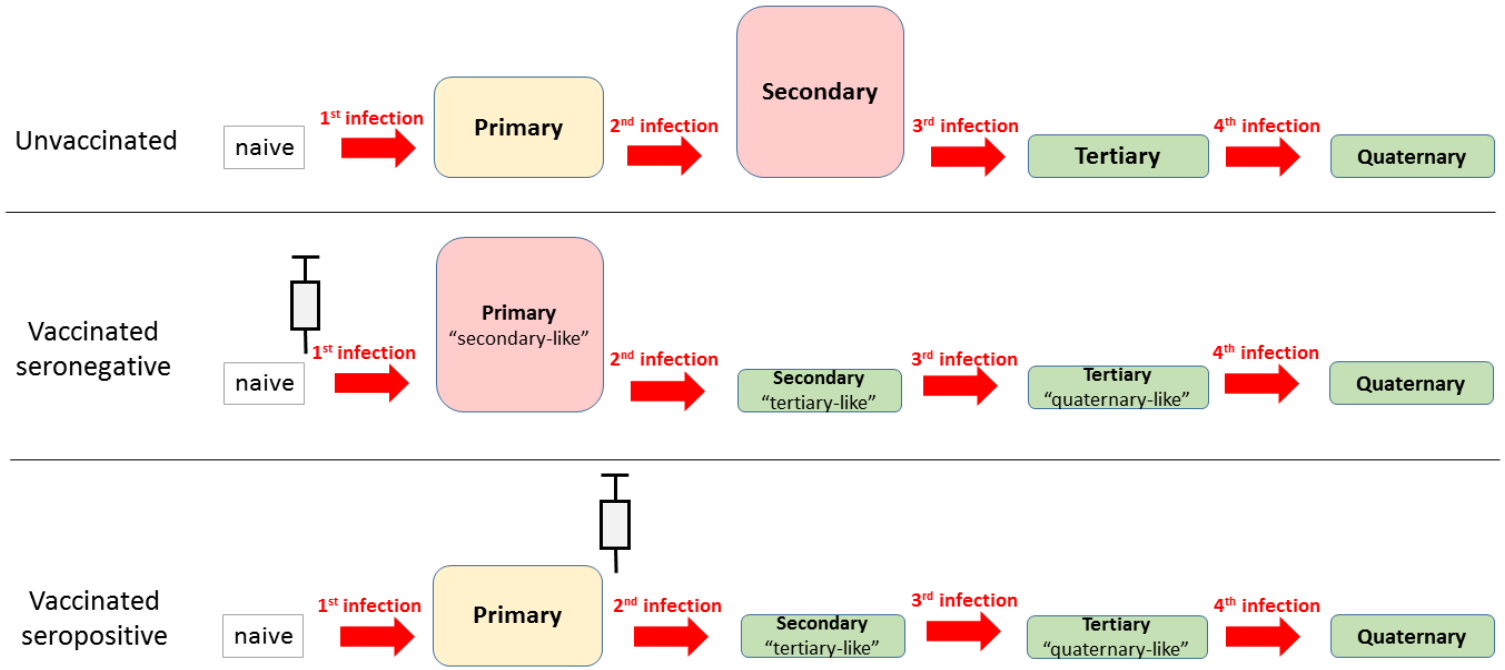
Dengue vaccine safety guidelines

Explanatory hypothesis for breakthrough infections

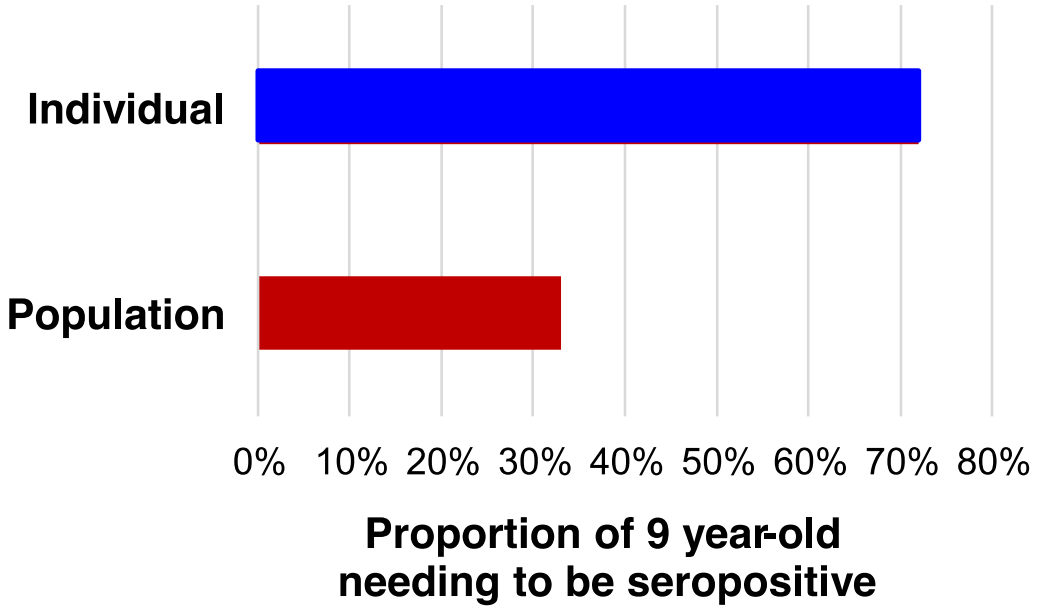
- Vaccination primes the immune system similarly to infection:
  1. Temporary high degree of cross-immunity in at least seronegative recipients
  2. Seronegative recipients have secondary-like breakthrough infection once cross-immunity wanes
  3. Seropositive recipients have tertiary-like breakthrough infection once cross-immunity wane
- In high transmission intensity settings, even seronegative recipients gain eventual benefit
- Mathematical models adopting these assumptions fit the original trial data well



Ferguson et al., Science 2016; Flasche et al., PLoS Med. 2016

Original modelling

Long-term impact of vaccination in seronegatives depends on transmission setting



- Minimum proportion of target age group that needs to be seropositive for vaccination to give:
  - Individual benefit (blue)
  - Population benefit (red)
- ***Evaluated over 30 years***
- Original SAGE guidance recommended that vaccine used if seroprevalence in recipients >70%, and not used if <50%

Ferguson et al., Science 2016

Benefits and Harm

Population seroprevalence without individual screening

BENEFIT
Overall substantial population benefit in areas with high seroprevalence predicted.

HARM
An identifiable subset of the population will be put at increased risk of severe dengue, at least in the short to medium term.

Pre-vaccination individual screening

BENEFIT
Maximizing the benefit (high efficacy and good safety) in seropositive while avoiding harm in correctly identified seronegatives.

HARM
Some seronegative individuals will be put at increased risk of severe dengue if vaccinated due to a false positive screening test result.

The trolley problem

Follow up for safety was continuing……

Vaccine safety and efficacy in seronegative children

- To address the question of the potential risk in seronegatives, Sanofi Pasteur utilised a new assay* on sera collected at month 13 (post-dose 3), which was designed to be able identify those who were seronegative at the time of vaccination (i.e. was not affected by the vaccine).
- Rationale for the assay was that the NS1 protein in Dengue virus is different from the NS1 protein in Yellow Fever virus
- The CYD vaccine has gene encoding NS1 from Yellow Fever
- The CYD vaccine is unlikely to produce antibodies against the Dengue NS1 protein
- Thus, the assay can be used to differentiate previous exposure to natural dengue virus from previous CYD vaccination

Sridhar et al, NEJM, 2018

Vaccine efficacy and safety on further analysis

Vaccine efficacy against symptomatic virologically confirmed dengue in the 25 months after dose 1 (2 - 16 year olds)		
Serostatus at dose 1	Vaccine efficacy	95% confidence interval
Seropositive	73%	59%, 82%
Seronegative	32%	-9%, 58%

Relative risk of hospitalised virologically confirmed dengue comparing vaccinated to controls in the 66 months after dose 1 (2-16 year olds)		
Serostatus at dose 1	Relative risk (CYD:Control)	95% confidence interval
Seropositive	0.32	0.23, 0.45
Seronegative	1.75	1.14, 2.70

Relative risk of SEVERE virologically confirmed dengue comparing vaccinated to controls in the 66 months after dose 1 (2-16 year olds)		
Serostatus at dose 1	Relative risk (CYD:Control)	95% confidence interval
Seropositive	0.31	0.17, 0.58
Seronegative	2.87	1.09, 7.61

April 2018 WHO SAGE Recommendations

- For countries considering vaccination as part of their dengue control program, a “pre-vaccination screening strategy” would be the preferred option, in which only dengue-seropositive persons are vaccinated

- Conventional serological testing for dengue virus IgG (dengue IgG ELISA) could be used to identify persons who have had previous dengue infections

- Sensitivity and specificity of dengue IgG ELISA should be assessed in a local context, and will depend on the prevalence of other flaviviruses, and past use of other flavivirus vaccines (Japanese encephalitis and yellow fever).

Updated predictions of screen and vaccinate policies

- Impact limited by monotypic prevalence in target age group (~40%)
- Models predict population impact of up to 20% long-term reduction in hospitalized dengue (25% for severe dengue)
- Population impact scales linearly with test sensitivity
- Population impact insensitive to test specificity in 90-100% range, but excess cases in seronegatives increase with decreasing specificity
- Individual impact: policy reduces post-vaccination disease in targeted cohort by up to 40% long-term (up to 60% in first 5 years), by ~70% in vaccine recipients

Transmission intensity (seroprev in 9 year-olds)	Optimal age to target	Long-term reduction in total burden of hospitalized dengue: 100% coverage, 100% sensitivity, 100% specificity, targeted at optimal age within range 9-18	Long-term reduction in total burden of hospitalized dengue: 80% coverage, 90% sensitivity of 90%, 95% specificity, targeted at optimal age within range 9-18
40	>18	17%	12%
50	18	20%	14%
60	16	20%	15%
70	13	21%	15%
80	9	21%	15%
90	7	20%	14%

Multiple rounds of test & vaccinate will increase impact, but subject to rapidly diminishing returns

Ferguson, SAGE, 2018

Expectation and GACVS recommendations

- During a 5-year follow-up, approximately 5 additional hospitalized dengue cases, or 2 additional severe dengue cases, per 1000 vaccinees with no previous dengue infection (i.e. dengue naïve subjects) could occur following vaccination, compared with unvaccinated seronegative children

- Global Advisory Committee on Vaccine Safety
  - Enhancement of measures that reduce exposure to dengue infection among populations where the vaccine has already been administered.
  - Adhere to other disease preventive measures and to seek prompt medical care in the event of dengue-like symptoms, regardless of whether vaccinated or not.
  - For vaccine recipients who present with clinical symptoms compatible with dengue virus infection, access to medical care should be expedited to allow for proper evaluation, identification, and management of severe forms of the disease.
  - Continued post-marketing surveillance.

The need for communication

- Given that no assay will be 100% specific, some truly seronegative individuals may be vaccinated due to a false positive test result

- Furthermore, although the efficacy against dengue infections in seropositive individuals is high, it is still not 100%

- Hence, the limitations of CYD-TDV will need to be clearly communicated to populations offered vaccination


Expose and oppose the collusion between Philippine government officials and Sanofi!
Coalition for People's Right to Health
Dengvaxia crime is a public health disaster not mass hysteria!
Coalition for People's Right to Health
DOH no cover-up!