Advancing the Fight Against Dengue:The Development of an Effective Vaccine

10-12 April 2024

11th National Summit of Health and Population Scientists in Nepal

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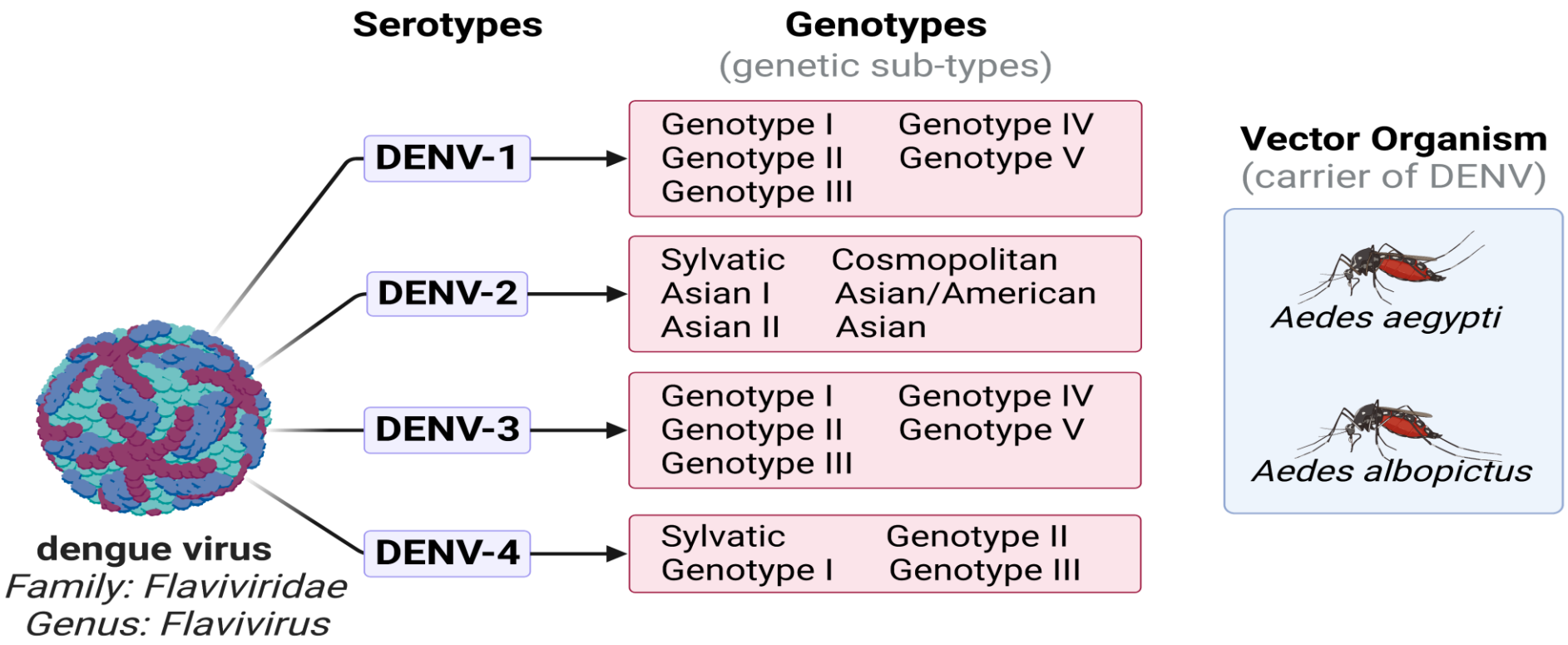
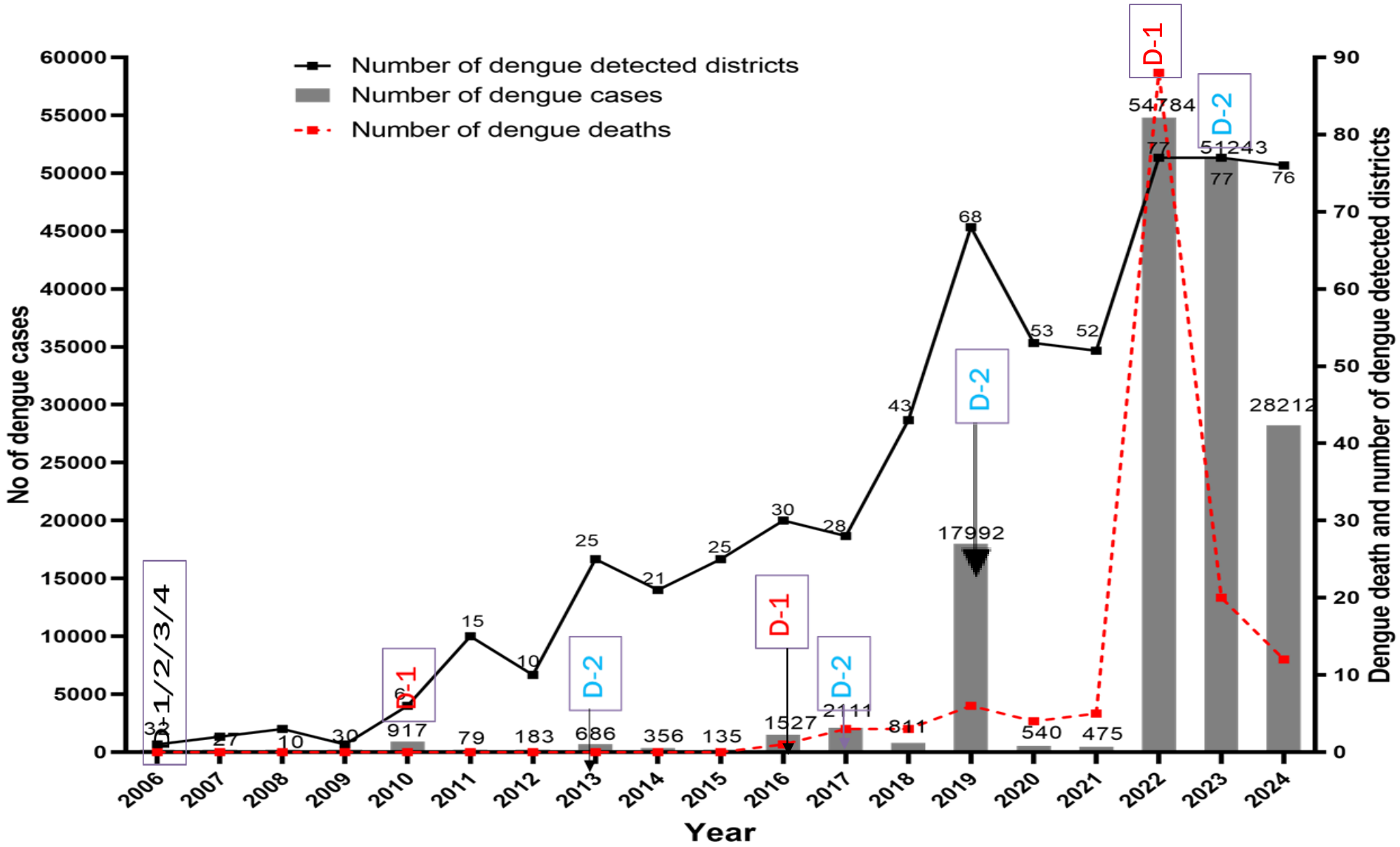
Overview of Dengue

- Dengue fever is the most prevalent mosquito-borne viral disease in the world.
- There is no specific treatment for dengue or severe dengue
- 80% or more dengue cases are asymptomatic
- Dengue is continuing to expand due to the climatic conditions and the movement of people and goods
- Innovative control activities and an effective vaccine are essential to achieve zero dengue deaths by 2030

Prevalent Dengue Sero and Geno-types



Prevalence of Dengue 2004-2024 in Nepal



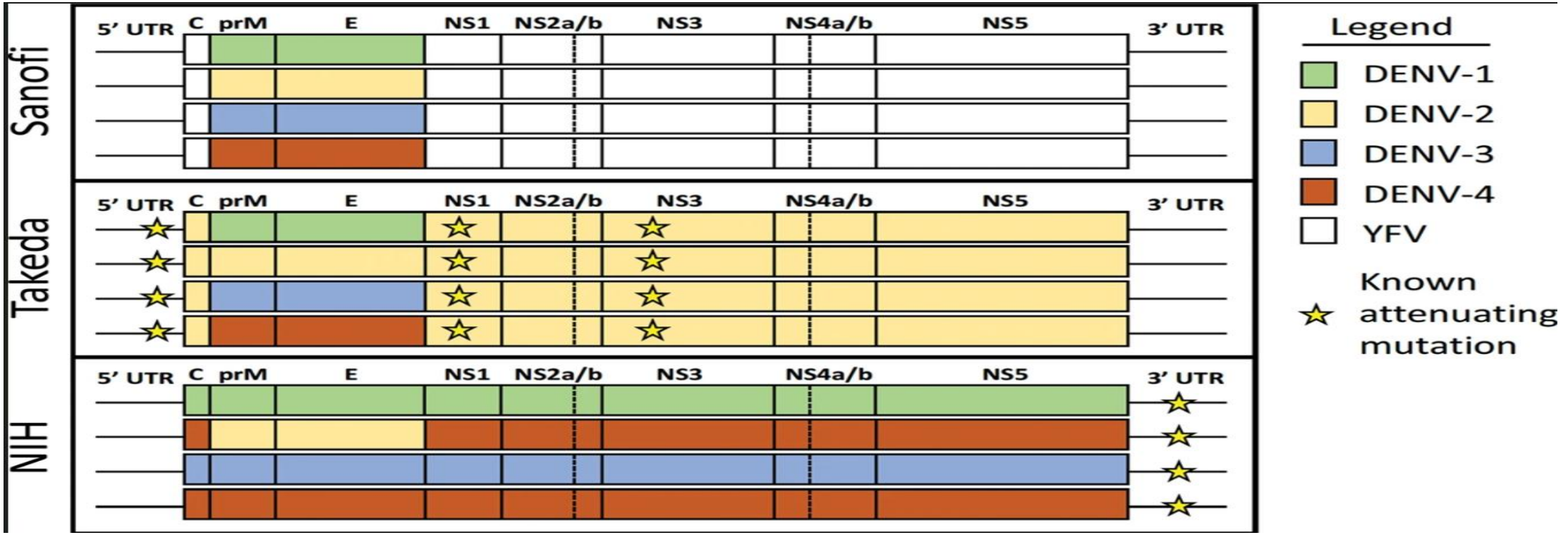
The trend of dengue cases in EDCD, Nepal, DENV serotypes distribution 2004 to 2023. Rimal et al Viruses ***2024****, 16(4), 594*

Challenges in Dengue Vaccine Development

- Existence of four DENV serotypes, each capable of causing infection, disease, and death
- The need for a tetravalent formulation that induces simultaneous and balanced protection against all serotypes
- No animal models have been validated for immune response and disease experience.
- Immunologic assays are unable to define DENV type-specific (homo typic) immune responses precisely
- Requirement for large efficacy trials to demonstrate benefit across diverse populations and clinical endpoints

Thomas et al npj Vaccines (2023)

Dengue Virus Genome Component in Sanofi, Takeda and NIH



- full genome DENV-1, DENV-3 and DENV-4 components with a DENV-2/-4 chimera based on a DENV-4 backbone
- possesses NS proteins from DENV-1, DENV-3 and DENV-4

Thomas, 2023, *npj Vaccines*

Vaccine Research and Development Center (In DIDA, October 1, 2022)

DEJIMA ID Alliance
VRDC
長崎大学感染症研究出島特区
ワクチン研究開発拠点

長崎大学
NAGASAKI UNIVERSITY

Director

MORITA Kouichi
Director, DIDA, Nagasaki University

Vice-Director

KIYAMA Ryuichi
General Manager, Corporate Strategy Division and Corporate Planning Department, Shionogi & Co.

Vice-Director

YAMAMOTO Hiroshi
Director, Clinical Research Center, Nagasaki University Hospital

Goal

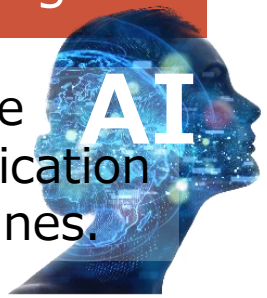
01
Responding to Highly Pathogenic Viruses and Tropical Pathogens

Development of vaccines for Ebola, dengue fever, and COVID-19 etc.

02
Establishment of an all-Japan system for vaccine development

Biosafety level-4 (BSL-4) facility and overseas fields

03
Innovative vaccine development through the use of artificial intelligence



Comprehensive epitope identification by AI for Vaccines.

Collaboration with SHIONOGI NEC NEC OncoImmunity AS kmb KM Biologics Co., Ltd.

DIDA DEJIMA ID Alliance
長崎大学 感染症研究出島特区

(1) Vaccine development for target infectious diseases and establishment of an mRNA vaccine platform

Goal: ・Develop vaccines against highly pathogenic and tropical infectious diseases
・Preparation of prototype vaccine to be completed in 5 weeks for nonclinical trial during a pandemic

Highly Pathogenic Virus Vaccine Development Team

Prof. Jiro Yasuda

KM Biologics Co., Ltd.

Tropical Virus Vaccine Development Team

Prof. Kouichi Morita

KM Biologics Co., Ltd.

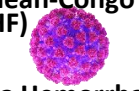
Vaccine Modality R&D Team

Prof. Yoshimasa Tanaka

Parasitic Vaccine Development Team

Prof. Osamu Kaneko

SHIONOGI

Target		Modality	Goals to be achieved in 2026
Severe Fever Thrombocytopenia Syndrome (SFTS)		Live Vaccine	Phase I Clinical Trial Started
Crimean-Congo Hemorrhagic Fever (CCHF)		Live Vaccine VLP	Non-Clinical Trial Completed
		LNP-mRNA	Non-Clinical Trial Completed
Ebola Hemorrhagic Fever		LNP-mRNA	Non-Clinical Trial Completed
Dengue Fever		Live Vaccine	Non-Clinical Trial Completed
		Nanoball-mRNA	Non-Clinical Trial Completed
COVID-19		Recombinant Protein	Non-Clinical Trial Completed
		LNP-mRNA	Non-Clinical Trial Completed
		Nanoball-mRNA	Non-Clinical Trial Completed
Malaria		LNP-mRNA	Non-Clinical Trial Completed
Leishmaniasis		Live Vaccine	Phase II Clinical Trial Completed

NEC NEC OncoImmunity AS

Prototype vaccine

Situation of Current Vaccine Development

Vaccnes	Phase 2 (Ph2)	Phase 3 (Ph3)	New Drug Application (NDA)	Commercially Available
Sanofi ➢ 3 shots vaccine ➢ DENV1~4: Chimera	Recommended only for people aged 9-45 years who had been infected with DENV previously.[1]		DEN1 DEN2 DEN3 DEN4	
Takeda • 2 shots vaccine • DENV1,3,4: Chimera • DENV2: Full Component	Under NDA of EU. In particular, the efficacy of DENV3 and 4 is not enough.[2]			
Butantan/NIH • 1 shot vaccine • DENV1,3,4: Molecular Mutant • DENV2: Chimera	Under Ph3. Tetravalent seropositive ratio is not enough. [3]			
KMB (KD-382) ➢ 1 shot vaccine ➢ DENV1~4: Full Component	Only KD-382 is completely full component.			

Vaccines		Doses	Sero Conversion Rate			
			DENV1	DENV2	DENV3	DENV4
Dengvaxia	Sanofi	1	12.1%	66.7%	27.3%	63.6%
TAK-003,QDENGA	Takeda	2	100%	100%	81.8%	45.5%
TV003	NIH	1	80.0%	100%	64.0%	80.0%
TV005	NIH	1	54.8%	100%	38.7%	51.6%
KD-382	KMB	1	100%	100%	100%	100%

Development in the stage after Ph2
There is no mRNA vaccine in the stage after Ph2

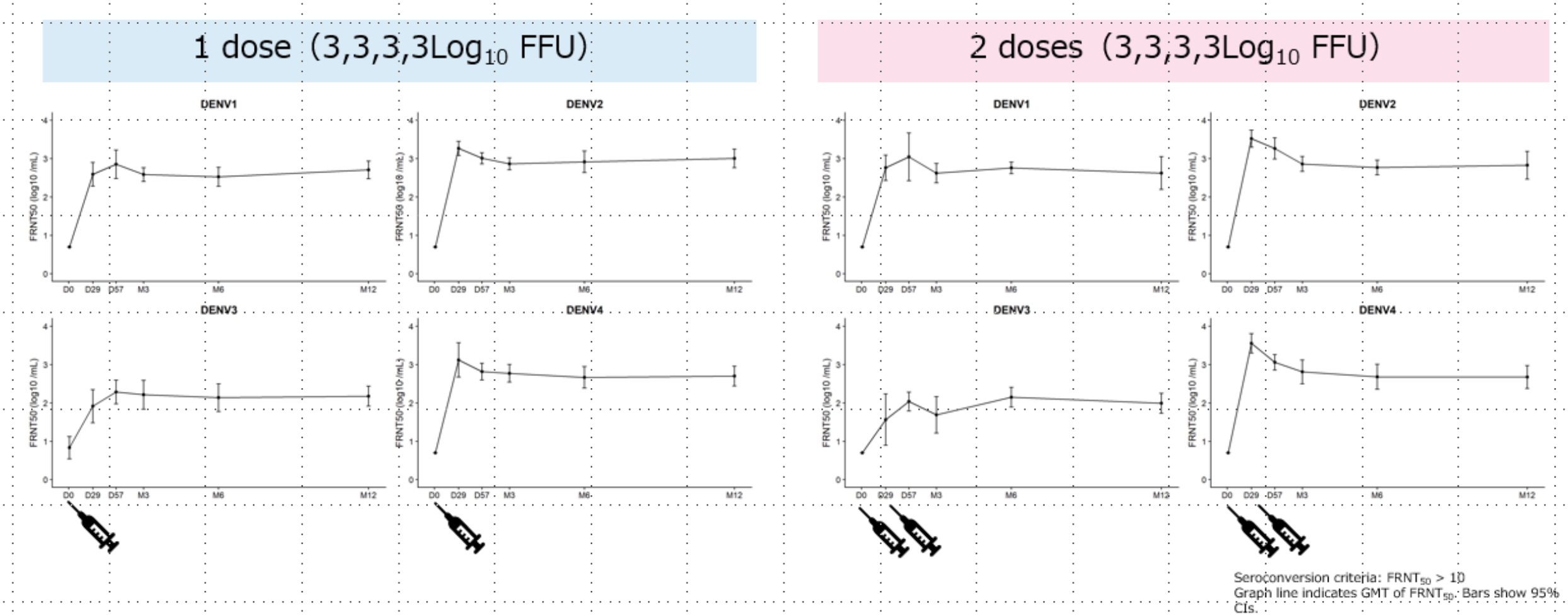
[1] N Engl J Med. 2018

[2] Clin Infect Dis. 2021

[3] HUMAN VACCINES & IMMUNOTHERAPEUTICS 2022

JID 2010;201(3):370-7
JID 2015 212(7):1032-41

Effectiveness data of Ph1 on KD-382



Safety data of Ph1 on KD-382

✓KD-382 is well tolerated by flavivirus antibody-naïve healthy subjects.

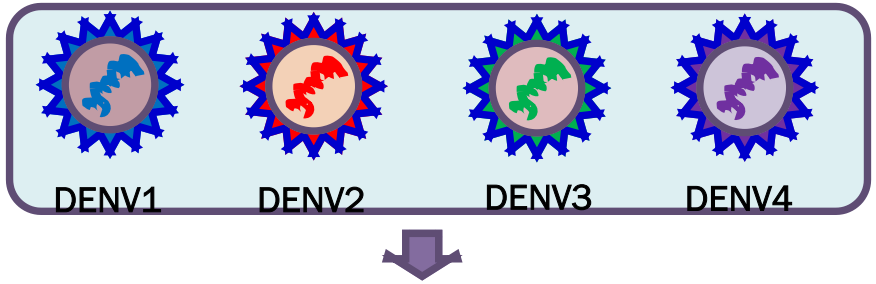
✓No serious treatment-emergent adverse events (TEAE) related to the study drug were observed. No TEAE leading to hospitalization and death was observed in this study.

✓Reported solicited local/systemic TEAEs were all mild or moderate intensity.

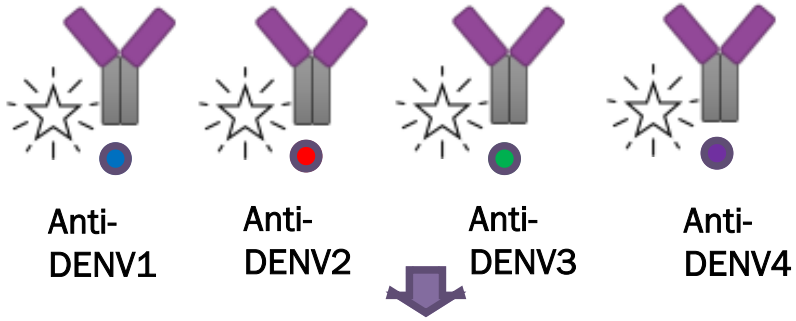
✓No clinically meaningful changes were observed in biochemistry, hematology or vital signs. No report on severe adverse events (SAEs) related to abnormal physical examination findings.

Key Messages on KD-382

① *Non-genetically-modified (Full Component), live-attenuated tetravalent vaccine*



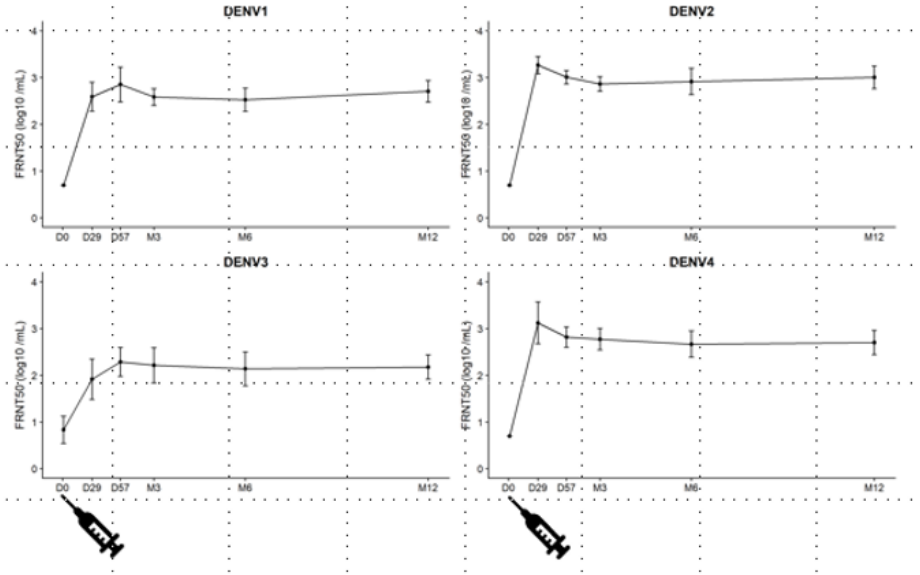
② *Long-lasting elevation of neutralizing antibody (NTAb) to all four serotypes (Well Balanced NTAb)*



③ *Low risk of ADE*

④ *Confirmed tolerability in human with favorable safety profile*

⑤ *Appropriate responses with single vaccination*



Conclusion

- Dengue is expected to spread globally, with Nepal at risk of major outbreaks and severe cases.
- Urgent action is needed in mosquito control, case management preparedness, and effective vaccines
- Nepal has an opportunity to collaborate on vaccine development for zero dengue-related deaths by 2030

Thank you very much for your attention

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