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How does the Sanofi NS1 data inform assessment of Dengvaxia action and use

Neil Ferguson

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Original Dengvaxia trial results

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Phase III trial results:

- ~60% efficacy overall
- Efficacy increasing with age
- High (~80%) in seropositive recipients, much lower in seronegatives
- V. similar results from both trials

- **But** – year 1 & 2 of long-term follow-up showed relative risk of *hospitalized dengue* significantly >1 in 2-5 year olds, reduced efficacy in other age groups
- **Hence** – only licensed for use in 9+ year olds

Articles

Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial

Maria Rosario Capeding, Ngoc Huu Tran, Sri Rezeki S Hadinegoro, Hussain Imam HJ Muhammad Ismail, Tawee Chotpitayasunondh, Mary Noreen Chua, Chan Quang Luong, Kusnandi Rusmil, Dewa Nyoman Wirawan, Revathy Nallusamy, Punnee Pitisuttithum, Usa Thisyakorn, In-Kyu Yoon, Diane van der Vliet, Edith Langevin, Thelma Laot, Yanee Hutagalung, Carina Frago, Mark Boaz, T Anh Wartel, Nadia G Tornieporth, Melanie Saville, Alain Bouckenooghe, and the CYD14 Study Group*

Summary

Background An estimated 100 million people have symptomatic dengue infection every year. This is the first report of a phase 3 vaccine efficacy trial of a candidate dengue vaccine. We aimed to assess the efficacy of the CYD dengue vaccine against symptomatic, virologically confirmed dengue in children.

Methods We did an observer-masked, randomised controlled, multicentre, phase 3 trial in five countries in the Asia-Pacific region. Between June 3, and Dec 1, 2011, healthy children aged 2–14 years were randomly assigned (2:1), by computer-generated permuted blocks of six with an interactive voice or web response system, to receive three injections of a recombinant, live, attenuated, tetravalent dengue vaccine (CYD-TDV), or placebo, at months 0, 6, and 12. Randomisation was stratified by age and site. Participants were followed up until month 25. Trial staff responsible for the preparation and administration of injections were unmasked to group allocation, but were not included in the follow-up of the participants; allocation was concealed from the study sponsor, investigators, and parents and guardians. Our primary objective was to assess protective efficacy against symptomatic, virologically confirmed dengue, irrespective of disease severity or serotype, that took place more than 28 days after the third injection. The primary endpoint was for the lower bound of the 95% CI of vaccine efficacy to be greater than 25%. Analysis was by intention to treat and per procotol. This trial is registered with ClinicalTrials.gov, number NCT01373281.

Findings We randomly assigned 10 275 children to receive either vaccine (n=6851) or placebo (n=3424), of whom 6710 (98%) and 3350 (98%), respectively, were included in the primary analysis. 250 cases of virologically confirmed dengue took place more than 28 days after the third injection (117 [47%] in the vaccine group and 133 [53%] in the control group). The primary endpoint was achieved with 56·5% (95% CI 43·8–66·4) efficacy. We recorded 647 serious adverse events (402 [62%] in the vaccine group and 245 [38%] in the control group). 54 (1%) children in the vaccine group and 33 (1%) of those in the control group had serious adverse events that happened within 28 days of vaccination. Serious adverse events were consistent with medical disorders in this age group and were mainly infections and injuries.

Interpretation Our findings show that dengue vaccine is efficacious when given as three injections at months 0, 6, and 12 to children aged 2–14 years in endemic areas in Asia, and has a good safety profile. Vaccination could reduce the incidence of symptomatic infection and hospital admission and has the potential to provide an important public health benefit.

Funding Sanofi Pasteur.

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Explanatory hypothesis: "Silent infection" mode of action

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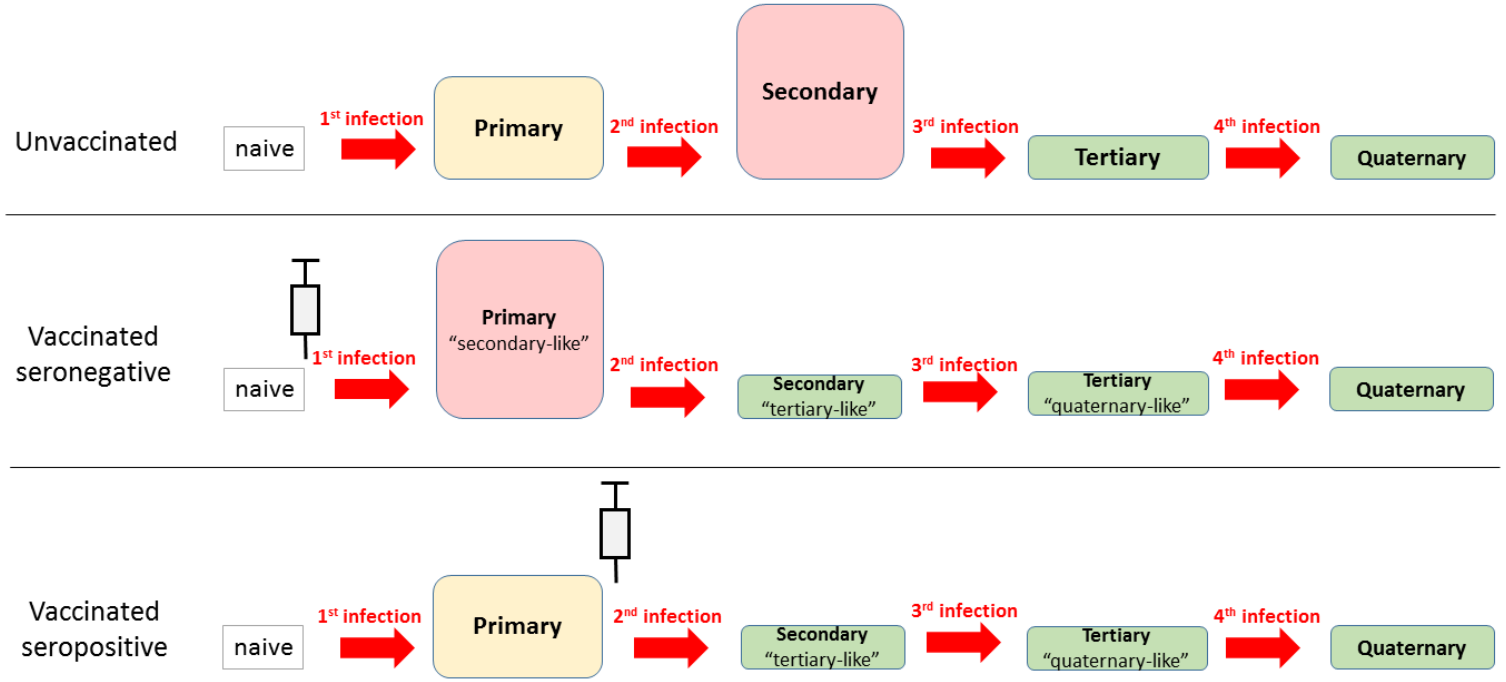
- Vaccination primes the immune system similarly to infection:
  1. Temporary high degree of cross-immunity in at least seronegative recipients
  2. Seronegative recipients have secondary-like breakthrough infection once cross-immunity wanes
  3. Seropositive recipients have tertiary-like breakthrough 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

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Original modelling: individual vs population benefit of vaccination

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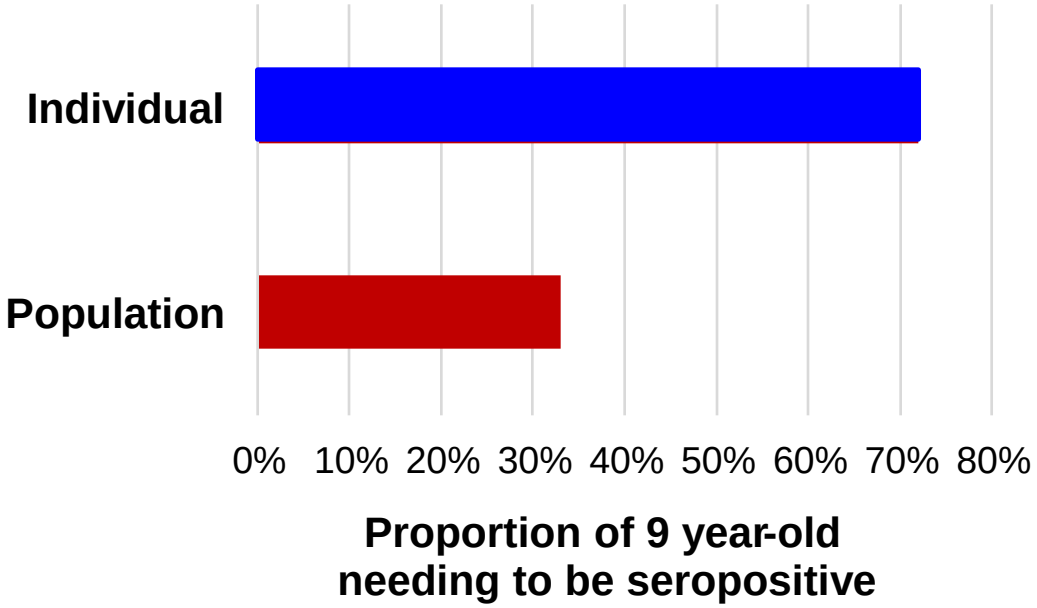
Long-term impact of vaccination in seronegatives depends on transmission setting



- 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

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Policy options to mitigate risk in seronegatives

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1. ***Mass-vaccination with seroprevalence threshold*** (original SAGE guidance) – vaccinate areas where transmission intensity exceeds a certain threshold – e.g. >70/80/90% seroprevalence in 9 year-olds

2. ***Screen and vaccinate*** (more risk-averse option) – screen every potential vaccine recipient with an RDT to determine serostatus, and only vaccinate those testing seropositive

Ferguson et al., Science 2016

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Analysis of NS1 data

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- Updated model fitted to new NS1 data (allowing for imperfect sensitivity/specificity of assay)
- **Previous 'silent infection' hypothesis largely supported**
- But age effects are statistically significant:
  - risk in seronegatives declines with age
  - protection in seropositives increases with age
- No statistical evidence that hospitalised/severe disease risk in seronegative vaccinees is greater than a non-vaccinee who experiences 2 lifetime infections
- But small case numbers (and level of aggregation) limit inferential power
- Updated impact modelling results broadly similar to past results
- Still a lot of uncertainties

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Mitigation options remain the same, but 'hypothetical' risk now demonstrated to be real

Ferguson et al., Science 2016

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Mass vaccination with seroprevalence threshold : principle and challenges

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- Aim: ensure even seronegatives get long-term benefit (despite short-term risk)
- Challenge 1 – heterogeneity:
  - Transmission intensity varies over fine geographic scales
  - Requires very large scale serosurveys to characterise
- Challenge 2 – coverage/impact:
  - Very few locations have seroprevalence > 80% in 9 year olds
  - Almost nowhere >90%
- Challenge 3 – communication/uncertainties:
  - Complex policy, open to misinterpretation (e.g. neither Philippines or Brazil followed WHO guidance for seroprevalence surveys prior to Dengvaxia introduction)
  - Long-term benefit in seronegatives not (yet) demonstrated in trial data
  - Risk occurs before benefit, and is quantifiable

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Test & Vaccinate: principle and challenges

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- Avoid risk associated with vaccinating seronegatives
- Maximize benefit from vaccinating seropositives
- Challenge 1 – age-targeting:
  - Too young, most seronegative
  - Too old, high proportion of seropositives have already had 2 infections
- Challenge 2 – test performance:
  - High specificity required to minimise risk
  - But consequence may be low sensitivity – and so reduced impact
- Challenge 3 – implementation:
  - Cost, logistics
  - Mass vaccination – single age, or multiple ages?
  - Private use – communicating context-specific benefits

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Mass-vaccination without individual testing: choice of seroprevalence threshold

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- Risk increase in seronegatives occurs soon after vaccination
- But predicted benefit (reduction in long-term cumulative risk of hospitalised dengue) takes much longer to accumulate
- Timescale over which seronegatives may eventually benefit depends on target age (& is sensitive to model uncertainties)
- May never occur in lower seroprevalence settings
- For positive benefit in seronegative 9 year-olds in <10 years, need >80% seropositivity in that age group (>90% for benefit in 6 years)
- Risk in seronegatives is clear from the data; eventual benefit is predicted by modelling but yet to be proven

Target age for vaccination (years)	Percent seroprevalence in target age group required for predicted benefit in seronegative recipients within 10 years
9	80 - 82
10	81 - 83
11	82 - 86
12	82 - 88
13	83 - 90
14	85 - 92
15	87 - 93
16	88 - 94
17	90 - 95
18	91 - 96

Predicted long-term population impact of mass-vaccination with seroprevalence threshold if optimally age targeted: 25% reduction in hospitalized dengue for 100% coverage, 20% reduction for 80% coverage

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Age-targeting and impact of screen & vaccinate policies

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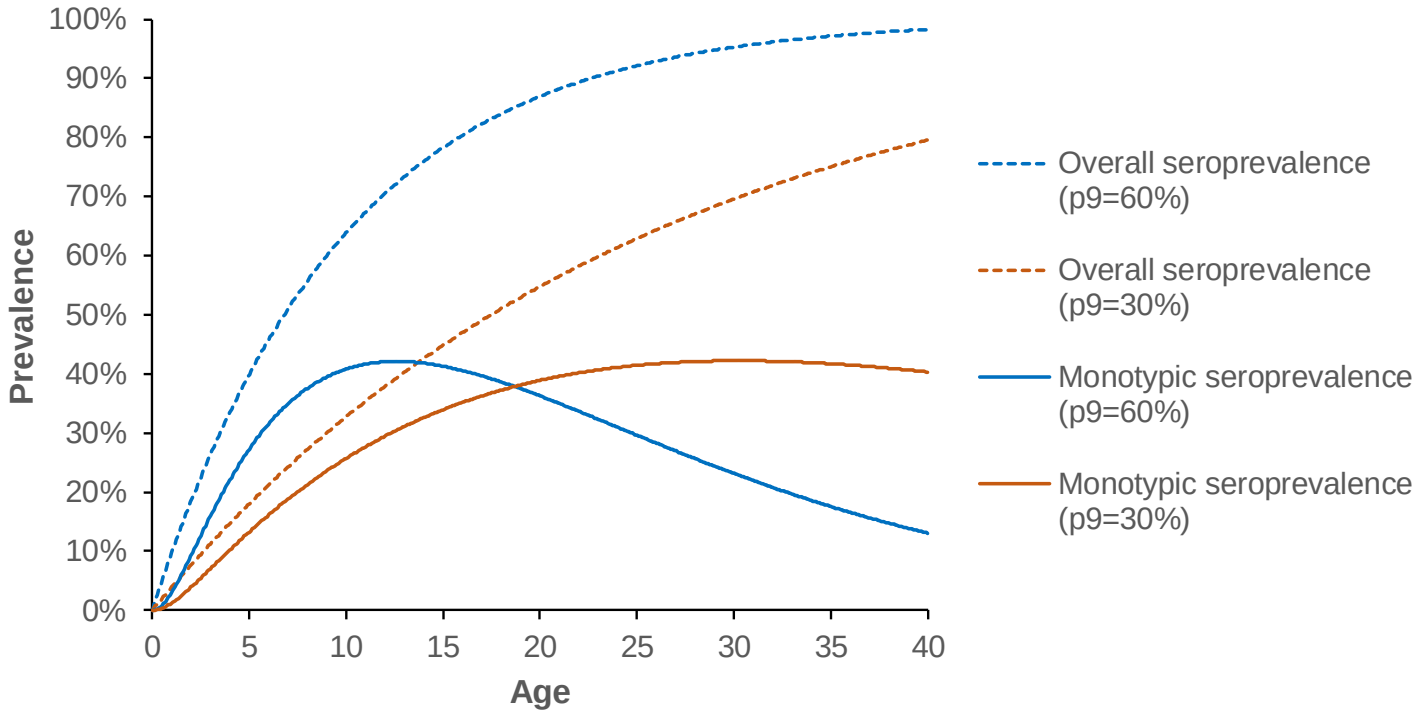
- Want to target people with monotypic immunity (*i.e.* only one prior dengue infection), since severe disease associated with secondary infection
- Optimal to target age where monotypic prevalence is highest
- Age of maximum monotypic seroprevalence varies with transmission intensity
- But if surveillance data available, age specific severe dengue incidence is a good proxy for monotypic seroprevalence
- *i.e.* optimal to target age group with highest (average) severe dengue incidence



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Updated predictions of impact of screen & vaccinate policies

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- 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

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Vaccine coverage: mass vaccination *vs* screen & vaccinate

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- Used age-stratified case incidence data to estimate annual average dengue force of infection at admin 1 level for a number of endemic countries
- These results can be used to estimate seroprevalence in 9 year-olds at same geographic scale
- Only a small proportion of admin 1 areas are predicted to have seroprevalence >80% in 9-year olds
- Hence coverage of a threshold-based mass-vaccination policy likely to be low or very low
- Coverage of a test-and-vaccinate policy always higher – since all seropositives are vaccinated

Predicted coverage of mass-vaccination with seroprevalence threshold vs test-and vaccinate policies for countries with dengue force of infection estimates for 5 or more admin 1 units

Country	Number of admin1 units	Proportion of admin 1 units with FOI estimates	Predicted coverage with 80% seroprevalence threshold in 9 year-olds applied at admin 1	Predicted coverage with 90% seroprevalence threshold in 9 year-olds applied at admin 1	Predicted coverage (proportion of 9 year-olds receiving vaccine) with screen and vaccinate policy
Brazil	27	93%	7%	0%	50%
Colombia	32	88%	4%	0%	64%
India	36	19%	44%	0%	64%
Mexico	32	84%	0%	0%	24%
Philippines	81	69%	17%	0%	67%
Thailand	77	94%	0%	0%	57%
Venezuela	25	96%	59%	0%	79%

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Conclusions

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- New data largely support previous ‘silent infection’ model of Dengvaxia action
- Unethical to increase risk of the disease being vaccinated against in a potentially identifiable subset of recipients
- So mass vaccination without testing only appropriate for very high transmission intensity settings – e.g. 80% seroprevalence in 9 year-olds
- Local heterogeneity in transmission intensity poses challenges for population seroprevalence screening
- Recommending mass vaccination with population seroprevalence thresholds is also a challenging policy to communicate given clear evidence of risk
- Screen & vaccinate strategies are more risk averse, yet might give similar impacts to mass-vaccination without testing (~20% reduction in hospitalised dengue)
- Multiple round policies could achieve more, if feasible
- Individual vaccine recipients in screen & vaccinate programme would see immediate large (>70%) reduction in future risk of hospitalised dengue
- Optimal age group for screen & vaccinate varies with transmission setting – age-stratified dengue surveillance data can inform targeting