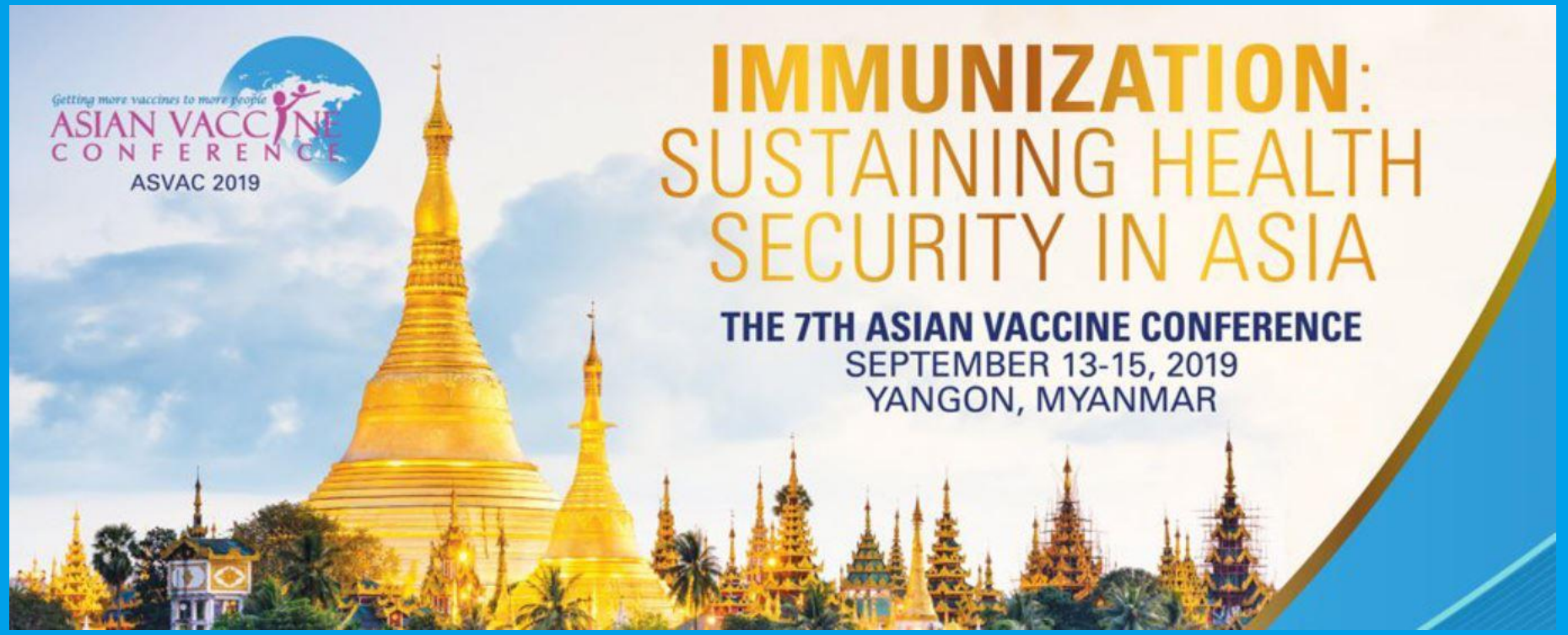


Where Next with the Dengue Vaccines?

Anh Wartel, MD
IVI, Head of Clinical Development and Regulatory Affairs

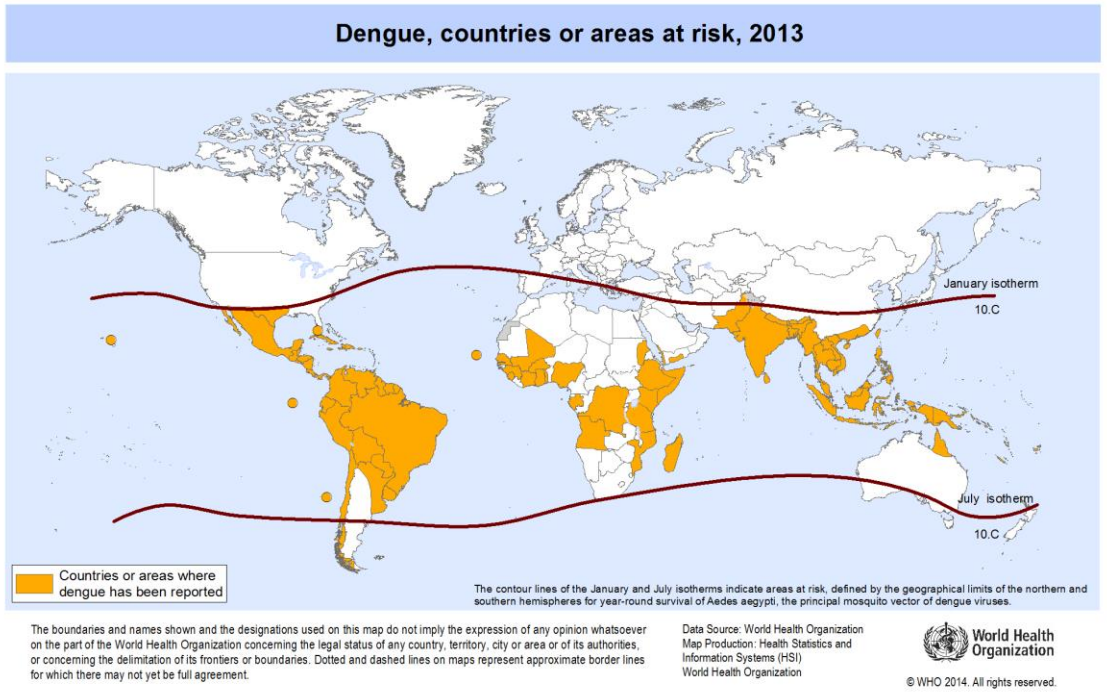
International Vaccine Institute

PRESENTATION OUTLINE

- Dengue Epidemiological Situation
- CYD-TDV Dengue Vaccine – Lessons Learnt
- Points for Consideration - 2nd Generation of Dengue Vaccine
- Summary

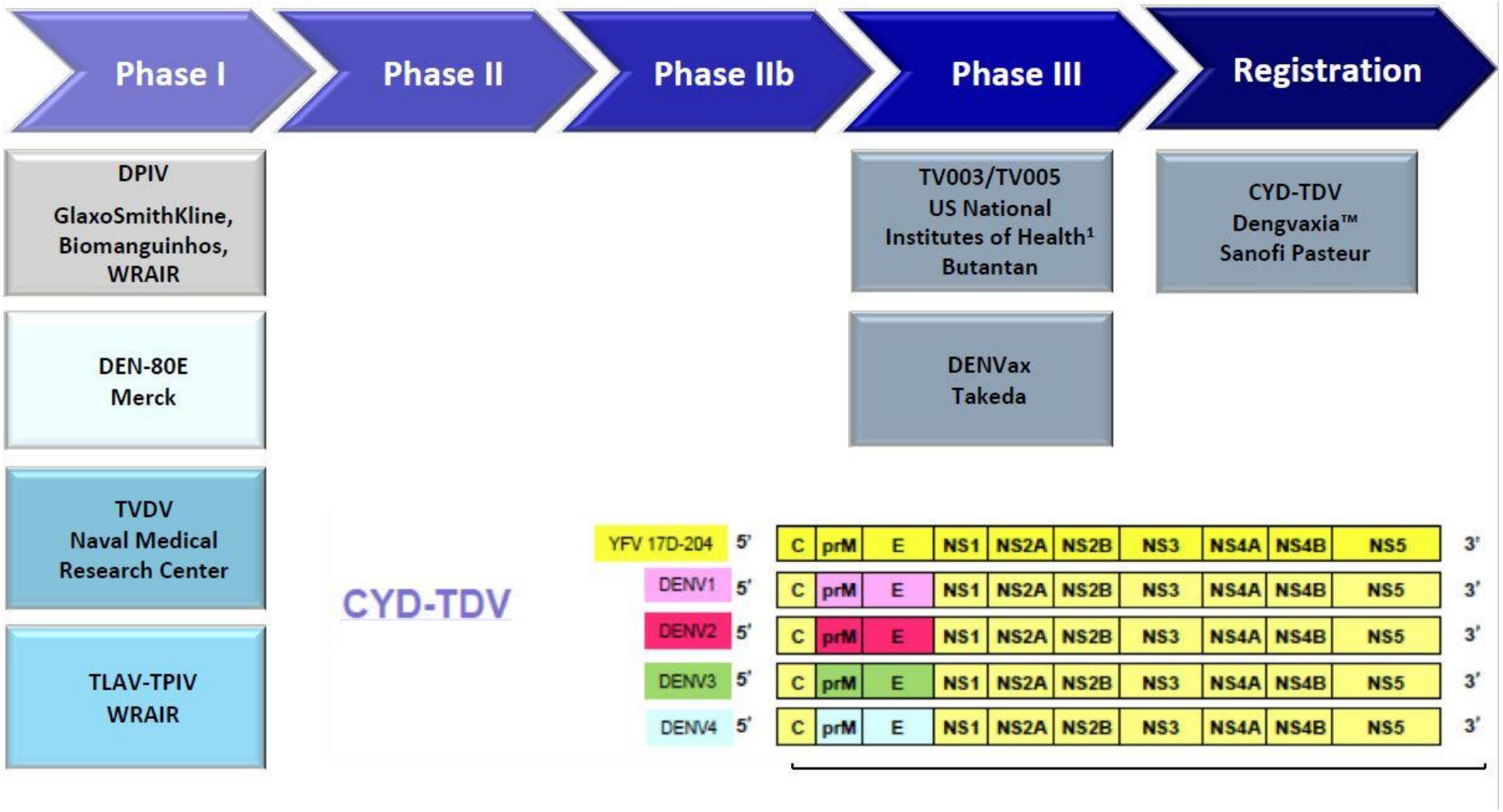
GLOBAL BURDEN OF DENGUE

- Dengue is a **mosquito-borne viral infection** and the infection causes **flu-like illness**, and occasionally develops into **severe dengue**
- The global incidence of dengue has grown dramatically in recent decades
  - **~ 390 million** dengue **infections per year,** of which **96 million** symptomatic infections with any severity.
- **About half** of the world's population is now at risk
  - **3.9 billion people**, in **128 countries**, are at risk of infection with dengue viruses
- **In 2019**, **significant increases** of number of cases are being observed in several countries in Asia: Cambodia, Lao, Malaysia, Singapore, Philippines, Vietnam, Thailand compared to the same periods in 2018. Similar rise is currently observed in Latin America (e.g., Brazil)



1) WHO (2019). Fact Sheet - Dengue and Severe Dengue. Available at: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue; 2) WHO (2014)- Dengue, countries or areas at risk, 2013;3) WHO - Dengue Situation Update No. 576. Available at: https://www.who.int/docs/default-source/wpro---documents/emergency/surveillance/dengue/dengue-20190829.pdf?sfvrsn=5160e027_14 ; 4) PAHO – Epidemiological Update Dengue. Available at: https://www.paho.org/hq/index.php?option=com_docman&view=download&category_slug=dengue-2217&alias=49149-24-june-2019-dengue-epidemiological-update-1&Itemid=270&lang=en (Accessed in Aug 2019)

DENGUE VACCINE DEVELOPMENT LANDSCAPE AT THAT TIME…



WHO (2018). Summary of WHO Position Paper, September 2018. Available at: https://www.who.int/immunization/policy/position_papers/pp_dengue_2018_presentation.pdf?ua=1 (Accessed in Aug 2019)

CYD-TDV SAFETY AND EFFICACY

- Pooled data from phase IIb and III efficacy trials in Asia and Latin America

- **2-8 yrs old**
  - VE for DENV-1 = 46.6 (95%CI, 25.7 to 61.5); DENV-2 = 33.6 (1.3 to 55.0); DENV-3 = 62.1 (28.4 to 80.3); DENV-4 = 51.7 (17.6 to 71.8)
  - VE in seropositive = 70.1 (32.3 to 87.3); seronegative = 14.4 (–111 to 63.5)
  - VE against hospitalized dengue = 56.1 (26.2 to 74.1)

- **9-16 yrs old**
  - VE for DENV-1 = 58.4 (47.7 to 66.9); DENV-2 = 47.1 (31.3 to 59.2); DENV-3 = 73.6 (64.4 to 80.4); DENV-4 = 83.2 (76.2 to 88.2)
  - VE in **seropositive = 81.9** (67.2 to 90.0); **seronegative = 52.5** (5.9 to 76.1)
  - VE against hospitalized dengue = 80.8 (70.1 to 87.7)

- Hospitalized dengue in vaccinees 2-5 yrs old in Yr 3 of Asian phase III: **RR = 7.45** (1.15–313.80)

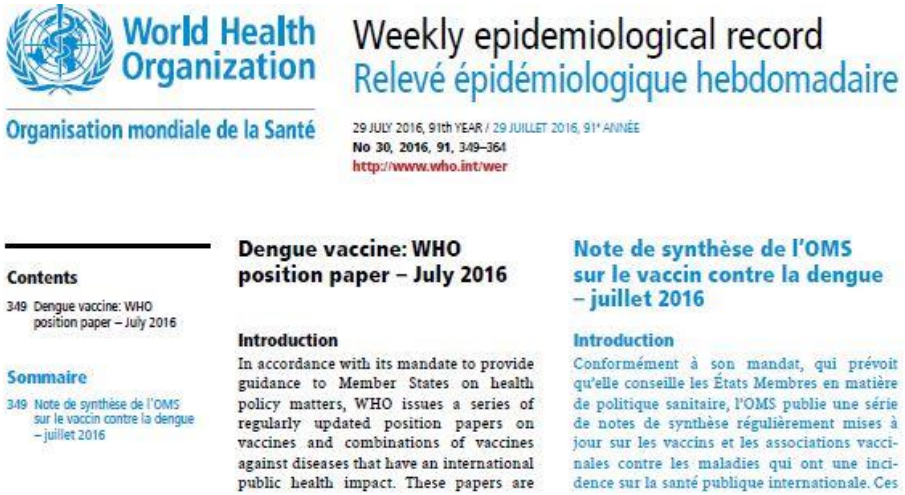
Hadinegoro et al. Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. N Engl J Med. 2015 Sep 24;373(13):1195-206. doi: 10.1056/NEJMoa1506223. Epub 2015 Jul 27

ONLY LICENSED DENGUE VACCINE, CYD TDV – WHO POSITION PAPER (2016)

- Based on the clinical data including the initial pivotal phase III results based on immuno-subset (dengue serostatus), WHO issued a position paper in Jul **2016** on the CYD TDV use as a 3-dose series (0/6/12M) in 9yrs and above

- Introduction of CYD-TDV dengue vaccine **only** in geographic settings with **high burden** of disease

- At least 70% seroprevalence in the targeted age group to maximize public health impact and cost effectiveness
  - Overall seroprevalence of the phase 3 studies in 9-16 yrs study participants was **80%**
  - Use of the CYD TDV vaccine in **lower seroprevalence** in the age group recommended for vaccination is **not recommended** because of **low efficacy** and potential **long-term risk of severe** dengue in vaccinated **seronegative individuals**



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29 JULY 2016, 91th YEAR / 29 JUILLET 2016, 91e ANNÉE
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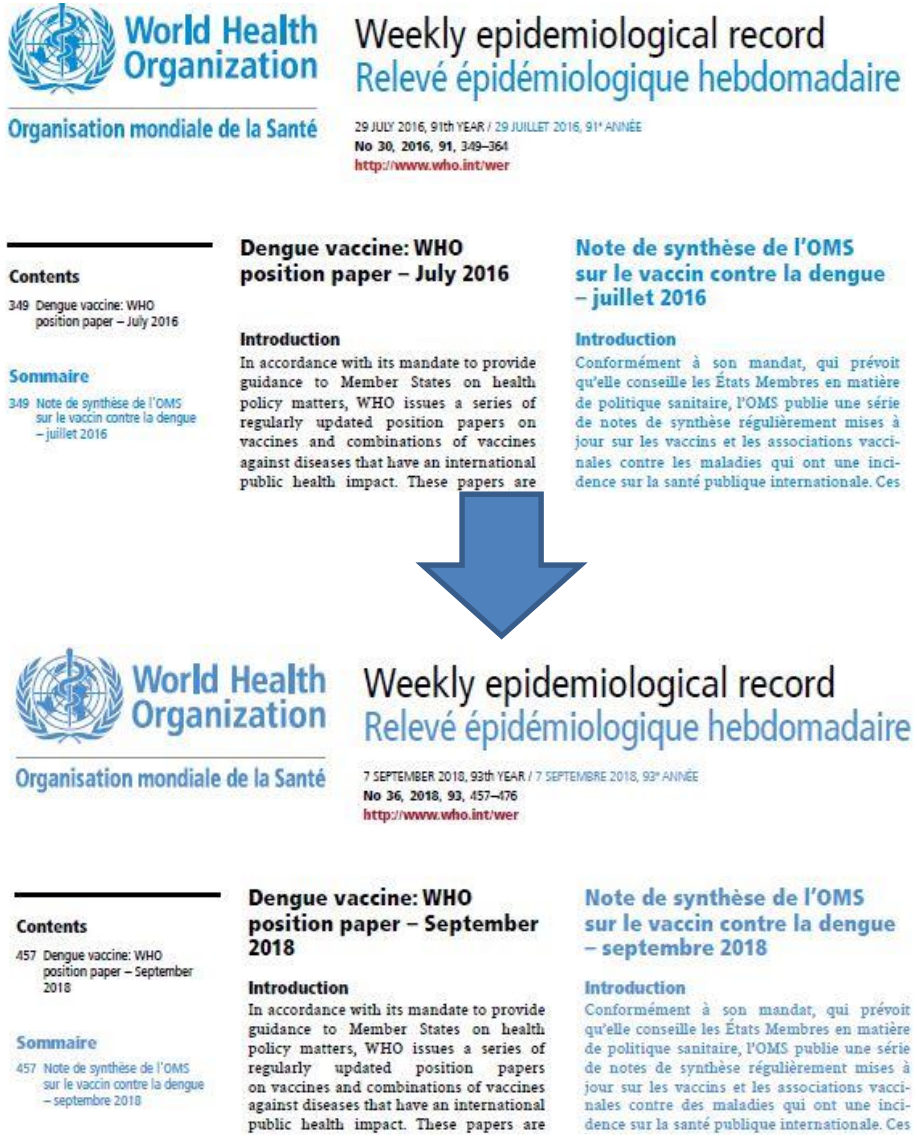
WHO (2016). WHO Position Paper on dengue No.30, 2016, 91, 349-364. Available at: https://www.who.int/wer/2016/wer9130.pdf?ua=1 (Accessed in Aug 2019)

ONLY LICENSED DENGUE VACCINE, CYD TDV – WHO POSITION PAPER (2018)

- This position paper in Sep **2018** replaces the WHO position paper on dengue vaccines published in Jul 2016
- In **November 2017**, additional results of a **retrospective analysis of data** from clinical trials, using a new serological assay
- The assay enabled classification of trial participants according to their **dengue serostatus** prior to receipt of the first vaccine dose:
  - sera collected at **month 13 (post-dose 3)** from all trial participants were tested to retrospectively classify trial participants by serostatus prior to vaccination
  - Rationale for the assay was that the **NS1** protein in Dengue virus is different from the NS1 protein in Yellow Fever virus
- These data revealed an **excess risk of severe dengue** in **seronegative vaccine** recipients compared to **seronegative non-vaccinated** individuals, while confirming **long-term protection in seropositive individuals**



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WHO (2018). WHO Position Paper on dengue No.36, 2018, 93, 457-476. Available at: https://apps.who.int/iris/bitstream/handle/10665/274315/WER9336.pdf?ua=1 (Accessed in Aug 2019)

CYD TDV POST LICENSURE ANALYSES IN ALL AGE

- Vaccine efficacy against symptomatic virologically confirmed dengue (VCD) in the 25 months after dose 1 (2-16 yrs)

Serostatus Pre-Vaccination	Vaccine Efficacy (VE)	95% CI (VE)
Seropositive	**72%**	58; 82
Seronegative	**32%**	-9; 58

- Relative risk of hospitalized dengue comparing vaccinated to controls in the 66 months after dose 1 (2-16 yrs)

Serostatus Pre-Vaccination	RR (CYD:Control)	95% CI (RR)
Seropositive	**0.29**	0.21; 0.42
Seronegative	**1.65**	1.04; 2.61

- Relative risk of severe VCD comparing vaccinated to controls in the 66 months after dose 1 (2-16 yrs)

Serostatus Pre-Vaccination	RR (CYD:Control)	95% CI (RR)
Seropositive	**0.28**	0.15; 0.52
Seronegative	**3.00**	1.10; 8.15

1) Sridhar et al. Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. N Engl J Med. 2018 Jul 26;379(4):327-340; 2) WHO (2018). Summary of WHO Position Paper, September 2018. Available at: https://www.who.int/immunization/policy/position_papers/pp_dengue_2018_presentation.pdf?ua=1 (Accessed in Aug 2019)

CYD TDV POST LICENSURE ANALYSES IN 9-16 YRS

- Vaccine efficacy against symptomatic virologically confirmed dengue (VCD) in the 25 months after dose 1 (9-16 yrs)

Serostatus Pre-Vaccination	Vaccine Efficacy (VE)	95% CI (VE)
Seropositive	**77%**	70; 82
Seronegative	**18%**	-18; 43

- Relative risk of hospitalized dengue comparing vaccinated to controls after dose 1 (9-16 yrs)

Serostatus Pre-Vaccination	RR (CYD:Control)	95% CI (RR)
Seropositive	**0.21**	0.15; 0.30
Seronegative	**1.46**	0.85; 2.49

- Relative risk of severe VCD comparing vaccinated to controls after dose 1 (9-16 yrs)

Serostatus Pre-Vaccination	RR (CYD:Control)	95% CI (RR)
Seropositive	**0.18**	0.09; 0.37
Seronegative	**6.25**	0.81; 48.32

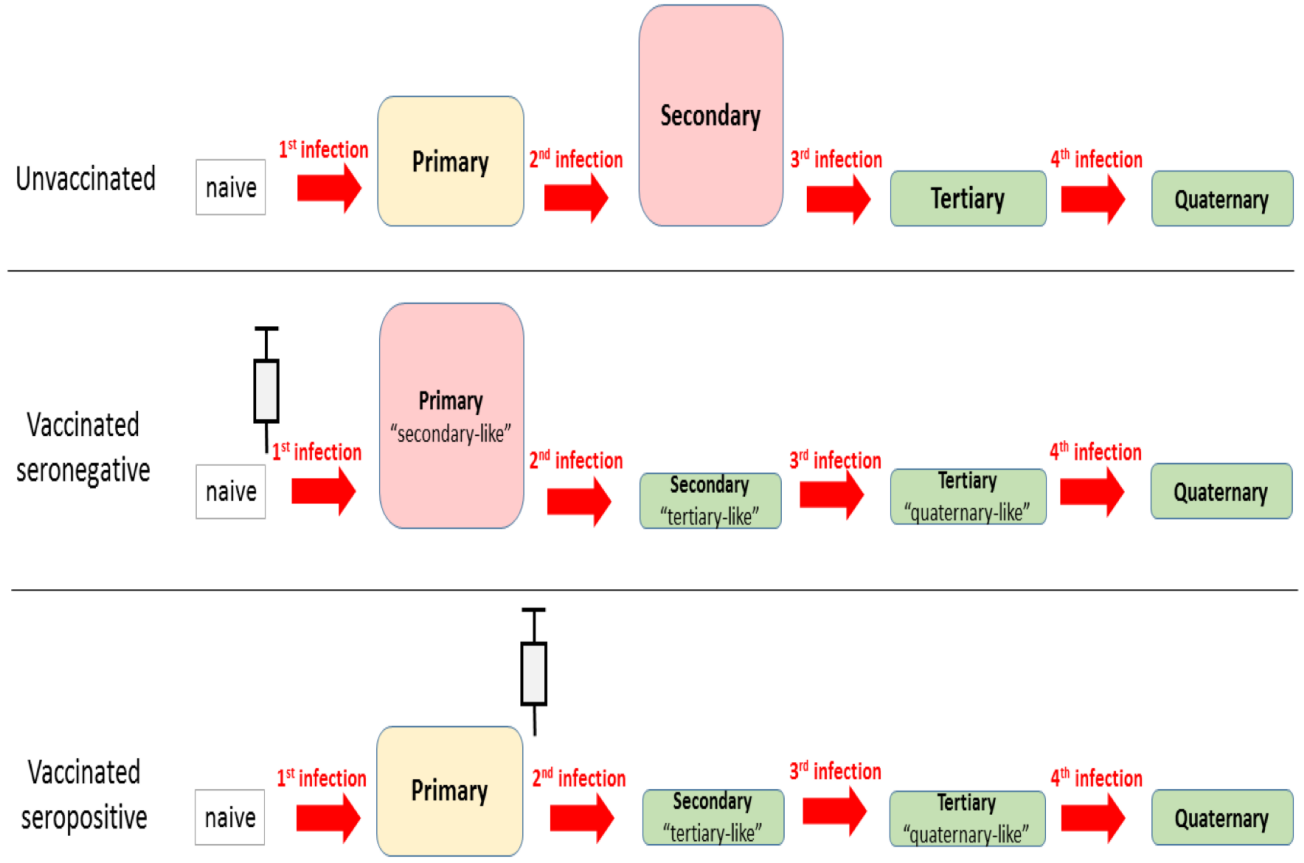
1) Sridhar et al. Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. N Engl J Med. 2018 Jul 26;379(4):327-340; 2) WHO (2018). Summary of WHO Position Paper, September 2018. Available at: https://www.who.int/immunization/policy/position_papers/pp_dengue_2018_presentation.pdf?ua=1 (Accessed in Aug 2019)

EXPLANATORY HYPOTHESIS FOR EXCESS CASES IN CYD-TDV SERONEGATIVE TRIAL SUBJECTS

- **Silent infection** as mode of action
- 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 (with their 1st WT infection) once cross-immunity wanes
3. **Seropositive recipients** have tertiary-like breakthrough infection (with their 2nd WT infection) once cross-immunity wanes

- In high transmission intensity settings, even seronegative recipients gain eventual benefit



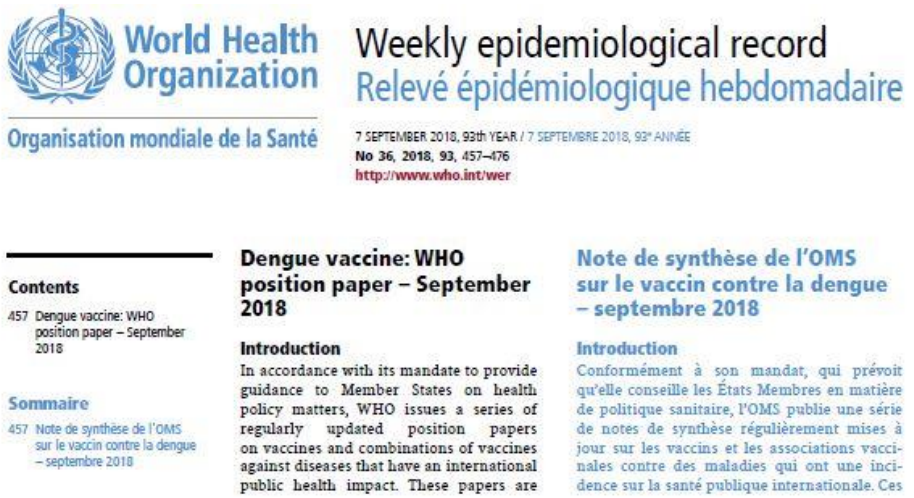
1) WHO (2018). Summary of WHO Position Paper, September 2018. Available at: https://www.who.int/immunization/policy/position_papers/pp_dengue_2018_presentation.pdf?ua=1 (Accessed in Aug 2019); 2) Ferguson et al., Science 2016; Flasche et al., PLoS Med. 2016

ONLY LICENSED DENGUE VACCINE, CYD TDV – WHO POSITION PAPER (2018), RECOMMENDATION AND POLICY

- The live attenuated dengue vaccine CYD-TDV has been shown in clinical trials to be **efficacious and safe** in persons who have had a dengue virus infection in the past (baseline **seropositive** individuals), but carries an **increased risk of hospitalized and severe dengue** in those who experience their first natural dengue infection after vaccination (baseline **seronegative** individuals)

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

- **Policy Options**
  - **Screen and vaccinate** – screen every potential vaccine recipient with a rapid diagnostic test (RDT) to determine serostatus, and only vaccinate those testing Seropositive
  - **Mass-vaccination with seroprevalence threshold** – vaccinate populations in areas where transmission intensity exceeds a certain threshold – e.g. >80% seroprevalence in 9 year-old children



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POSSIBLE REASONS FOR CYD-TDV PERFORMANCES

- **Interference after 1st dose in dengue naïve persons**
  - **DENV-4 immunodominant** after 1st dose, but balanced Neut Ab titers after 3rd dose (due to cross-reactive immunity)

- **CYD-TDV vaccination mimics primary infection in dengue naive persons leading to "secondary-like" infection by first natural infection**
  - CYD-TDV may behave like a monovalent DENV-4 vaccine
  - But primary natural infection leads to monotypic Neut Ab profile, while "primary" CYD-TDV leads to multitypic (cross-reactive) Neutr Ab profile

- **CYD-TDV did not elicit relevant CMI responses to dengue antigens**
  - CD8+ T cell responses elicited by non-structural proteins from YF 17D rather than dengue
  - T cell responses are important for protection from severe disease

- **Relevant epitopes for protection may be different in CYD-TDV and natural virus**
  - e.g., Role of relevant conformational epitopes?

1) Dorigatti et al., *Modelling the immunological response to a tetravalent dengue vaccine from multiple phase-2 trials in Latin America and South East Asia*, Vaccine 2015; 2) Torresi et al., *Replication and excretion of the live attenuated tetravalent dengue vaccine CYD-TDV in a flavivirus-naive adult population: assessment of vaccine viremia and virus shedding*, JID 2017; 3) Ferguson et al., Science 2016; Flasche et al., PLoS Med. 2016; 4) Harenberg et al., *Persistence of Th1/Tc1 responses one year after tetravalent dengue vaccination in adults and adolescents in Singapore*, HVI 2013

LESSONS LEARNT FOR OTHER DENGUE VACCINES

- **Induction of long-term type-specific, and short or long-term cross-reactive immune responses need to be clarified**
  - For live vaccines, presence of **interference** leading to variable type-specific and cross-reactive immune responses should be evaluated (i.e., immunodominant vaccine serotype)
    - – Infectivity of vaccine monotypic components assessed in **early clinical studies**
  - **Duration** of protection/risk needs to be determined
    - – Active surveillance for symptomatic dengue and severe dengue should be extended for **several years**
  - Role in protection against **symptomatic infection vs severe disease**
  - **Virus strain differences from vaccine** may lead to lower efficacy especially with type-specific immunity

- **Dengue serostatus before vaccination is critical**
  - Pre-vaccination blood samples from all trial participants
  - Analysis should be done by dengue serostatus
  - Non-dengue flaviviruses will likely affect immune response, but with unclear clinical effect

Courtesy slide, Dr In-Kyu Yoon, GDAC director

LESSONS LEARNT FOR OTHER DENGUE VACCINES – Cont'ed

- **Traditional neutralization assays are only crude measures of clinically relevant immune responses**
  - Other markers of long-term type-specific vs. short or long-term cross-reactive immune responses should be investigated for protection and risk
    - Marker of protection against **symptomatic infection vs severe disease**
    - Different role at **different time points** after vaccination
    - E.g., importance of **conformational** epitopes
    - E.g., **NS1** Abs; **cellular immunity** against severe disease

- Importance of **investigating immune correlates** of protection/risk

- **Studies with clinically relevant endpoints are necessary**
  - **Clinical efficacy trials** are still needed for definitive evidence to support licensure
  - Controlled **human infection models** for proof-of-concept and down selection
  - **Better NHP models** should be evaluated

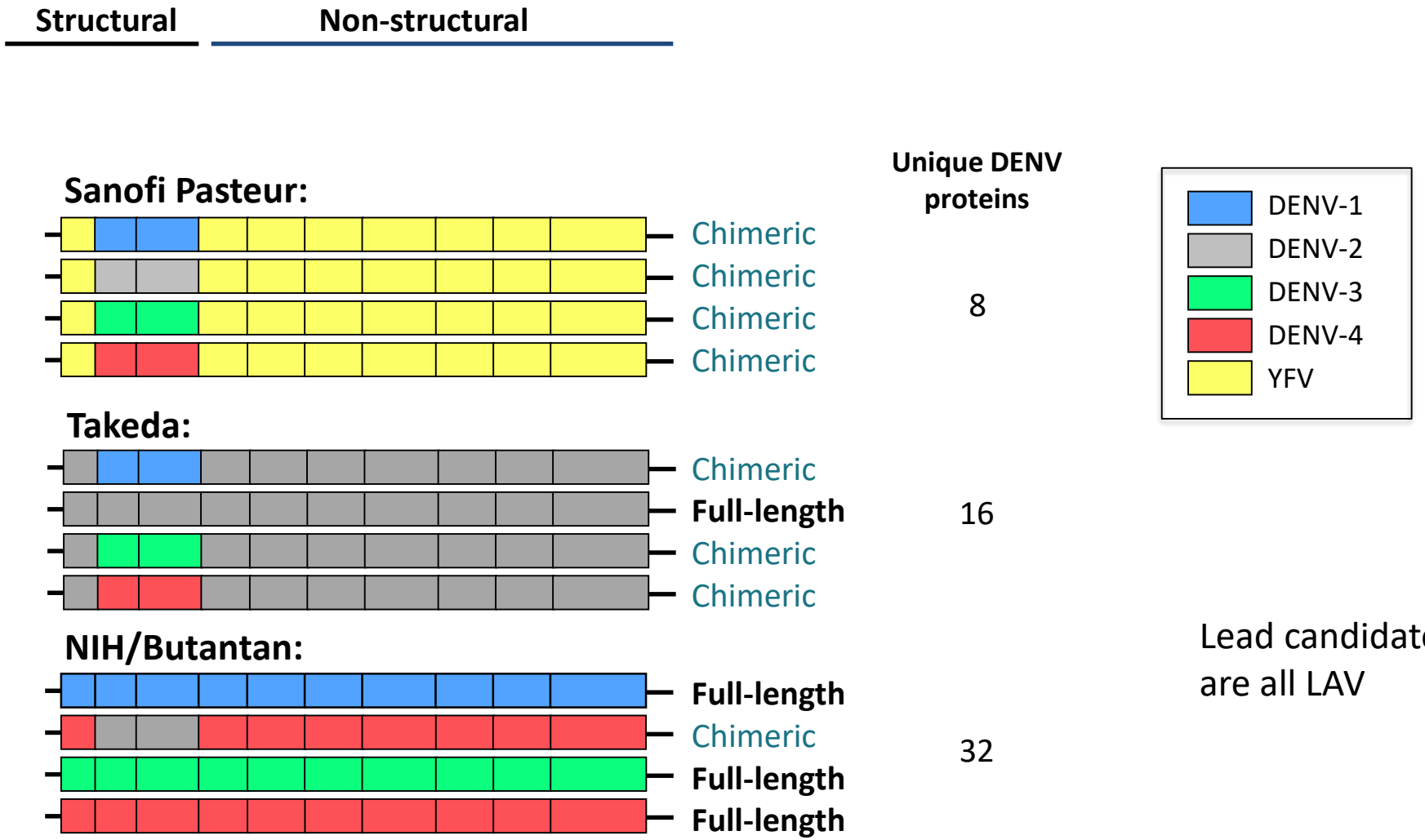
Courtesy slide, Dr In-Kyu Yoon, GDAC director

CURRENT STATUS OF DENGUE VACCINE DEVELOPMENT AS OF TODAY

Vaccine (type)	Sponsor	Trial identifier	Phase	Number (age range, years)	Site(s)	End date
TetraVax-DV[b] (LAV)	Butantan	NCT02406729[c]	III	16 944 (2–59)	Brazil	Dec 2022
Dengue tetravalent vaccine[d]	Panacea Biotec Ltd	CTRI/2017/02/007923	I/II	200 (2–60)	India	Not known
TDV[e] (LAV)	Takeda	NCT02747927[f]	III	20 100 (4–16)	Asia, Latin America	Dec 2021
TDENV (LAV)	WRAIR and GSK	NCT00239577	II	132 (18–45)	Maryland, USA	Jun 2007
		NCT00370682	II	120 (20–25)	Bangkok, Thailand	Feb 2008
		NCT00350337	II	88 (18–45)	Maryland, USA	Jul 2008
		NCT00468858[g]	II	636 (1–50)	Puerto Rico	Apr 2010
		NCT00384670	I/II	7 (6–10)	Bangkok, Thailand	May 2004
		NCT00322049	I/II	51 (1–1.25)	Bangkok, Thailand	Jun 2009
TDENV-PIV (Inactivated)	WRAIR and GSK	NCT02421367	I/II	140 (20–49)	Maryland, USA	Jun 2019
		NCT03141138[h]	I	40 (18–42)	Maryland, USA	Jan 2022
		NCT01666652	I	100 (18–39)	Maryland, USA	Sep 2018
		NCT01702857	I	100 (20–39)	Puerto Rico	Mar 2017
		NCT02239614[h]	I	80 (18–49)	Maryland, USA	Feb 2017
TVDV (DNA)	WRAIR and NMRC	NCT01502358	I	40 (18–50)	Maryland, USA	Dec 2013
V180 (r-protein)	NIAID and MSD	NCT02450838[i]	I	20 (18–50)	Maryland and Vermont, USA	Oct 2015
	MSD	NCT01477580	I	98 (18–49)	Unknown	Dec 2014

Swaminathan S and Khanna N. Dengue vaccine development: Global and Indian scenarios. Int J Infect Dis. 2019 Jul;84S:S80-S86. doi: 10.1016/j.ijid.2019.01.029. Epub 2019 Jan 23.

CYD-TDV Construct Comparisons with 2 other Dengue Vaccine Candidates in Phase III



Lead candidate vaccines are all LAV

POINTS FOR CONSIDERATION – 2nd GENERATION OF DENGUE VACCINE

- **Early clinical studies** are valuable to evaluate the potential for interference between individual vaccine viruses and the impact on the development of **type-specific versus heterotypic immunity**

- Measuring antibody neutralization activity remains the best method of defining dengue vaccine immunogenicity; however, current assays do not easily distinguish between type-specific antibodies, transient heterotypic antibody, and long-lasting heterotypic antibody. Given this uncertainty, the critical time point for assessment of immunogenicity as a **correlate of durable protection** should be **more than 12 months after the last vaccine dose**

- **Controlled Human Infection Model** (CHIM) trials can provide initial **proof-of-concept** that a vaccine may have potential for **clinical benefit**, but greater confidence is required in Dengue CHIM performance and challenge should be complete **12 months or more after the last vaccine dose**

- For licensure, in the absence of an accepted correlate of protection or risk, **vaccine efficacy** will need to be demonstrated based on clinical outcomes collected over a **multiyear period (**multiple dengue seasons) that support durable benefit

Vannice KS et al. Clinical development and regulatory points for consideration for second-generation live attenuated dengue vaccines. Vaccine. 2018 Jun 7;36(24):3411-3417. doi: 10.1016/j.vaccine.2018.02.062. Epub 2018 Mar 7

POINTS FOR CONSIDERATION – 2nd GENERATION OF DENGUE VACCINE (Cont'ed)

- **Pre**-vaccination and **post**-vaccination blood samples should be collected and sera stored from all trial participants

- **Dengue serostatus at baseline** is a critical variable, and safety and efficacy by serostatus should be presented in a stratified analysis

- **Active surveillance** used to assess efficacy against all dengue disease and severe dengue disease should be in place preferably **for at least 3–5 years after the last vaccine dose**

- **Immunogenicity and efficacy** results should be interpreted in the context of **potential transient heterotypic immunity** that could wane over time

Vannice KS et al. Clinical development and regulatory points for consideration for second-generation live attenuated dengue vaccines. Vaccine. 2018 Jun 7;36(24):3411-3417. doi: 10.1016/j.vaccine.2018.02.062. Epub 2018 Mar 7

SUMMARY

- Dengue remains a global public health concern in endemic regions and 2019 Year is a high year for dengue

- There is a need to develop a safe, efficacious, and affordable vaccine (LMIC)

- 1st licensed vaccine was a scientific breakthrough

- 2nd Generation of dengue vaccines should address the identified questions following the development of the first dengue vaccine that is now licensed with the indication in seropositive subjects only from 9 yrs and above

- The two most advanced vaccines candidates are at the phase III development and will have to address the points of interest
  - safety including LTFU and severe dengue and efficacy in seronegative and seropositive subjects
  - Antibody response (i.e., Quantitative Neutr Ab titer associated with protection, Qualitative evaluation of Neutr Ab response; Type-specific Neutr Abs in dengue naïve; Cross-reactive Neutr abs in dengue pre-immune)
  - CMI
  - Vaccine viremia and immunodominance…

THANK YOU !