WHO global position on dengue vaccination

Joachim Hombach, Exec. Secretary SAGE,

Immunization, Vaccines & Biologicals; World Health Organization

ACIP February 2020, Atlanta, Georgia

Dengue is a global public health priority

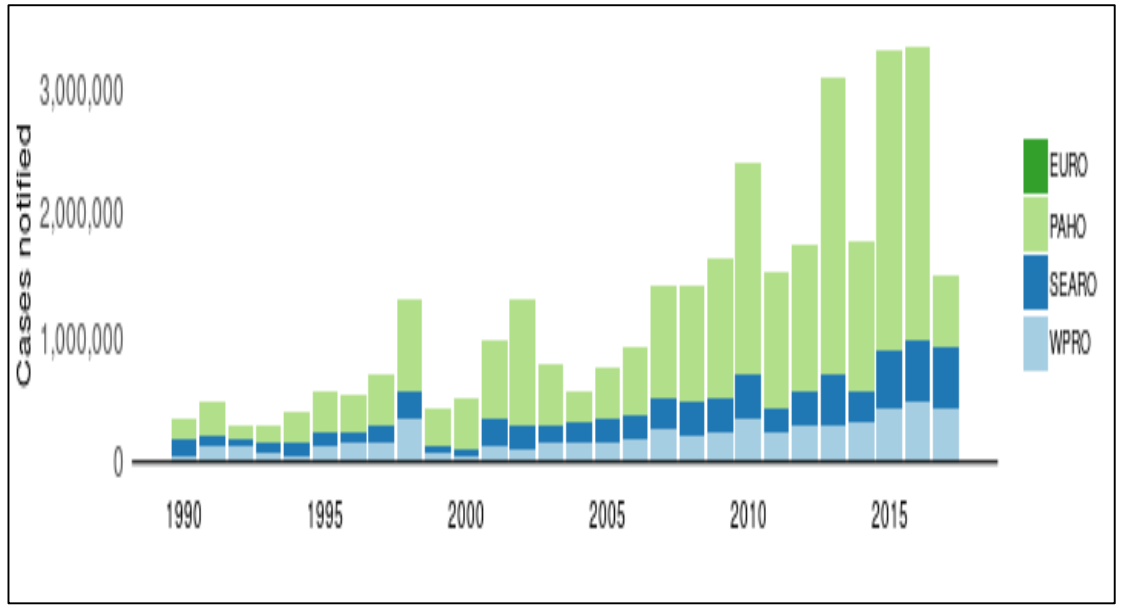
In 2019, WHO had listed dengue among the ten biggest public health threats for the year.

There are several factors contributing to the increase in dengue:

- Climate change with intensified rainy seasons
- Unplanned urbanization and population growth
- Increased travel
- Poor implementation of effective control measures

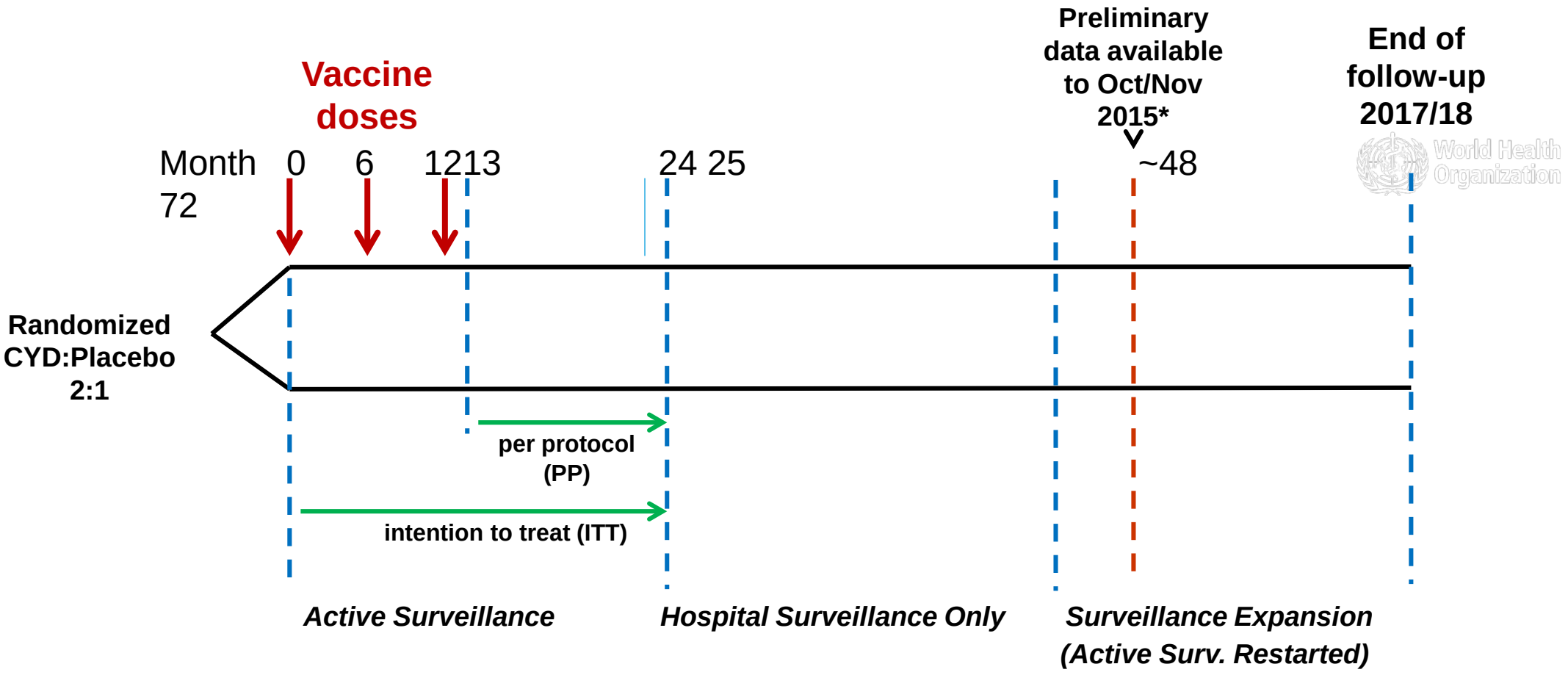
(environmental management and vector control)

- No easily scalable vaccine intervention



Global dengue cases reported to WHO

CYD-TDV 14 & 15 study design overview



*(*Data reviewed for WHO's first position paper from 2016)*

Slide adapted from Prof P Smith

Original licensure data*

VE against Symptomatic, Severe and Hospitalized Dengue (ITT) (M0-M25)

Outcome	Cases in Vaccine group (n)	Cases in Placebo group (n)	Pooled (2-16 years)	Pooled (9-16 years)
Symptomatic VCD	563	694	**60.3%** (55.7-64.5)	**65.6%** (60.7-69.9)
Hospitalized VCD	57	104 (15%)	**72.7%** (62.3-80.3)	**80.8%** (70.1-87.7)
Severe VCD	13	31 (4.5%)	**79.1%** (60.0-89.0)	**93.2%** (77.3-98.0)

Overall robust efficacy, in particular against more severe forms

Efficacy increasing with age

High efficacy (~80%) in seropositive recipients, much lower in seronegatives (subset)

Results consistent across trials

Increased risk observed in 2-5 y age group for hospitalized and severe VCD, during third year of follow-up

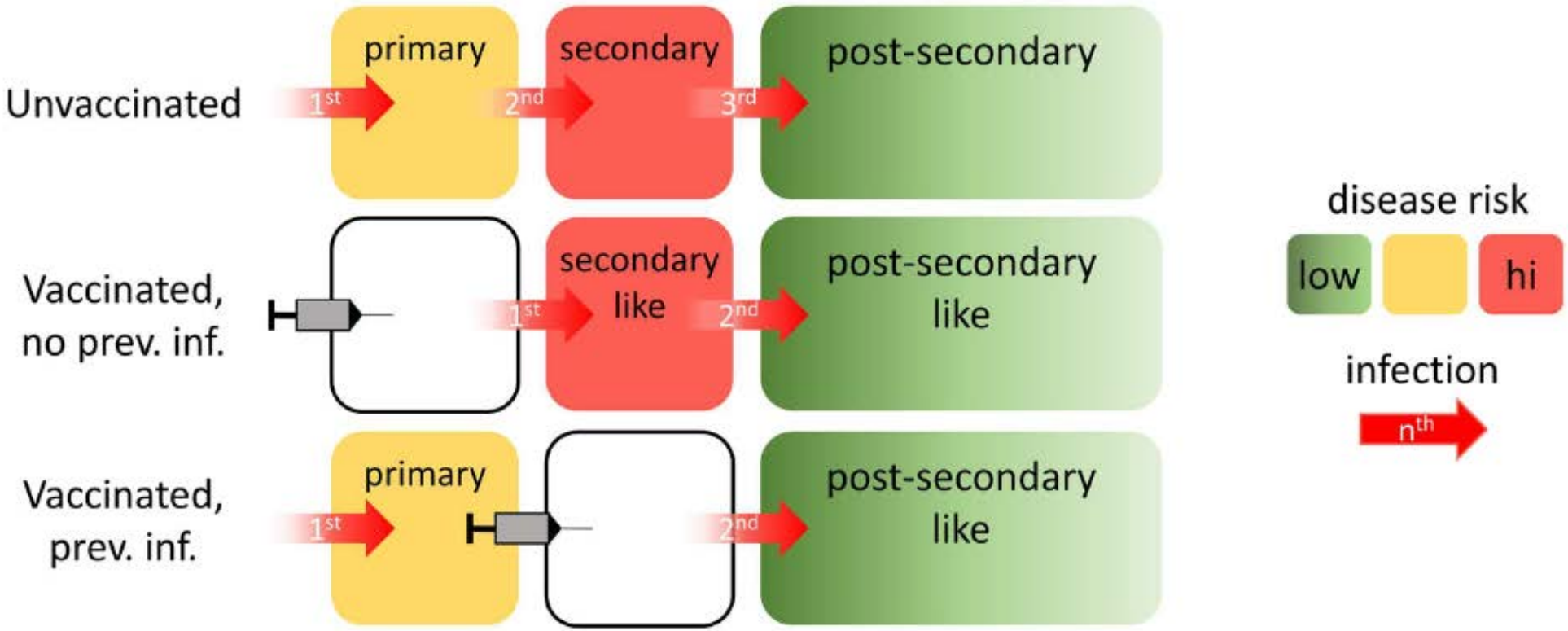
Insufficient data for a conclusive analysis if risk associated with serostatus**

**Hadinegoro et al., N Engl J Med 2015*

***see SAGE background paper 2016*

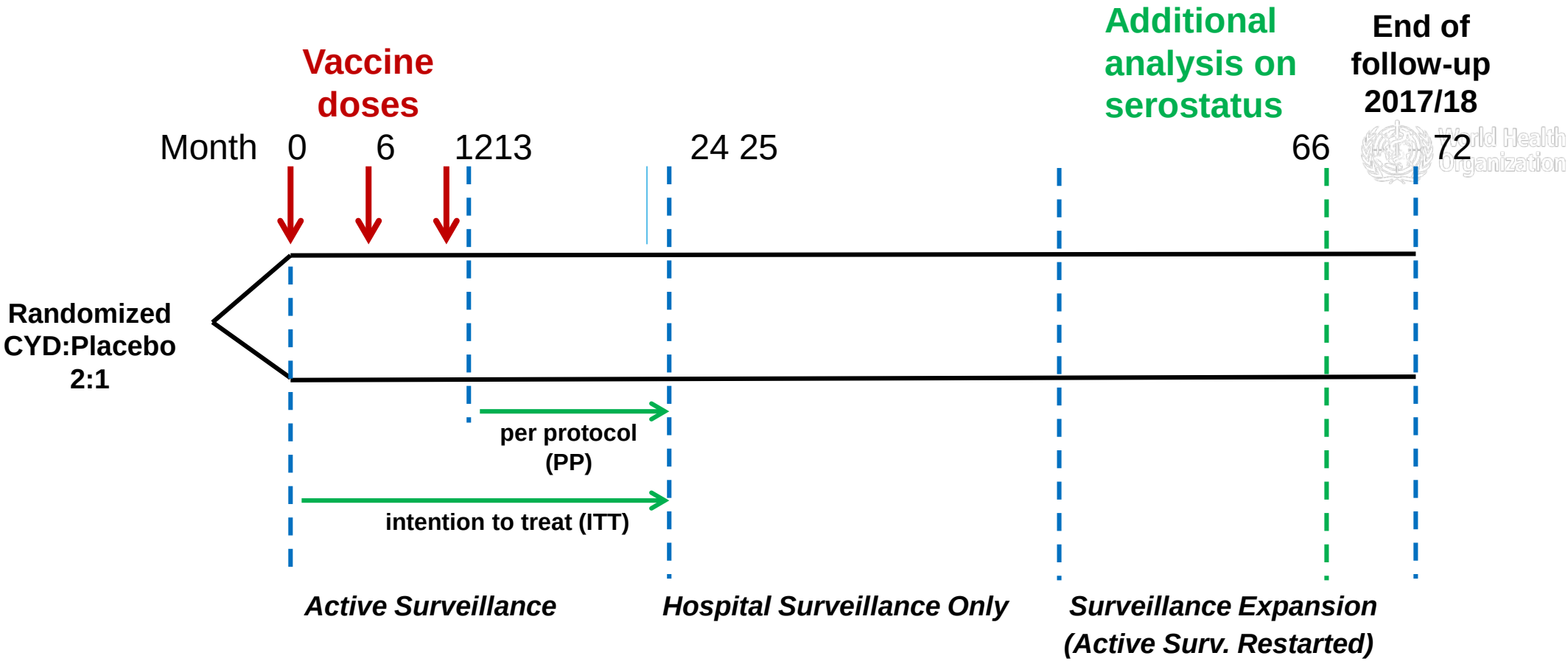
Assumed vaccine mode of action

Modeling the impact of dengue vaccine CYD-TDV



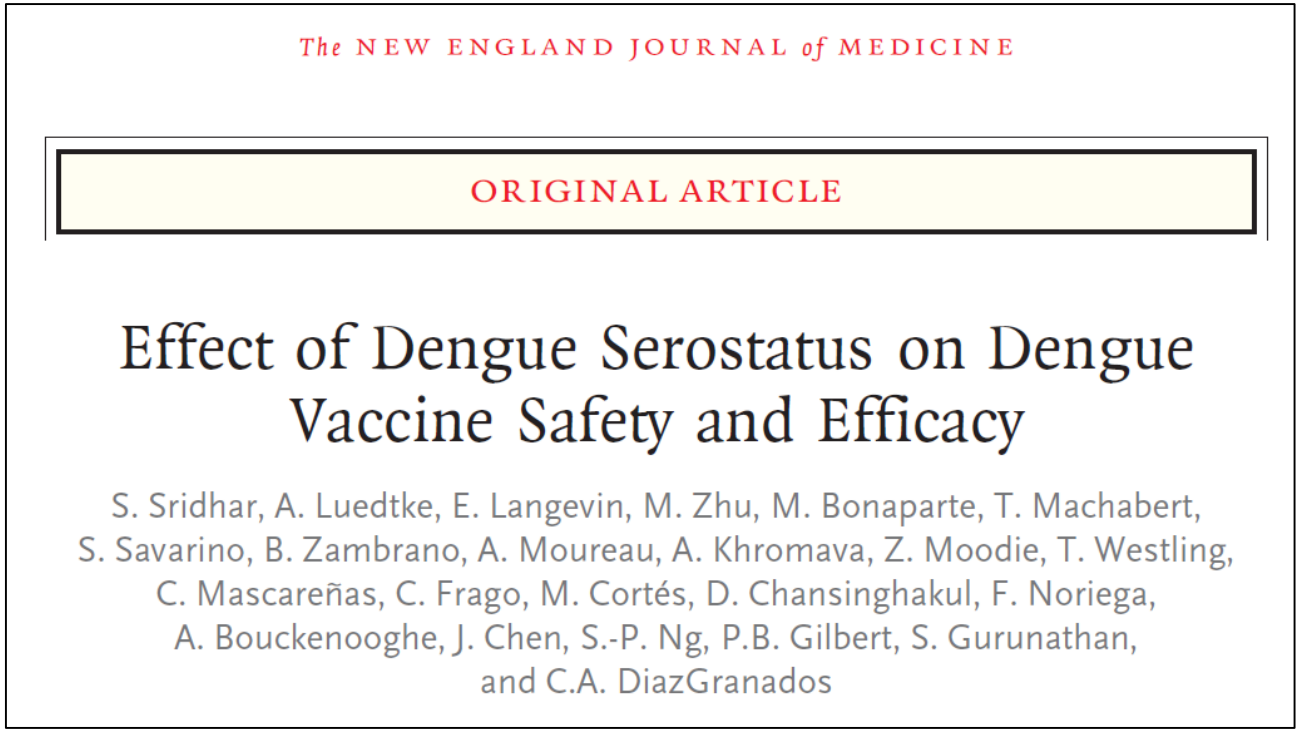
Flasche et al, PLoS Medicine, November 2016

CYD 14 & 15 study design overview



Slide adapted from Prof P Smith

Additional analysis on the effect of serostatus on CYD-TDV performance



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy

S. Sridhar, A. Luedtke, E. Langevin, M. Zhu, M. Bonaparte, T. Machabert, S. Savarino, B. Zambrano, A. Moureau, A. Khromava, Z. Moodie, T. Westling, C. Mascareñas, C. Frago, M. Cortés, D. Chansinghakul, F. Noriega, A. Bouckenooghe, J. Chen, S.-P. Ng, P.B. Gilbert, S. Gurunathan, and C.A. DiazGranados

A case cohort study to re-analyse all symptomatic virologically confirmed dengue cases

Method of analysis

From Month 13 onwards:
- NS1 assay at month 13.

From Month 0 onwards:
- Multiple Imputation (MI) by which PRNT50 results are inferred prior to vaccination.
- Probability Weighted Targeted Minimum Loss-Based Estimation (TMLE), a statistical model.

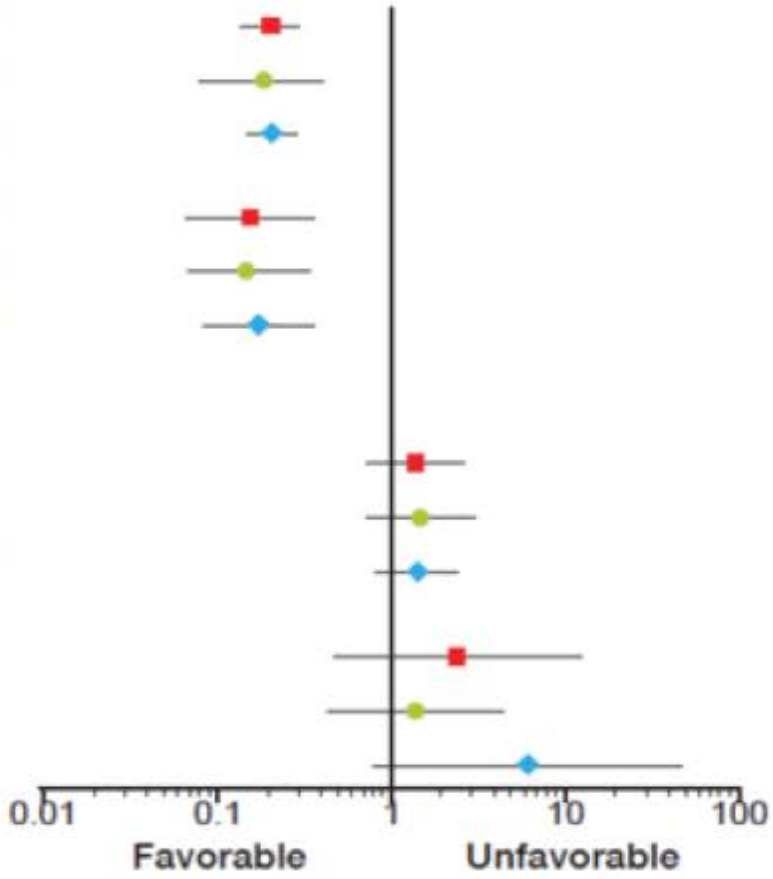
All 3 methods gave similar results

Risk of hospitalized and severe VCD by serostatus in trial participants aged 9–16 years, M0-M66

World Health Organization

Age 9-16 years

Dengue serostatus	Vaccine group (n/M)	Placebo group (n/M)	Relative risk/ Hazard ratio	95% CI	p-value
Seropositive					
Hospitalized VCD MI-M0	58.8/1502.9	137.7/729.8	0.21	(0.14, 0.31)	<.001
Hospitalized VCD TMLE-M0	43.6/1442.6	121.3/699.3	0.19	(0.08, 0.42)	<.001
Hospitalized VCD NS1-Th9-M13	49/1450	110/687	0.21	(0.15, 0.30)	<.001
Severe VCD MI-M0	11.2/1502.9	33.4/729.8	0.16	(0.07, 0.37)	<.001
Severe VCD TMLE-M0	8.6/1442.6	29.9/699.3	0.15	(0.07, 0.35)	<.001
Severe VCD NS1-Th9-M13	10/1450	27/687	0.18	(0.09, 0.37)	<.001
Seronegative					
Hospitalized VCD MI-M0	64.2/375.1	25.3/207.2	1.41	(0.74, 2.68)	0.287
Hospitalized VCD TMLE-M0	78.1/359.7	31.7/201	1.51	(0.73, 3.11)	0.263
Hospitalized VCD NS1-Th9-M13	56/330	20/171	1.46	(0.85, 2.49)	0.171
Severe VCD MI-M0	14.8/375.1	3.6/207.2	2.44	(0.47, 12.56)	0.283
Severe VCD TMLE-M0	15.2/359.7	6.8/201	1.41	(0.44, 4.46)	0.562
Severe VCD NS1-Th9-M13	12/330	1/171	6.25	(0.81, 48.32)	0.079



SAGE background paper April 2018 (Fig 6)

Policy options to minimize risk to seronegatives and maximize vaccine impact

Population Seroprevalence Criteria without Screening	***Individual-level Pre-Vaccination Screening***

Compare along a number of dimensions:

- Benefits and harm (population, individual, eligible populations)
- Ethical considerations
- Risk perceptions and communication
- Screening tests versus serosurveys (feasibility, test limitations, costs)
- Implementation challenges
- Impact, age, cost-effectiveness

WHO dengue position – update 2018 (i)

WER 7 September 2018

Countries should consider introduction of the dengue vaccine CYD-TDV **only if the minimization of risk** among seronegative individuals can be assured;

For countries considering vaccination as part of their dengue control programme, **pre-vaccination screening is the recommended strategy**;

Screening tests would need to be **highly specific** to avoid vaccinating truly seronegative persons and to have high sensitivity to ensure that a high proportion of seropositive persons are vaccinated.

Point-of-care tests, i.e. RDTs, would facilitate the implementation of the pre-vaccination screening strategy, but have **not yet been validated** for that purpose.

Decisions about implementing a pre-vaccination screening strategy with the currently available tests will require **careful assessment at the country level**, including consideration of the sensitivity and specificity of available tests.

WHO dengue position – update 2018 (ii)

WER 7 September 2018

The **age group** to target for vaccination depends on the dengue transmission intensity in a given country, and will be lower in countries with high transmission, and higher in countries with low transmission.

The **optimal age group** to be targeted is the age before which severe dengue disease incidence is highest;

If pre-vaccination screening is not feasible, vaccination **without** individual screening could be considered in areas with recent documentation of seroprevalence rates conducted at **high resolution;**

Documented seroprevalence rates of **at least 80%** at age 9 years should be aimed at;

Communication needs to ensure appropriate and **full disclosure of the risks** of vaccination of persons with unknown serostatus (but also on false positives if prescreening with RDT is done).

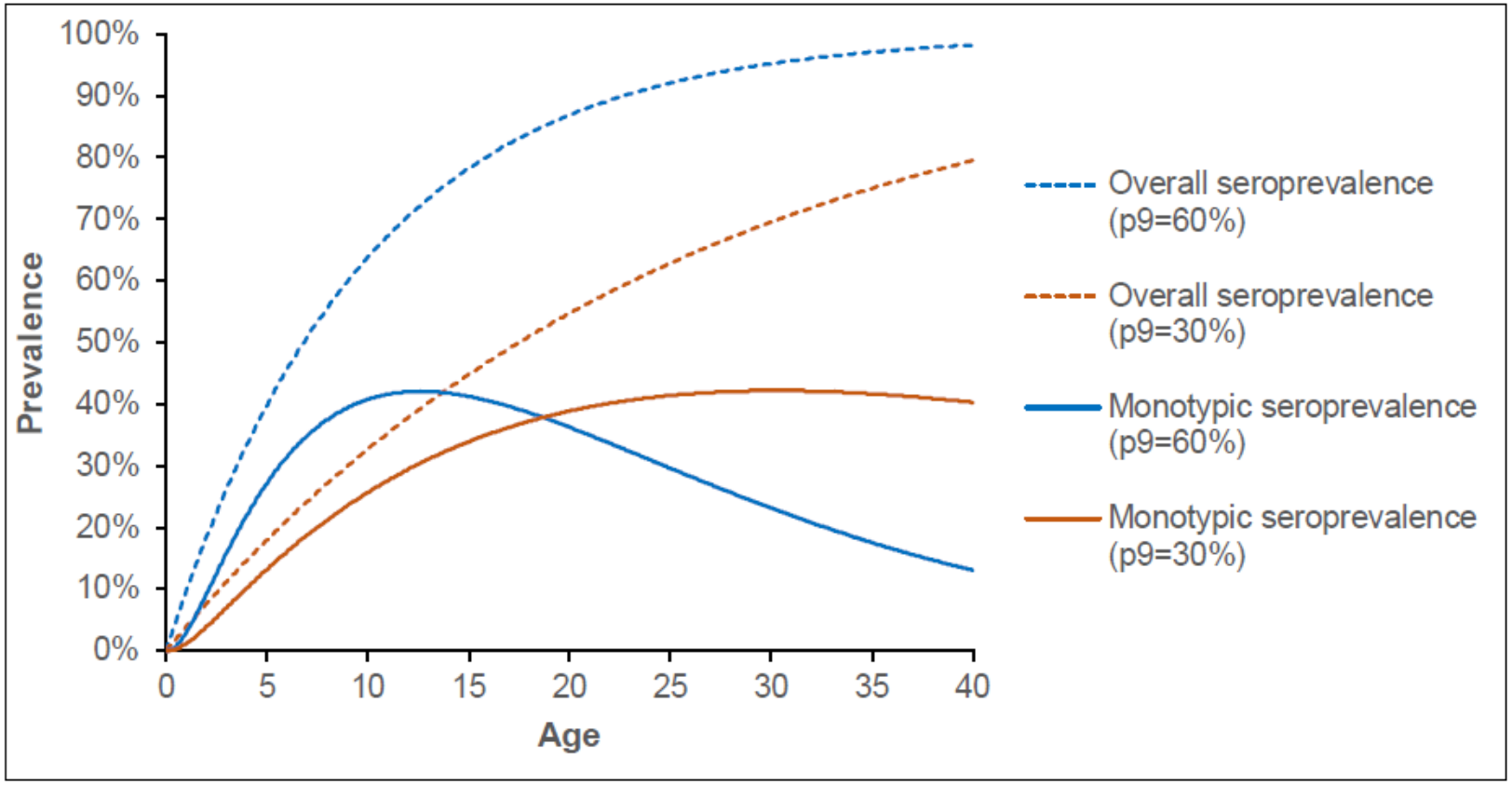
Implementation considerations

- Knowledge of **local burden of disease**, age distribution an information on seroprevalence
- Available **RDT** and test characteristics as applied to the **specific epidemiologic setting**
- **Affordability** and cost effectiveness (vaccine & test & programme operations)
- **Implementation strategies** depending on the age group chosen*, follow-up and record-keeping (3 dose schedule)
- **Complex logistics** depending on route of programme delivery* and diagnostic procedure
- **Complex communication**: dealing with ineligible populations; repeat screening in seronegatives, partially effective vaccine
- **Local priorities,** sustainability and alternative investments
- **Surveillance** needs

*(*School-based vaccination is favoured before children graduate from primary school, typically around 12 years of age)*

Optimizing the pre-screening approach:

Targeting the age of peak monotypic seroprevalence



Illustrative profiles of overall seroprevalence (one or more past infections, dashed line) and monotypic seroprevalence (one infection, solid lines) by age for two transmission scenarios.

from: SAGE background paper 2018; figure prepared by N Ferguson, Imperial College, London

Diagnostic tests for prior dengue infection

Key considerations:

Safety: High specificity and low cross-reactivity to minimize false-positives

- Of particular importance in low-moderate transmission settings, and setting with other circulating flaviviruses

Public health benefit: high sensitivity to minimize the number of individuals omitted from vaccination (false negatives)

- A particular consideration to increase effectiveness of programmes

Journal of Travel Medicine
International Society of Travel Medicine
Promoting healthy travel worldwide
Established 1991
Journal of Travel Medicine, 2019, 1–11
doi: 10.1093/jtm/taz078
Original Article

Original Article

Evaluation of rapid diagnostic tests and conventional enzyme-linked immunosorbent assays to determine prior dengue infection

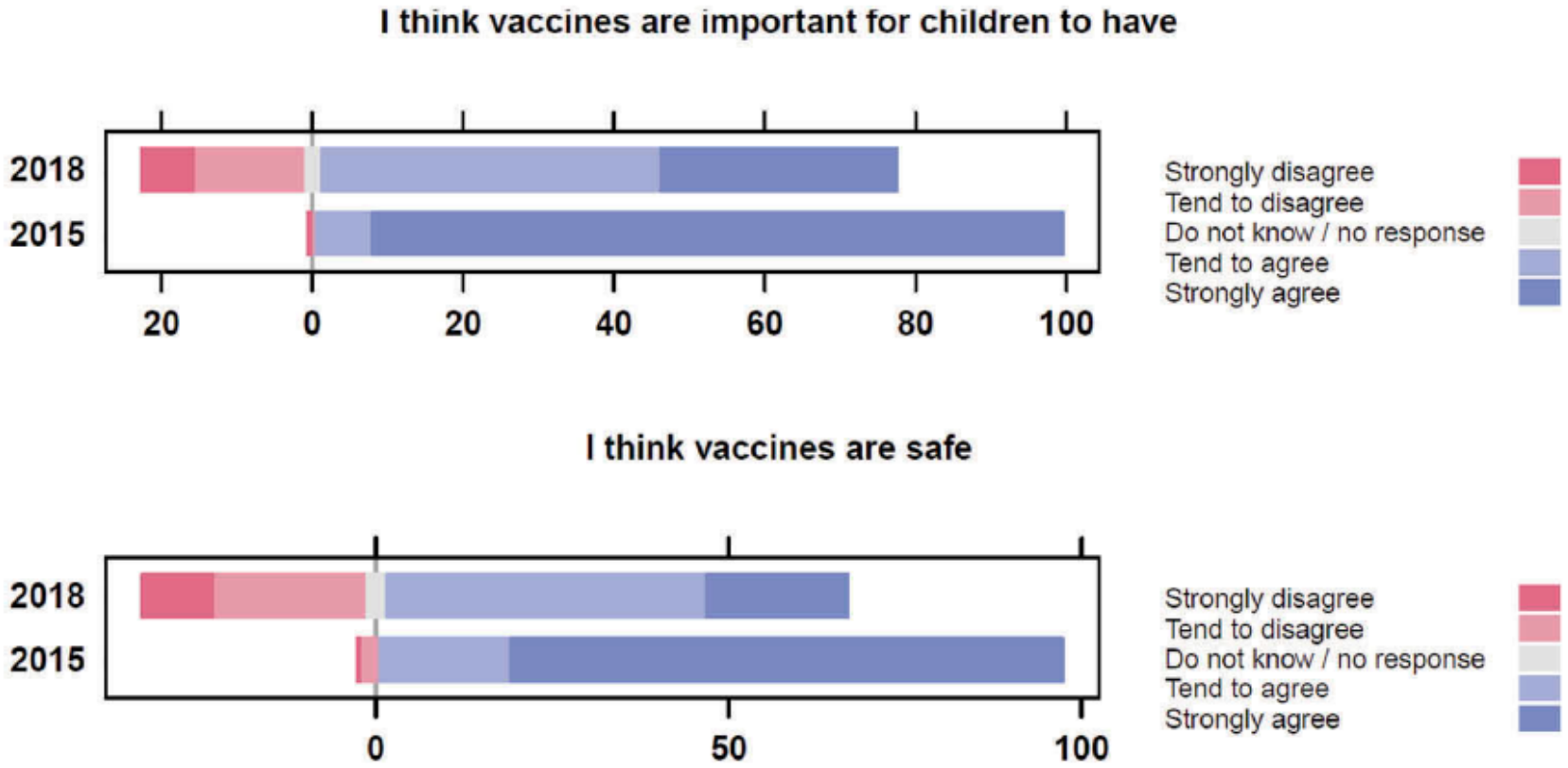
Matthew Bonaparte PhD [1], Lingyi Zheng MS [2], Sanjay Garg PhD [1], Bruno Guy PhD [3], Yaniv Lustig PhD [4], Eli Schwartz MD [5], Carlos A. DiazGranados MD [6], Stephen Savarino MD [7] and Yasemin Ataman-Önal PhD [8,*]

➢ All of the tested RDT's show high specificity and low cross-reactivity, but have limited sensitivity

Positive and negative predictive values as measures to define what constitutes an acceptable level of misclassification in a given transmission setting *(Rodríguez-Barraquer et al., Lancet ID 2019)*

Communicating about complex vaccine performance (I)

The consequences of public outcry and political instrumentalization in the Philippines



Larson HJ et al., Human Vaccines and Immunotherapeutics, 2019

What are the facts?

Estimation of the proportion of vaccine-induced cases of hospitalized dengue – based on CYD15 data*

Assumptions: seroprevalence in the population 85% (from RCT); relative risks in the Philippines school vaccination programme are similar to those observed in the Phase 3 trial CYD15, and irrespective if either 1, 2 or 3 doses of vaccine had been administered.

Estimation: over the five years following vaccination in the Philippines, CYD-TDV will likely have averted about 18 dengue hospitalisations among seropositive vaccinees for each precipitated dengue hospitalisation in dengue-naïve vaccinees, and about 10 severe dengue cases among seropositive vaccinees for each precipitated severe dengue case in dengue-naïve vaccines.

*(*Flasche et al., Wellcome Open Research 2019)*

Communicating about complex vaccine performance (II)

The need for tailored and targeted communication

Key topics for dengue

- Clear communication on benefits and risks
- Rationale for pre-vaccination testing
- Risk of vaccinating seronegatives due to false-positive test
- Exclusion of tested persons from vaccination due to false-negative test
- Partial effectiveness of the vaccine and continued need for vector control measures
- Information on vaccine schedule
- Information on duration of immunity and possible needs for booster vaccination

Key considerations in developing a communication strategy:

- Communication needs to be anticipated from the outset and must be proactive; avoid reactive communication
- The strategy needs to segment to different audiences (medical professional associations, general HCW's, teachers, parents, adolescents, journalists…);
- Messaging and materials need to be targeted to different audience groups;
- Communications isn't enough: there needs to be opportunities for actual dialogue to build understanding and support.

Concluding remarks

- Dengue is a high **public health priority** in many countries;
- Current vaccine CYD-TDV has **shortcomings** but offers significant **clinical benefit** in seropositive target population;
- Any use of the vaccine must be accompanied with a **risk minimization strategy;**
- **Pre-vaccination screening** is the method of choice to miminize risk;
- Vaccine performance is expected to be best in individuals with a history of **monotypic infection;**
- This population can most easily be targeted and identified in **high-transmission settings;**
- Rapid diagnostic **test characteristics** must be assessed in context of the epidemiological setting;
- Significant investments are needed in relation **programmatic implementation**, **monitoring** and **communication;**
- Failure to do so can has dramatic consequences for **public health confidence.**

References:

WHO position paper 2018 on dengue: https://www.who.int/immunization/policy/position_papers/dengue/en/

SAGE background materials 2018: https://www.who.int/immunization/sage/meetings/2018/april/presentations_background_docs/en/

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