Dengue Vaccines: Status and Future

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GLOBAL DENGUE+AEDES-TRANSMITTED DISEASES CONSORTIUM

IVI International Vaccine Institute

Outline

- Tetravalent vaccination strategy
- Sanofi Pasteur's CYD-TDV results
- Implications for 2nd generation vaccines
- Dengue vaccine pipeline in human trials
- Status of selected 2nd generation vaccines
- Other questions
- Conclusions

Global dengue burden continues to rise

- Global burden of disease study 2013 & 2015
- Modelled incidence from officially reported cases
  - Adjusted for under-reporting based on published expansion factors (14 countries)
- Modelled mortality from vital registration, verbal autopsy, and surveillance data
- Estimated **58.4** million symptomatic cases (23.6-121.9 million) in 2013 [Stanaway JD et al. Lancet Infect Dis. 2016 Jun;16(6):712-23]
  - **21.1** million in Southeast Asia alone
- From 2005 to 2015, dengue deaths increased by **48.7%** (15.1-90.9), resulting in 18,400 deaths (11,800-22,700) in 2015 [Lancet. 2016 Oct 8;388(10053):1459-1544]

❖ **One of few infectious diseases with increasing mortality trend**

Vaccine is feasible

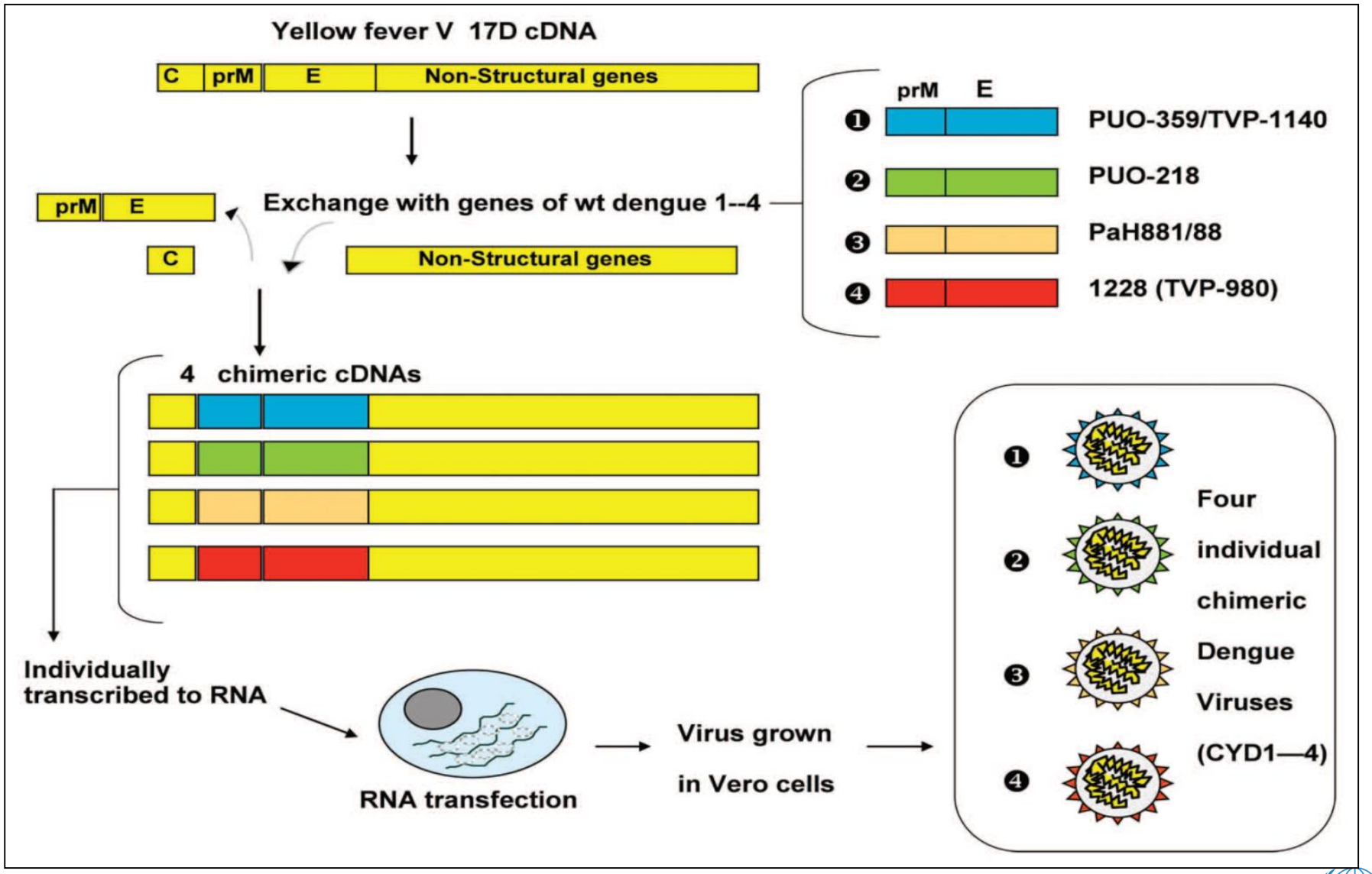
- Natural immunity exists
  - Infection confers long-term protection against disease with same serotype (homotypic immunity)
  - Short-term (2 months to 2-3 years) heterotypic protection against other serotypes
  - Sequential natural infection with 2 different serotypes may confer protection against severe disease by other serotypes
    - Not many DHF cases from known 3rd or 4th infections [Gibbons RV et al. AJTMH 2007 Nov;77(5):910-3]
    - 3rd or 4th infections more likely to be subclinical than symptomatic [Olkowski S et al. JID 2013 Sep;208(6):1026-33]

Major challenges exist

- Mainly due to existence of four serotypes that can potentially interact with each other in unclear ways
  - Protection (long term or partial and/or temporary)
  - Enhancement
    - Suboptimal or waning immune response could enhance subsequent natural infection
  - Interference (for live vaccines)

- Theoretical risk of enhancement has led to main vaccination strategy of inducing **simultaneous tetravalent homotypic immunity**
  - Not same as immunity from sequential natural infections

Sanofi Pasteur's CYD-TDV (Dengvaxia®)



Human Vaccines 6:9, 696-705; September 2010; © 2010 Landes Bioscience

CYD-TDV phase IIb and III trials

Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial

Arunee Sabchareon, Derek Wallace, Chukiat Sirivichayakul, Kriengsak Limkittikul, Pornthep Chanthavanich, Saravudh Suvannadabba, Vithaya Jiwariyavej, Wut Dulyachai, Krisana Pengsaa, T Anh Wartel, Annick Moureau, Melanie Saville, Alain Bouckenooghe, Simonetta Viviani, Nadia G Tornieporth, Jean Lang

Sabchareon A et al. Lancet 2012 Nov 3;380(9853)

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*

Capeding MR et al. Lancet 2014 Oct 11;384(9951)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America

Luis Villar, M.D., Gustavo Horacio Dayan, M.D., José Luis Arredondo-García, M.D., Doris Maribel Rivera, M.D., Rivaldo Cunha, M.D., Carmen Deseda, M.D., Humberto Reynales, M.D., Maria Selma Costa, M.D., Javier Osvaldo Morales-Ramírez, M.D., Gabriel Carrasquilla, M.D., Luis Carlos Rey, M.D., Reynaldo Dietze, M.D., Kleber Luz, M.D., Enrique Rivas, M.D., Maria Consuelo Miranda Montoya, M.D., Margarita Cortés Supelano, M.D., Betzana Zambrano, M.D., Edith Langevin, M.Sc., Mark Boaz, Ph.D., Nadia Tornieporth, M.D., Melanie Saville, M.B., B.S., and Fernando Noriega, M.D., for the CYD15 Study Group*

Villar L et al. NEJM 2014 Nov 3

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 24, 2015 VOL. 373 NO. 13

Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease

S.R. Hadinegoro, J.L. Arredondo-García, M.R. Capeding, C. Deseda, T. Chotpitayasunondh, R. Dietze, H.I. Hj Muhammad Ismail, H. Reynales, K. Limkittikul, D.M. Rivera-Medina, H.N. Tran, A. Bouckenooghe, D. Chansinghakul, M. Cortés, K. Fanouillere, R. Forrat, C. Frago, S. Gailhardou, N. Jackson, F. Noriega, E. Plennevaux, T.A. Wartel, B. Zambrano, and M. Saville, for the CYD-TDV Dengue Vaccine Working Group*

Hadinegoro SR et al. NEJM 2015 Sep 24;373(13)

> 35,000 children in 10 countries in Asia and Latin America

CYD-TDV phase IIb/III summary (up to 2017)

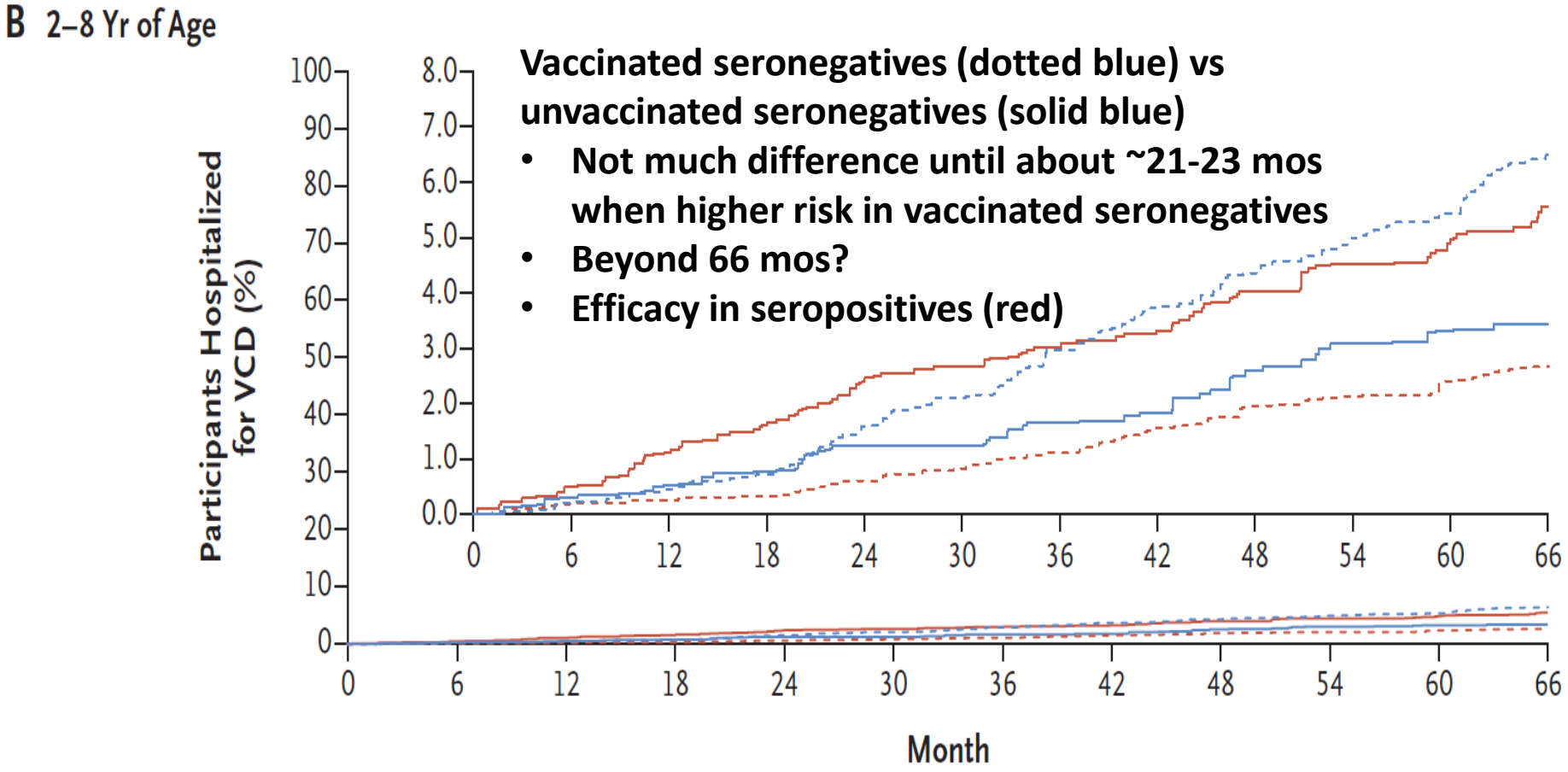
- **Serotype-specific differences** in efficacy
  - Poor efficacy against DENV-2
  - Moderate efficacy against DENV-1
  - Good efficacy against DENV-3 and 4
  - But **balanced Nabs** by PRNT after 3rd (final) dose
    - Relevance of Nabs titers?
    - Vaccinees with higher month 13 titer to a serotype had lower risk of symptomatic dengue from that serotype (hazard ratios, 0.19–0.43 per 10-fold increase in titer). Nabs are only a crude indicator of clinical outcomes [Moodie Z et al. J Infect Dis. 2018 Feb 14]
- Poor efficacy in **very young** children and dengue **seronegative** persons (not independent of age)
- Higher efficacy against severe and hospitalized dengue than overall symptomatic dengue
- Elevated **risk of hospitalized dengue** in vaccinated 2-5 year olds in Year 3 (RR=7.5)
  - Risk diminished in Years 4 and 5
  - **Not seen consistently in older age groups (indicated age ≥ 9 yrs)**
    - Few seronegative older age subjects

Post-hoc analysis of serostatus

- Dengue anti-NS1 IgG ELISA to test samples from month 13 of phase IIb/III trials to infer baseline dengue serostatus
- In seronegative persons, cumulative 5-year incidence of hospitalized dengue was:
  - If 2 to 16 years old
    - 3.06% in vaccine recipients & 1.87% in controls
    - Hazard ratio of **1.75** (95% CI, 1.14 to 2.70)
  - If 9 to 16 years old (within indicated age for licensure)
    - 1.57% in vaccine recipients & 1.09% among controls
    - Hazard ratio of **1.41** (95% CI, 0.74 to 2.68)

[Sridhar S et al. NEJM. 2018 Jun 13]

Post-hoc analysis of serostatus (2-8 yrs old)



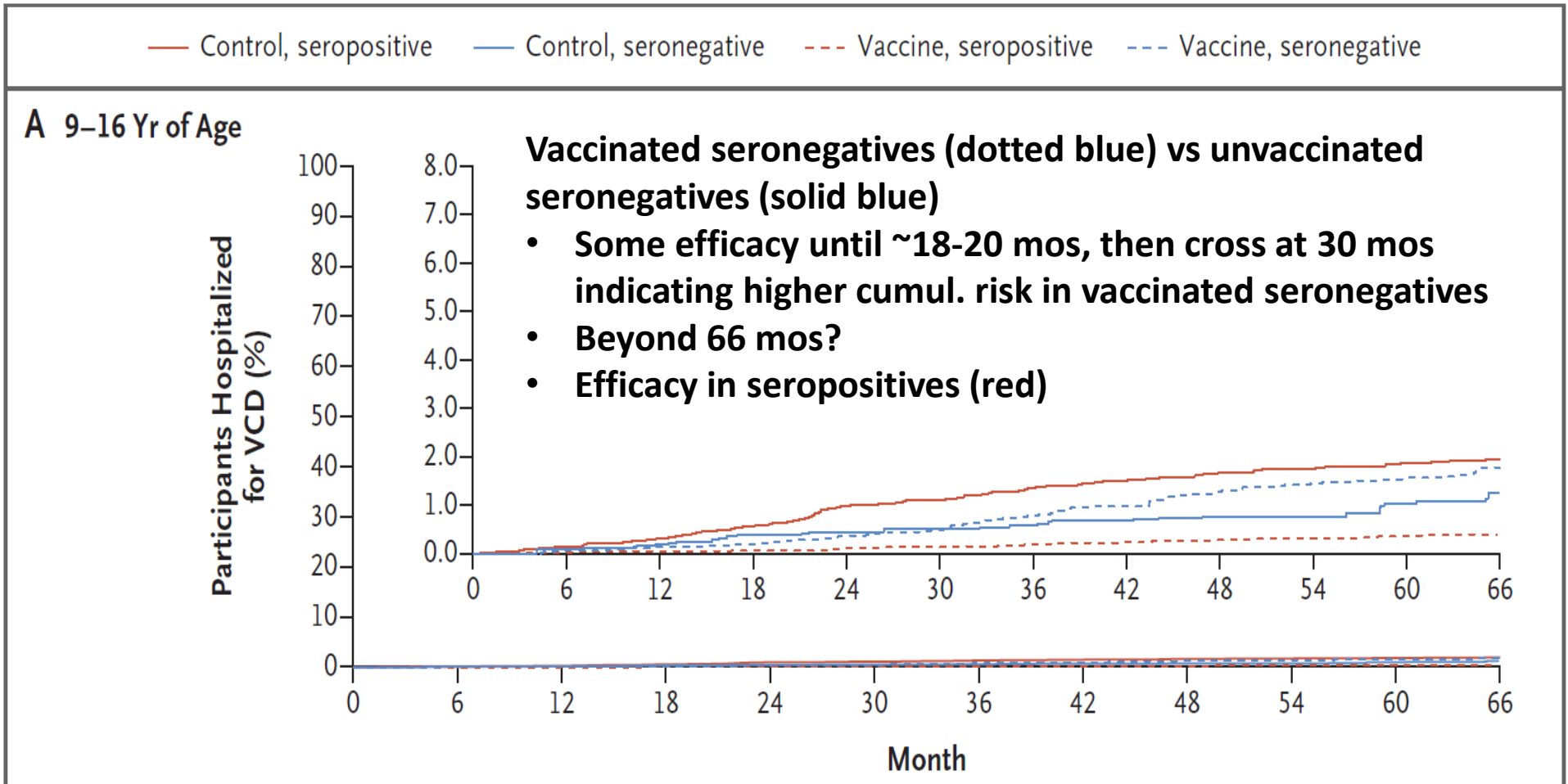
Vaccinated seronegatives (dotted blue) vs unvaccinated seronegatives (solid blue)

- **Not much difference until about ~21-23 mos when higher risk in vaccinated seronegatives**
- **Beyond 66 mos?**
- **Efficacy in seropositives (red)**

No. at Risk

Control, seropositive	156	156	153	150	150	150	150	149	148	146	144	89
Control, seronegative	101	100	100	98	98	97	97	97	96	96	96	57
Vaccine, seropositive	313	313	312	311	310	308	307	304	301	298	294	208
Vaccine, seronegative	193	192	192	192	190	187	186	186	182	180	177	106

Post-hoc analysis of serostatus (9-16 yrs old)



Vaccinated seronegatives (dotted blue) vs unvaccinated seronegatives (solid blue)

- **Some efficacy until ~18-20 mos, then cross at 30 mos indicating higher cumul. risk in vaccinated seronegatives**
- **Beyond 66 mos?**
- **Efficacy in seropositives (red)**

No. at Risk

Control, seropositive	730	725	705	699	695	689	688	686	658	615	592	150
Control, seronegative	207	207	201	199	199	195	194	192	185	174	167	58
Vaccine, seropositive	1503	1490	1462	1453	1447	1434	1422	1403	1351	1284	1226	308
Vaccine, seronegative	375	374	368	366	364	361	358	350	339	322	311	96

Revised WHO SAGE recommendation in Apr 2018

New information

- Vaccine efficacy against symptomatic dengue in **first 25 months** after first dose (i.e., up to 13 months after 3rd [final] dose)
  - High among inferred baseline **seropositive participants ≥ 9 years old**: **76.0%** (95%CI, 63.9 to 84.0)
  - Much lower among inferred baseline **seronegative participants ≥ 9 years old**: **38.8%** (95%CI, –0.9 to 62.9%)

- **Increased risk** of hospitalized and severe dengue in seronegative individuals **[including ≥ 9 years old] starting about 30 months** after first dose

Revised WHO SAGE recommendation in Apr 2018

Recommendation

- 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

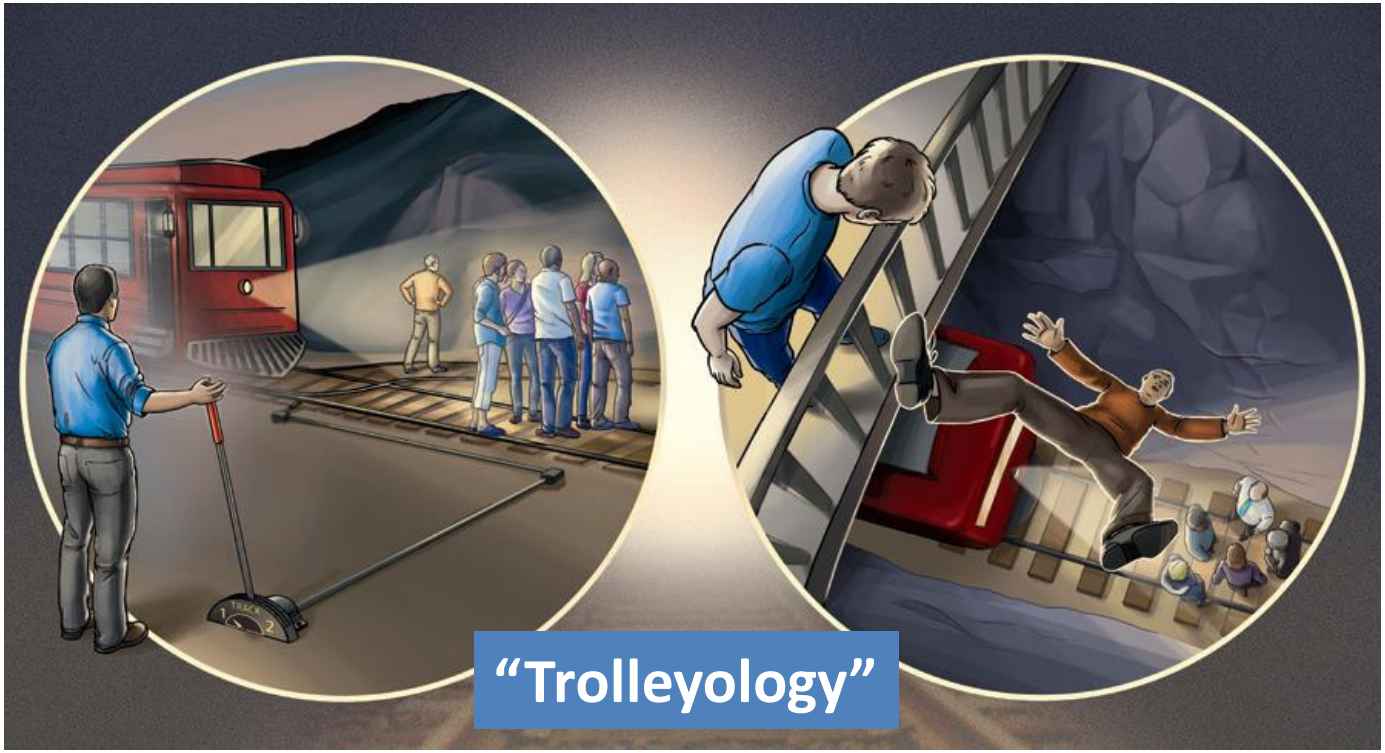
- *Developing an **accurate point-of-care assay for dengue serostatus** is a priority*
- *Given that no assay will be 100% specific, some truly seronegative individuals may be vaccinated due to a false positive test result*

Benefit of moderately effective vaccines

- Overall population level benefit of Dengvaxia® remains favorable in high transmission populations [WHO SAGE revised recommendations, Apr 2018]
  - In areas with 70% dengue seroprevalence, over a 5-year period:
    - For every 4 severe cases prevented in seropositive vaccinees, there would be 1 excess severe case in seronegative vaccinees per 1,000
    - For every 13 hospitalizations prevented in seropositive vaccinees, there would be 1 excess hospitalization in seronegative vaccinees per 1,000
- In general, vaccines with moderate efficacy may have high public health impact for diseases that:
  - Have high burden, severity, economic costs
  - Cause frequent outbreaks
  - Disrupt healthcare systems
  - Cause political instability

Benefit of moderately effective vaccines

However, safety concerns have been true hurdle to implementation



- Utilitarianism (maximize benefit, minimize harm) vs. intentional harm
- "Regulating for utilitarian algorithms may paradoxically increase casualties by postponing the adoption of a safer technology [self-driving cars]."

[Rosenbaum L. NEJM. 2018 Jun 13]

Possible reasons for CYD-TDV performance

- Interference after 1st dose in dengue naïve persons
  - DENV-4 immuno-dominant after 1st dose, but balanced PRNT titers after 3rd dose (prob. due to heterotypic immune responses) [Dorigatti et al. Vaccine 2015 Jul 17;33(31):3746-51]
  - Using PRNT titers to guide vaccine formulation may not have been appropriate for all serotypes
- CYD-TDV vaccination served as “primary-like” infection in dengue naive persons leading to “secondary-like” infection by first natural infection
  - Implies CYD-TDV behaves like monovalent dengue vaccine due to interference

Possible reasons for CYD-TDV performance

- CYD-TDV did not elicit substantial T cell responses to dengue antigens
  - T cell responses are elicited by non-structural proteins which were from YF 17D in CYD-TDV
  - T cell responses may be important for protection from severe disease
- Relevant epitopes for protection may be different in CDY-TDV and natural virus
  - E.g., Role of conformational epitopes
- Younger children with immature immune systems and physiology
  - Possible differences in strength and/or duration of immune response, and in clinical presentation

Implications for 2nd generation vaccines

- Induction of **long term homotypic** vs. **transient heterotypic** vs. **long term heterotypic** immune responses need to be addressed
  - For live vaccines, presence of **interference** leading to homotypic vs. heterotypic immune responses should be evaluated
    - Infectivity of vaccine serotype components can be assessed in **early clinical studies**
  - **Duration** of protection and/or risk should be assessed
    - Active surveillance for symptomatic dengue and severe dengue should be extended for **several transmission seasons**
- Dengue **serostatus** before vaccination may be critical
  - Pre-vaccination blood samples from all trial participants should be collected
  - Analysis should be done by serostatus

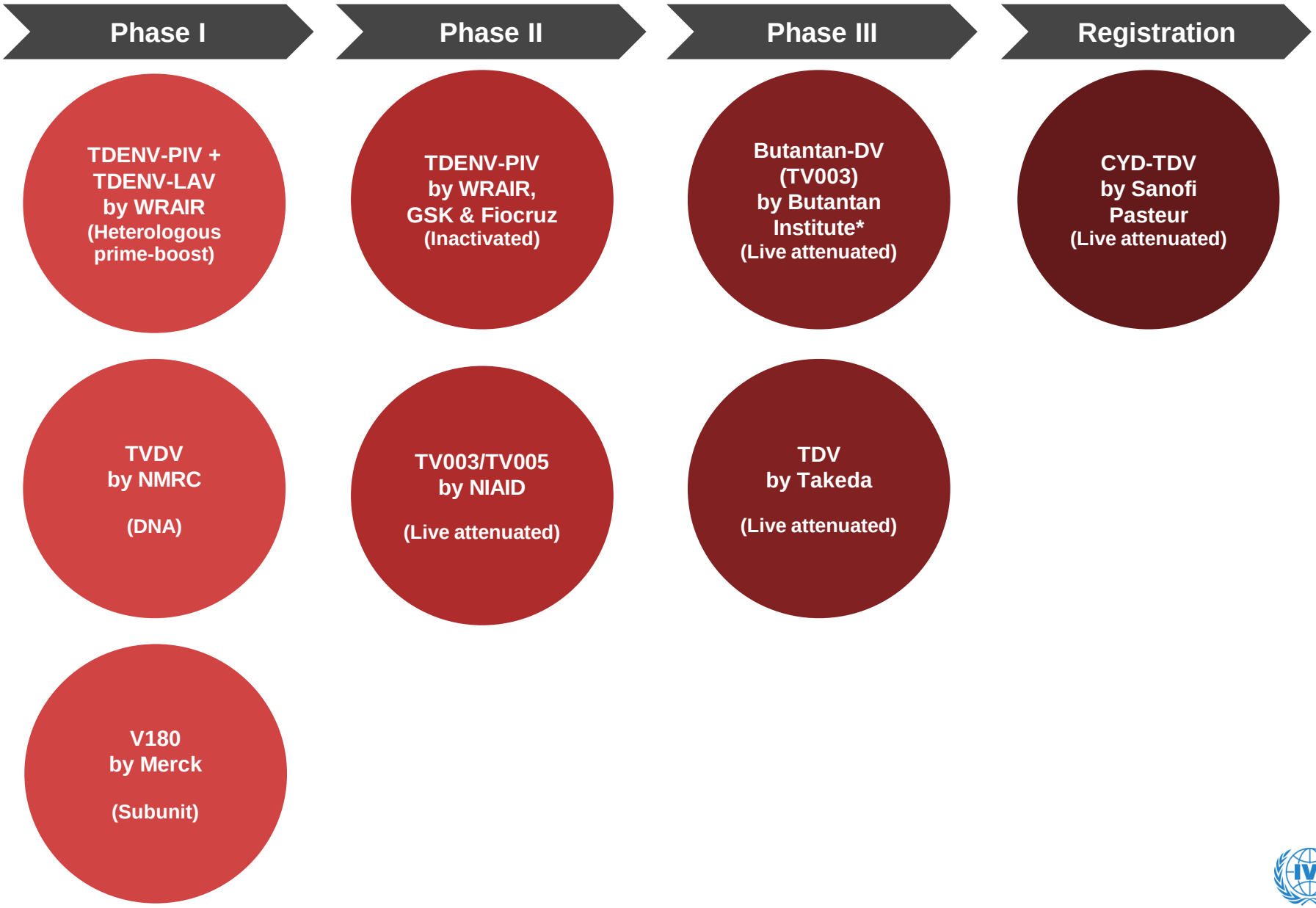
Implications for 2nd generation vaccines

- Traditional **neutralization assays** are crude measures of clinically relevant immune responses
  - Other markers of long term homotypic vs. transient heterotypic vs. long term heterotypic immune responses should be investigated for risk and protection
    - Potential importance of **conformational** epitopes
    - Assessment at **different time points** after vaccination
  - Role of **CMI** in protection
    - Potential importance of non-structural protein epitopes
  - Importance of investigating **immune correlates**
- Studies with clinically relevant endpoints are needed
  - Clinical efficacy trials for definitive evidence to support licensure
  - Controlled **human infection models** for proof-of-concept and down selection
- Other vaccine design approaches are worth pursuing

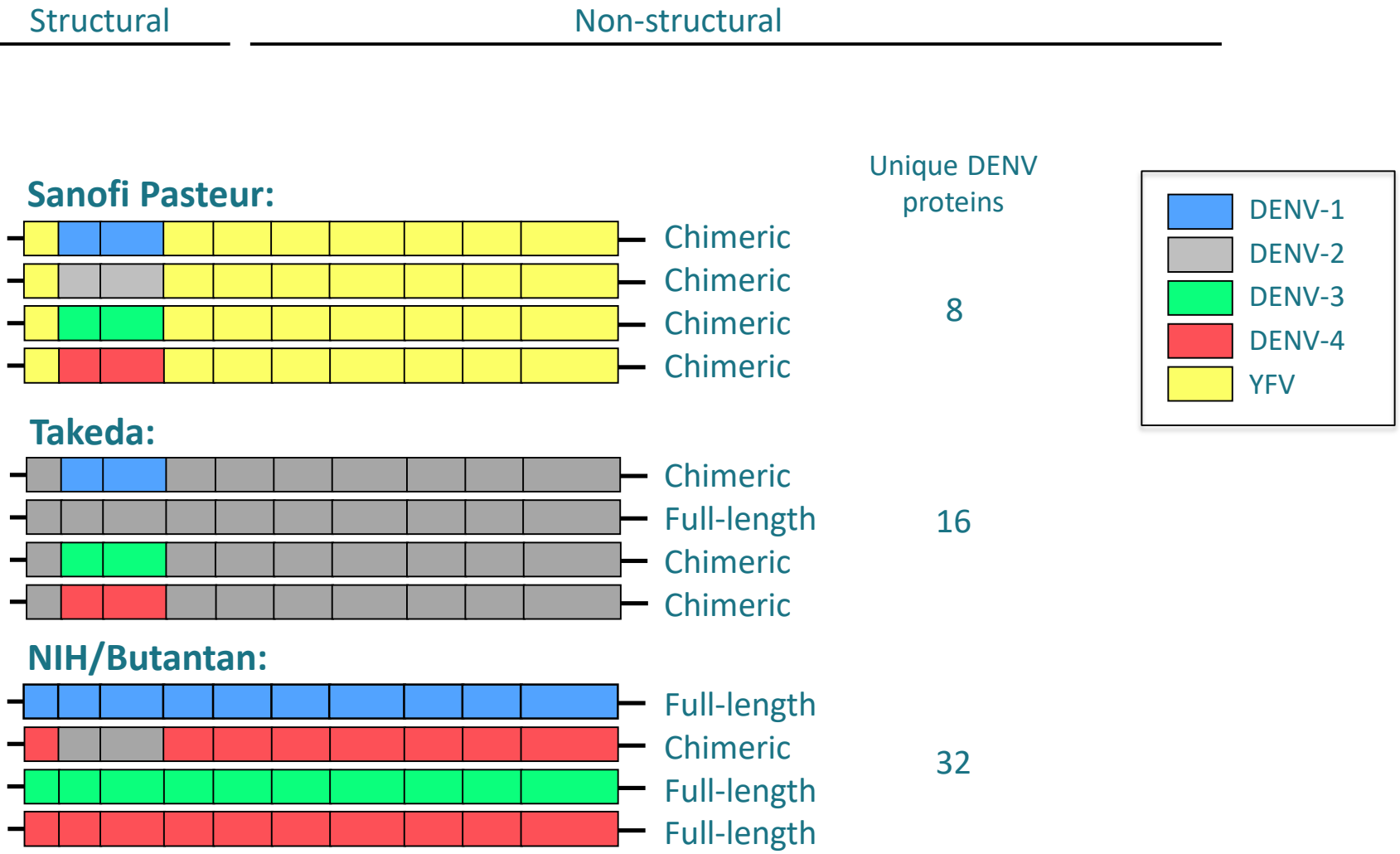
Dengue vaccine pipeline in human trials

Sponsor/ Developer	Design (ALL tetravalent)	Name
Sanofi Pasteur	**Live attenuated recombinant (chimera with YF17D backbone)**	**Dengvaxia® (CYD-TDV)**
Takeda	**Live attenuated recombinant (chimera with DENV-2 backbone)**	**TDV**
US NIH Brazil (Butantan) Vietnam (Vabiotech) India (Panacea, Serum Institute, Indian Immunologicals) Taiwan (Medigen Biotech) Merck (Excl: US, Can, EU, China, Japan)	**Live attenuated recombinant (full length or DENV-2 chimera with DENV-4 backbone)**	**TV003/TV005**
GSK/ Fiocruz/ US Army	**Inactivated whole virus + adjuv**	**TDENV-PIV DPIV**
Merck	**Recombinant protein subunit (80% E protein) + adjuv**	**V180**
US Navy	**DNA (plasmid) + adjuv**	**TVDV**
US Army	**Heterologous prime-boost (inact whole + live atten)**	**TDENV-PIV + TDENV-LAV**

Dengue vaccine pipeline status in human trials



Two live attenuated vaccines in phase III trials



TV003/TV005 (US NIH) status

- DENV attenuated by deletions in 3'UTR, or rDENV-2/DENV4Δ30 chimerization (for DENV-2 component)
- TV003 contains 3log10 PFU/component, TV005 contains 10-fold higher dose of rDENV2/4Δ30
- Extensively studied in phase I trials, including controlled human infection studies
- Elicits transient viremia in most subjects (~75%)
- For all 4 serotype components, **no boost observed with 2nd dose**

TV003 in human infection model

RESEARCH ARTICLE

INFECTIOUS DISEASE

The live attenuated dengue vaccine TV003 elicits complete protection against dengue in a human challenge model

Beth D. Kirkpatrick,[1]* Stephen S. Whitehead,[2]* Kristen K. Pierce,[1] Cecilia M. Tibery,[3] Palmtama L. Grier,[3] Noreen A. Hynes,[4] Catherine J. Larsson,[1] Beulah P. Sabundayo,[3] Kawsar R. Talaat,[3] Anna Janiak,[3] Marya P. Carmolli,[1] Catherine J. Luke,[4] Sean A. Diehl,[1] Anna P. Durbin[3†]

- TV003 or placebo recipients were challenged after 6 months with DENV-2 strain (rDEN2Δ30)
- Of 21 TV003 recipients who were challenged, NONE developed rDEN2Δ30 viremia, rash, neutropenia
- Of 20 placebo recipients, ALL developed viremia, 80% rash, 20% neutropenia
- Role of human infection model in down selecting candidates

Kirkpatrick BD et al. Sci Trans Med 2016 Mar 16;8(330):330ra36

Butantan-DV (Butantan) status

- Butantan-DV (equivalent to TV003)
- Phase III trial ongoing (NCT02406729)
  - DB-RCT at multiple sites in Brazil
  - 2:1 ratio of vaccine:placebo
  - **Single dose**, lyophilized product
  - Age groups: 18-59 years, 7-17 years, 2-6 years
  - Study population N=16,944
  - Primary efficacy outcome is incidence density of symptomatic virologically confirmed dengue
  - **Results delayed by low dengue incidence in Brazil in 2017-18; preliminary efficacy results in late 2019?**

TDV (Takeda) status

- DENV/DENV chimeric live tetravalent vaccine based on attenuated DENV-2 backbone
- Has been evaluated in multiple trials in dengue-naïve and exposed subjects, addressing:
  - Delivery routes (SQ, IM, ID)
  - Vaccine formulations (high, low dose)
  - Scheduling (one vs two doses)
- Randomized controlled phase II trial
  - Vaccine administered in 1 or 2 doses separated by 3 or 12 mos
  - 1800 subjects aged 2-17 years
  - Domincan Republic, Panama, Philippines
  - **Preliminary results**: Virologically confirmed dengue was significantly lower in vaccinees (21/1596 [1.3%]) than in controls (9/198 [4.5%]) during 18 month study period

[Sáez-Llorens X et al. Lancet ID. 2018 Feb]

TDV phase III trial

- Phase III multi-country trial ongoing (NCT02747927)
  - DB-RCT trial in children 4-16 years, placebo controlled
  - 0.5 ml TDV SQ day 1 and day 90
  - Study population N=20,100
  - Countries: Brazil, Colombia, Dom. Republic, Nicaragua, Panama, Philippines, Sri Lanka, Thailand
  - **Preliminary efficacy results in early 2019?**

Is tetravalent vaccination needed?

- Are all 4 serotype components needed in tetravalent vaccination to provide protection against all 4 serotypes?
  - Following sequential natural infection with heterotypic DENV, cross-reactive immunity may provide protection against severe disease from other serotypes
  - Is a similar level of cross-protection elicited with simultaneous multivalent dengue vaccination?
- Evaluated protection by heterotypic Nabs following trivalent dengue vaccination and subsequent DENV challenge

[Whitehead S et al. ASTMH Annual Meeting Abstract. 2018 Nov]

Is tetravalent vaccination needed?

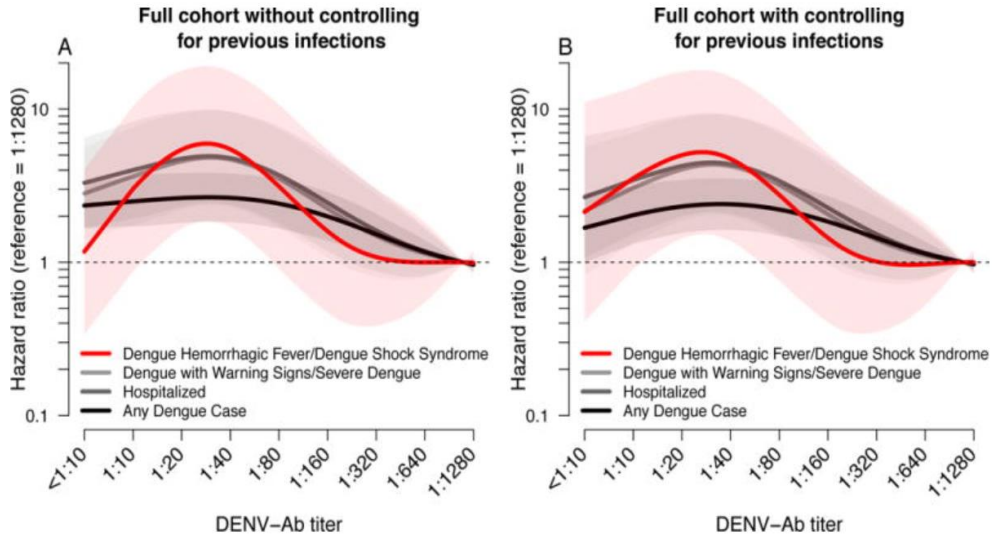
- Subjects were vaccinated with trivalent NIH live attenuated vaccine (DENV-1, 3, 4), then challenged at 6 months with rDEN2Δ30 (DENV-2 strain in CHIM)
  - Whereas TV003 tetravalent vaccination conferred 100% protection against rDEN2Δ30 viremia after challenge, trivalent vaccination conferred only limited protection against rDEN2Δ30 viremia and DENV-2 Nab boost

➢ Protection against each serotype may require each homotypic vaccine serotype component

[Whitehead S et al. ASTMH Annual Meeting Abstract. 2018 Nov]

Are Abs associated with risk and protection?

Fig. 2



Continuous hazard ratio curves for severe dengue disease or any dengue case by pre-existing DENV-Ab titer for the Pediatric Dengue Cohort. Cox proportional hazard models were fit without (**A**) or with (**B**) control for number of previous infections. Models were also adjusted for sex, epidemic season, and age.

Binding Abs were associated with both clinical risk and protection at different levels

[Katzelnick L et al. Antibody-dependent enhancement of severe dengue disease in humans. Science. 2017 Nov 17]

- 12 yr pediatric cohort study in Nicaragua
- iELISA binding Abs to E fusion loop & prM

- Pre-existing anti-DENV **Abs 1:21–1:80**, DHF/DSS hazard was **7.64-fold higher**

- Anti-DENV **Abs 1:21–1:80** had cumulative DHF/DSS hazard of **11.4%**
- Anti-DENV A**bs <1:21 with past dengue** had hazard of **6.6%**
- **DENV-naïve & anti-DENV Abs >1:1280** had hazard of **1.6% and 1.5%**, respectively

Are Abs associated with risk and protection?

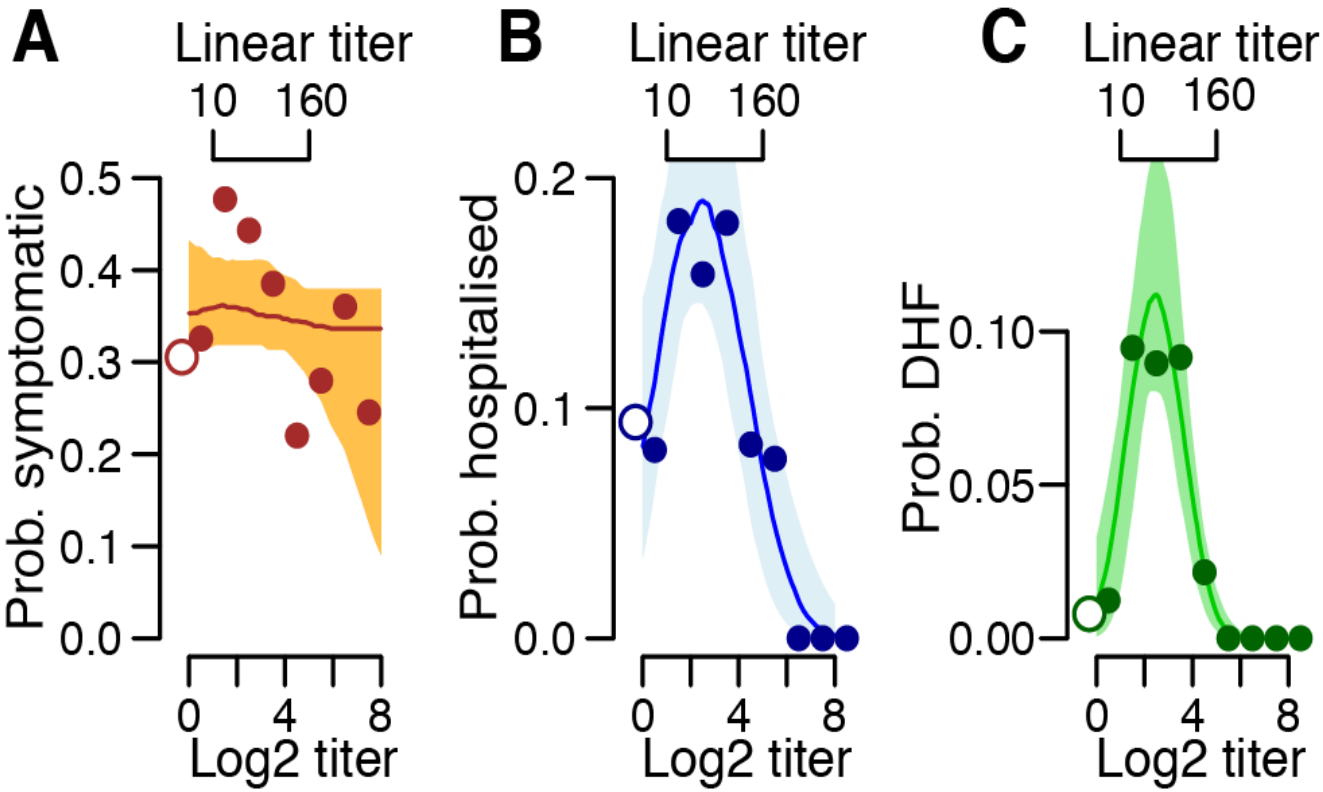


Figure S8. Among those infected, relationship between PRNT titer and probability of outcome. For those infected, the probability of developing any symptoms as a function of mean PRNT titer. (C) For those infected, the probability of being hospitalized. (D) For those infected, the probability of developing DHF as a function of mean PRNT titer. The open circles on the left represent primary infections.

[Salje H et al. Nature. 2018 May]

- Long-term pediatric school-based cohort in Thailand
- Pre-existing **HI titer ≤1:40** had DHF **7.4 times** (95% CI: 2.5-8.2) as often as naïve
- HI >1:40 had DHF 0 times as often
- **PRNT titers ≤1:100** had DHF **7.5 times** (95%CI: 2.4-11.6) as often as naïve
- PRNT >1:100 had DHF 0 times as often

HI and NAbs were associated with both clinical risk and protection at different levels

Pursuit of immune correlates

- Existence of clinically relevant data and samples
  - Well-characterized natural cohort studies in several countries
  - Dengue vaccine studies with clinical endpoints
    - SP phase IIb and III trials (~30,000 subjects, ~4000 with baseline serum)
    - NIH P01 “piggy-back” study (PI: Alan Rothman) leveraging SP phase III trial in Cebu, Philippines
    - Univ of Phil-Manila cohort in Cebu, Philippines during Dengvaxia® vaccination campaign (~3000 subjects with baseline serum, ~50% vaccinated with one dose of Dengvaxia®)
    - Butantan phase III trial (~16,000 subjects with baseline serum)
    - Takeda phase II and III trials (~21,000 subjects with baseline serum)
  - Controlled human infection models
    - US NIH/JHU (viremia, rash)
    - WRAIR/SUNY (fever, other signs/symptoms)
- Broadly coordinated/harmonized effort to investigate correlates…but, immune correlates will likely differ by vaccine and assay

New approaches to dengue vaccine design

- In longer term, other approaches should be pursued that may avoid some of the challenges of serotype interactions
  - Target epitopes that induce highly neutralizing response
    - Guided by structural biology
    - Conformational epitopes
    - Serotype-specific and cross-protective
  - NS1-based vaccines
  - Transmission blocking vaccines

- For now, current pipeline in human trials will need to be optimized as public health tools and to advance scientific knowledge in order to accelerate overall dengue vaccine development

Conclusions

- Dengue vaccine is possible but challenging due to interactions of 4 serotypes
- Sanofi Pasteur's CYD-TDV had mixed efficacy and safety results
  - Likely overall public health benefit has been hampered by safety concerns
  - Important lessons for 2nd generation vaccines
- Performance of two live attenuated vaccines currently in phase III trials will be critical to overall field

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