Decimate Dengue : The Pre-Summit Webinars Series (5th Webinar)

PRE-VACCINATION SCREENING – WHAT'S NEXT

NOVEMBER 15, 2021

INTRODUCTION

Due to the ongoing COVID-19 pandemic, 5th Asia Dengue Summit has been postponed to January 2022. In the meantime, the Asia Dengue Voice and Action (ADVA) Group, in collaboration with the Global Dengue and Aedes transmitted Diseases Consortium (GDAC), Fondation Merieux (FMx), International Society for Neglected Tropical Diseases (ISNTD) and Southeast Asian Ministers of Education Tropical Medicine and Public Health Network (SEAMEO) bring a series of online meetings titled "Decimate Dengue: The Pre-Summit Webinars." ***The fifth webinar in the series titled "Pre-vaccination screening – What's next?"*** was held on November 15, 2021. ***Prof. Zulkifli Ismail***, Consultant Pediatrician and Pediatric Cardiologist at KPJ Selangor Specialist Hospital, Malaysia, and ***Prof. Maria Rose Capeding***, Head of Medical Research Unit, Tropical Disease Foundation in Philippines, chaired the webinar. The webinar featured talks by ***Prof. Sutee Yoksan***, Emeritus Professor of Pathobiology and Consultant of Centre for Vaccine Development at the Institute of Molecular Biosciences, Mahidol University, Thailand, and ***Prof. Usa Thisyakorn***, Executive Director of Tropical Medicine Cluster, Chulalongkorn University, Thailand.

UPDATE ON DENGUE SEROPREVALENCE AND RAPID DIAGNOSTIC TESTS

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1. The efficacy and safety of the first licensed dengue vaccine, Dengvaxia (CYD-TDV) depends on dengue serostatus
   - CYD-TDV confers protection against severe virologically confirmed dengue (VCD) and hospitalization at least 5 years to individuals who have had dengue infection before vaccination (seropositive) [1]
   - However, there is a higher risk of VCD and hospitalization in vaccinated individuals with no prior dengue infection (seronegative) [1]
   - With a seroprevalence of >70%, for every 4 severe cases prevented in seropositive individuals, 1 excess severe case in seronegative individuals per 1000 vaccinees is expected. Similarly, for every 13 hospitalizations prevented in seropositive individuals, 1 excess hospitalization in seronegative vaccine recipients is expected.[2]
2. The World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) on immunization recommends two strategies for CYD-TDV vaccination[2]
   - Strategy 1 - Using the vaccine only in populations with a high seroprevalence of >80% [2]
   - Strategy 2 - Is the preferred option, where pre-vaccination screening is performed to detect seropositivity and only dengue seropositive individuals are vaccinated [2]
3. Vaccine introduction strategies need to consider population dengue seroprevalence
   - Dengue seroprevalence in Thai healthcare workers (HCW) in Bangkok is very high [3]
   - Majority HCWs are exposed to all 4 dengue virus serotypes[3]
   - 95% of the participants have PRNT50 ≥10 for at least one serotype[3]
4. Plaque reduction neutralization test (PRNT) titres are associated with protection from dengue infection
   - Data from Thai cluster studies indicates association between PRNT titres and protection from infection by DENV-1, -2 and -4
   - Protective neutralizing antibodies are serotype dependent [4]
5. Proposed approaches to accelerate dengue vaccine introduction include:
   - Policy making decision level: Seroprevalence of dengue in endemic areas should be determined by plaque reduction neutralization test (PRNT50) with defined immune correlate of protection. This will define age group for vaccination without pre-vaccination screening.
   - Point of care level - Rapid diagnostic tests (RDTs) and conventional enzyme-linked immunosorbent assays (ELISA) to be used to determine prior dengue infection
   - Establishment of reference serum panel - A reference serum panel should be established to evaluate the sensitivity and specificity of commercially available RDTs

Table 1: Comparison of pre-vaccination screening tests

Test	Advantages	Disadvantages
Plaque reduction neutralization test (PRNT)	• Most specific serological test for determining type-specific neutralizing antibodies[5]	• Laborious[5] • Expensive[5] • Inconvenient for routine surveillance[5]
IgG enzyme-linked immunosorbent assay (ELISA)	• Most widely used[6] • Relatively easy to perform[6]	• Time-consuming[7] • Need laboratory infrastructure[7] • Cross-reactivity with other flaviviruses[7]
IgG rapid diagnostic test (RDT)	• Quick and simple[7] • Point-of-care use[7] • Convenient in resource-limited setting[7] • No need for specialised laboratory capacity[7]	• Low sensitivity[7] • Low specificity[7]

"Majority of patients presenting with severe dengue are children under 15 years of age. Therefore, children should be the primary target for dengue immunization programs. Seroprevalence studies in children are urgently needed. A regional task force for establishing seroprevalence and evaluation of RDTs is required." – Prof. Sutee Yoksan

STRATEGIES FOR DENGUE PRE-VACCINATION SCREENING

Prof. Usa Thisyakorn
Executive Director, Tropical Medicine Cluster, Chulalongkorn University, Bangkok, Thailand

1. The WHO targets to reduce the burden of dengue by 2030 include:[8]
   - Reduce case fatality rate to 0
   - Reduce the burden of dengue disease and its incidence by 25% (2010-2020 as baseline)
   - 75% countries to be able to detect and respond to dengue outbreaks
2. Continued development of preventive vaccines is one of the critical actions to achieve 2030 WHO targets of dengue control.[8]
3. Safety and efficacy of the CYD TDV dengue vaccine was demonstrated in 3 trials across Asia and Latin America
   - Phase 3 trial in five countries in the Asia-Pacific region in 10,275 healthy children aged 2-14 years [9]
   - Phase 3 efficacy trial in five Latin American countries in 20,869 healthy children aged 9 and 16 years [10]
   - Phase 2b, proof-of-concept trial in 4002 Thai schoolchildren aged 4-11 years [11]
4. CYD TDV vaccine offers protection against severe VCD and hospitalization for VCD in seropositive individuals[1]

Table 2: Incidence of VCD in seropositive and seronegative individuals[1]

	SEROPOSITIVE		SERONEGATIVE	
	Vaccine	Control	Vaccine	Control
Cumulative incidence of hospitalization for VCD (2-16 years)	0.75%	2.47%	3.06%	1.87%
Cumulative incidence of hospitalization for VCD (9-16 years)	0.38%	1.88%	1.57%	1.09%

5. IgG ELISA is more suitable than RTD for pre-vaccination screening in Ratchaburi province of Thailand[5]
   - Study in 115 individuals aged 10-22 years in Ratchaburi province to identify target population for vaccination[5]
   - Performance of IgG RDT and IgG ELISA was evaluated with PRNT as reference [5]
   - 81% participants were exposed to one or more of the dengue serotypes [5]
   - Both RDT and ELISA showed 100% specificity [5]
   - RDT had low sensitivity of 35% while ELISA had much higher sensitivity of 87% [5]
   - Low sensitivity of RDT implies individuals with negative result might lose the benefits of vaccination, and therefore RDT is not recommended to identify prior dengue infection in this population [5]

"In Asia Pacific region dengue seroprevalence is very high. However, each country needs to consider its own seroprevalence data, and evaluate the sensitivity and specificity of available screening tests while deciding pre-vaccination screening strategy" – Prof. Usa Thiskiyorn

TAKE HOME MESSAGES

- ✓ Development of safe and effective vaccines against all 4 dengue serotypes is a critical component in reducing the dengue disease burden.[8]
- ✓ Pre-vaccination screening is the preferred strategy to identify and vaccinate only seropositive individuals with the CYD-TDV vaccine.[2]
- ✓ Seroprevalence in endemic areas, availability, sensitivity, and specificity of pre-screening tests, dengue hospitalization rates, and cost of pre-screening tests and vaccine will determine the decision on pre-vaccination screening [2]
- ✓ RDTs appear to be simple, cost-effective, and convenient for pre-vaccination screening.[7] A reference serum panel should be established to evaluate the sensitivity and specificity of commercially available RDTs.
- ✓ A coordinated approach is needed to ensure effective immunization programs in dengue endemic countries. Development of regional task force for establishing seroprevalence and evaluating RDTs performance is essential.
- ✓ Several new candidate dengue vaccines, which may or may not need pre-vaccination screening and newer RDTs are under development and expected soon.

REFERENCES: 1. Sridhar S, Luedtke A, Langevin E, 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 Weekly Epidemiological Record, No 23, 8 June 2018, 93, 329–344. **3.** Vandepitte WP, Chaweethamawat A, Yoksan S. Seroprevalence Of Neutralizing Antibody Against Dengue Virus In Healthcare Workers In Bangkok, Thailand. Southeast Asian J Trop Med Public Health 2019;50:816-24. **4.** Buddhari D, Aldstadt J, Endy TP, et al. Dengue virus neutralizing antibody levels associated with protection from infection in thai cluster studies. PLoS Negl Trop Dis. 2014;8(10):e3230. **5.** Limothai U, Tachaboon S, Dinhuzen J, et al. Dengue pre-vaccination screening test evaluation for the use of dengue vaccine in an endemic area. PLoS One. 2021;16(9):e0257182. **6.** Raafat N, Blacksell SD, Maude RJ. A review of dengue diagnostics and implications for surveillance and control. Trans R Soc Trop Med Hyg. 2019;113(11):653-660. **7.** Luo R, Fongwen N, Kelly-Cirino C, Harris E, Wilder-Smith A, Peeling RW. Rapid diagnostic tests for determining dengue serostatus: a systematic review and key informant interviews. Clin Microbiol Infect. 2019 Jun;25(6):659-666. **8.** Ending the neglect to attain the Sustainable Development Goals: a road map for neglected tropical diseases 2021–2030 access https://www.who.int/publications/i/item/9789240010352). **9.** Capeding MR, Tran NH, Hadinegoro SR, et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. Lancet 2014;384(9951):1358-65. **10.** Villar L, Dayan GH, Arredondo-García JL, et al. Efficacy of a tetravalent dengue vaccine in children in Latin America. N Engl J Med 2015;372(2):113-23. **11.** Sabchareon A, Wallace D, Sirivichayakul C, et al. Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. Lancet. 2012;380(9853):1559-67.

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