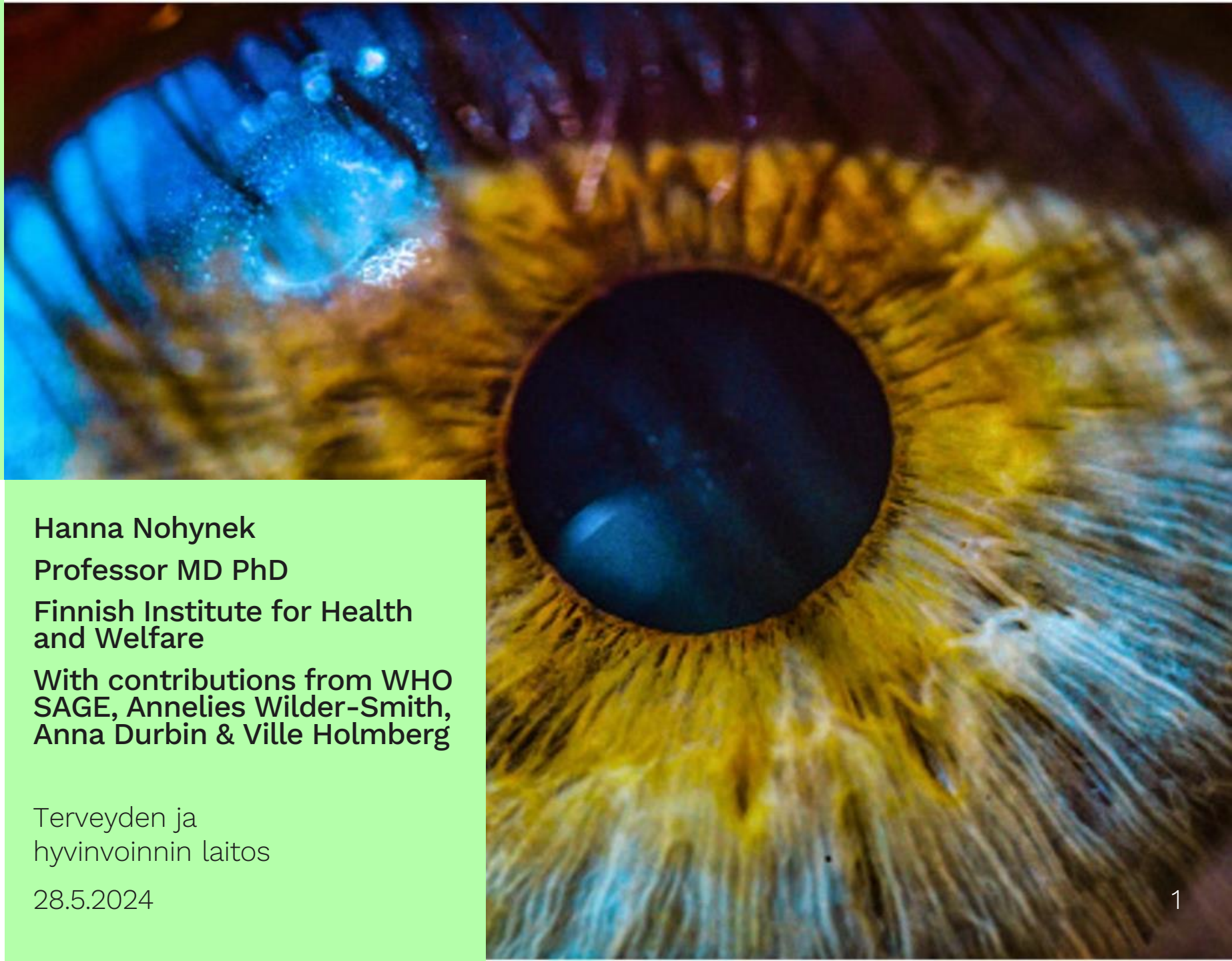


Vaccination against Dengue

NECTM9
22 May 2024

Hanna Nohynek

Professor MD PhD

Finnish Institute for Health and Welfare

With contributions from WHO SAGE, Annelies Wilder-Smith, Anna Durbin & Ville Holmberg

Terveyden ja hyvinvoinnin laitos

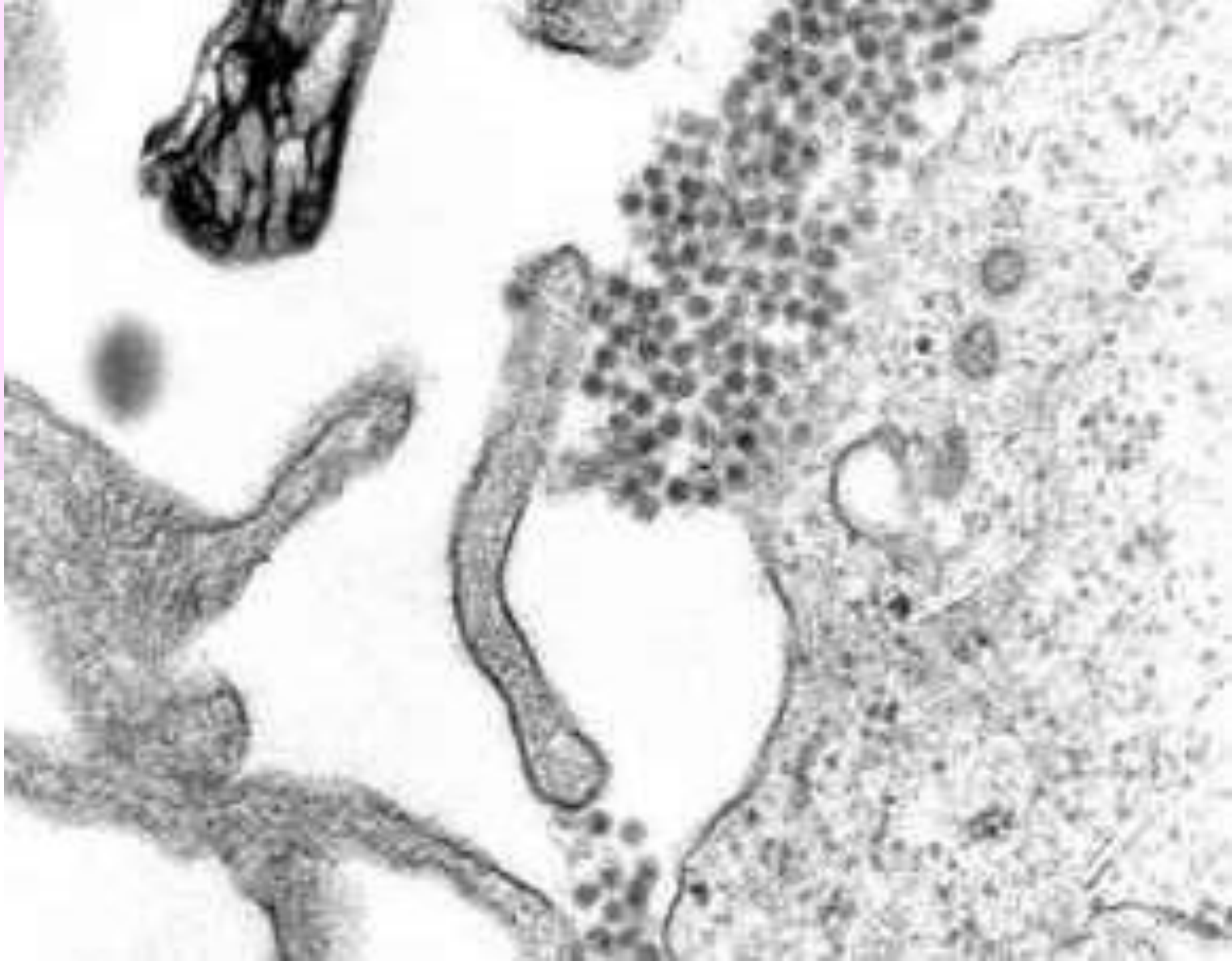
28.5.2024

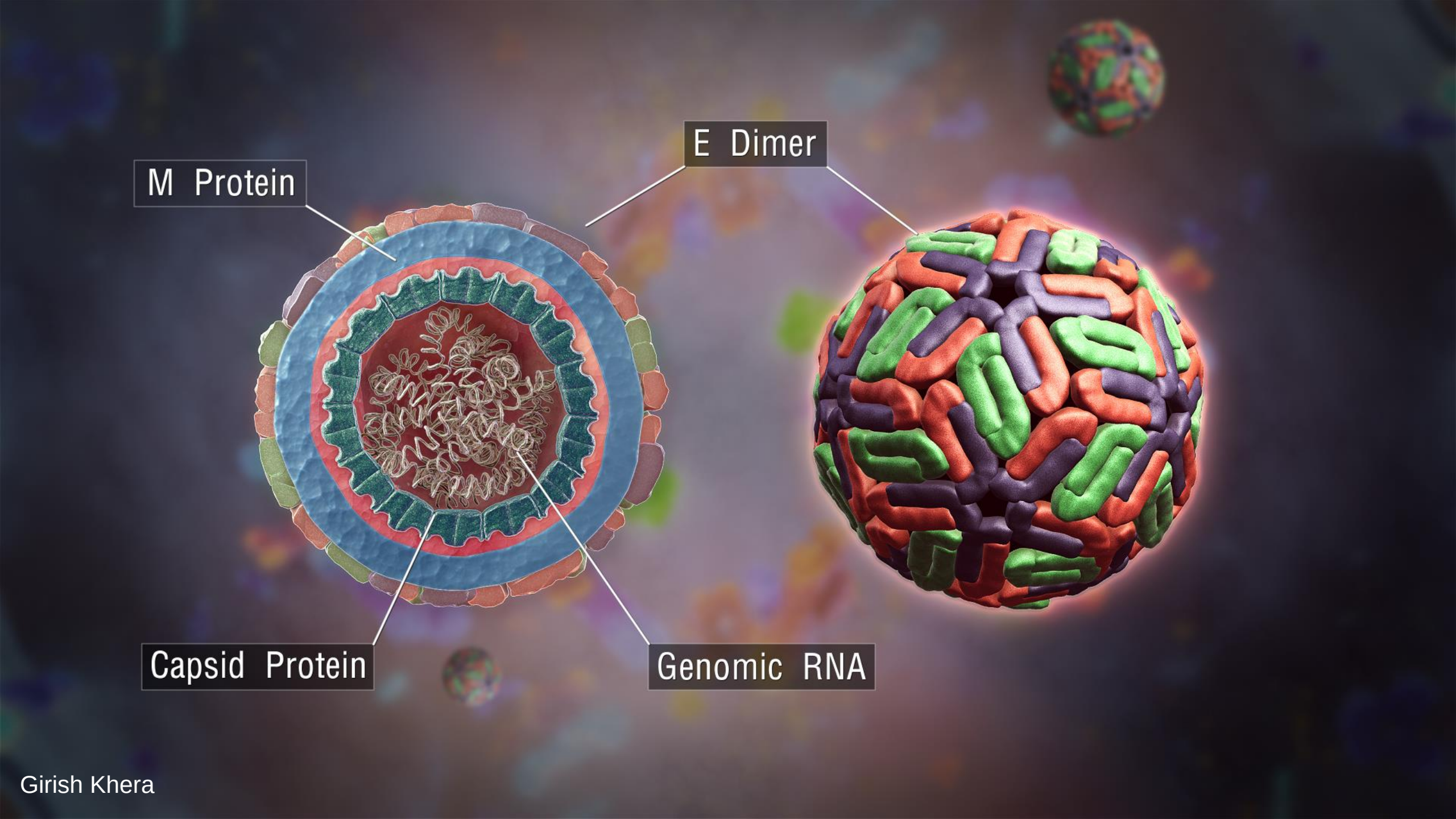
Conflicts of interest

Vaccinologist, government official at THL
public health
Private practitioner Aava
individual (travel) health

WHO SAGE chair since 1/2023 – global health

Was ill with severe dengue in 1998

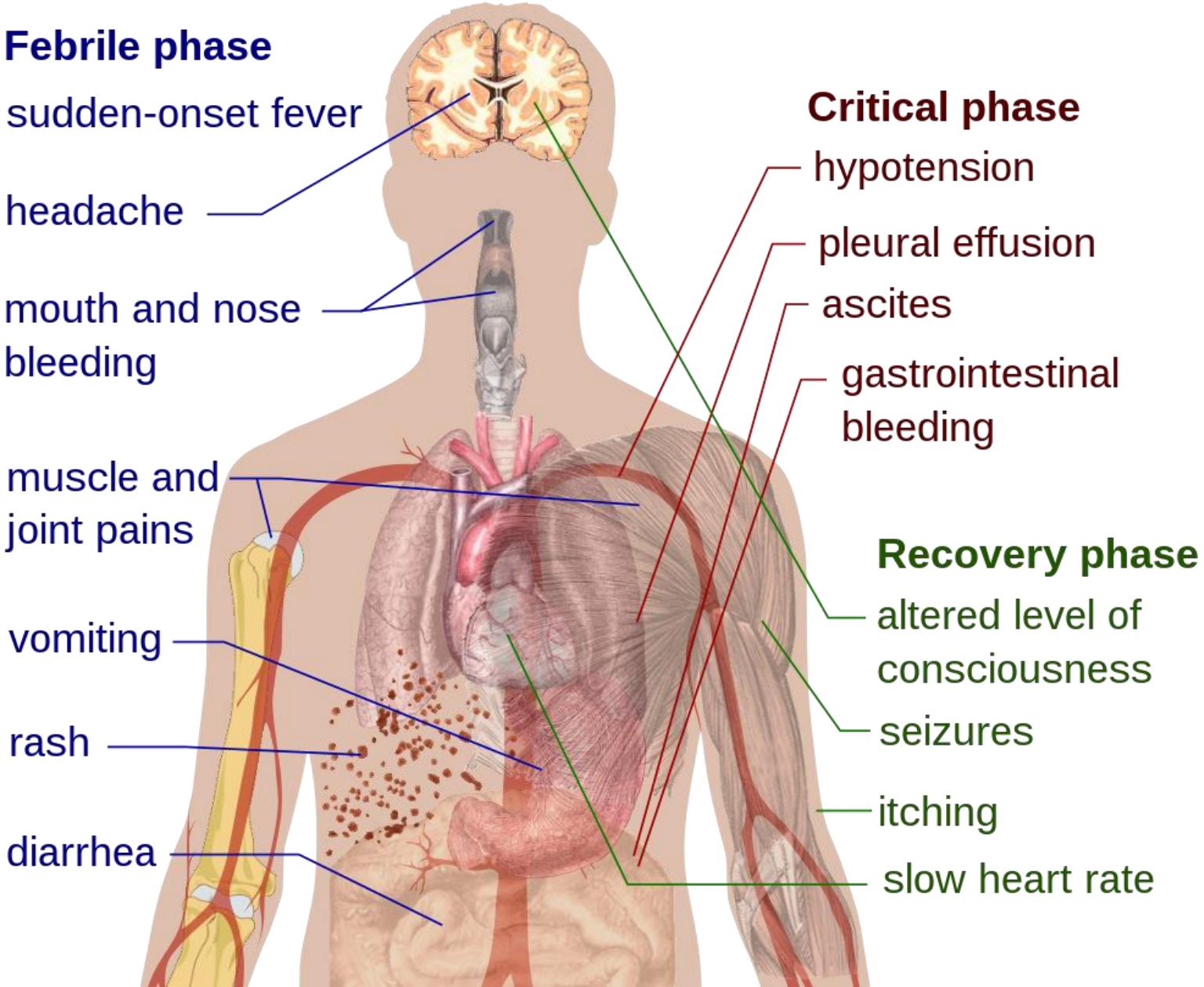




Girish Khera

Symptoms of

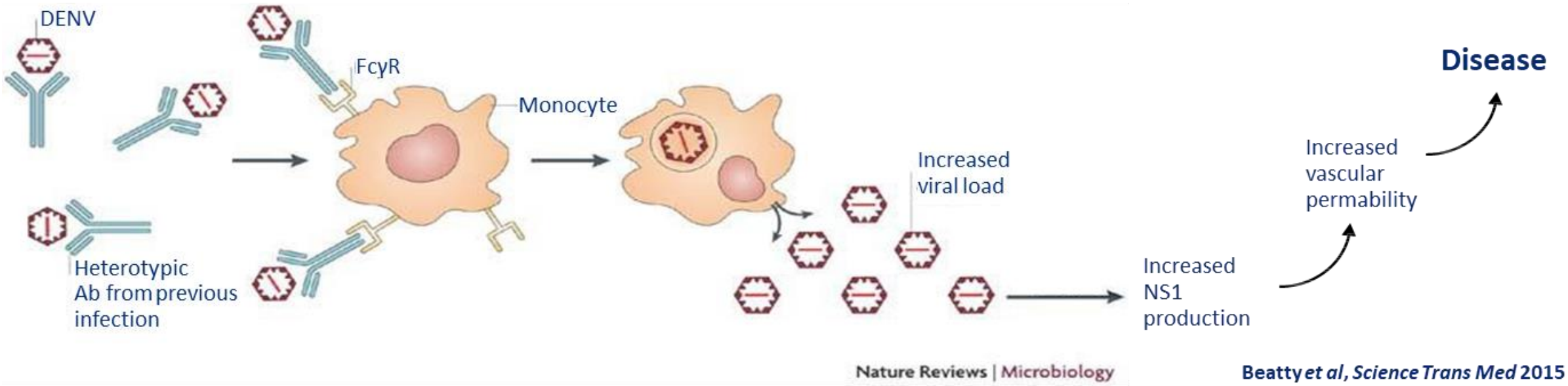
Dengue fever

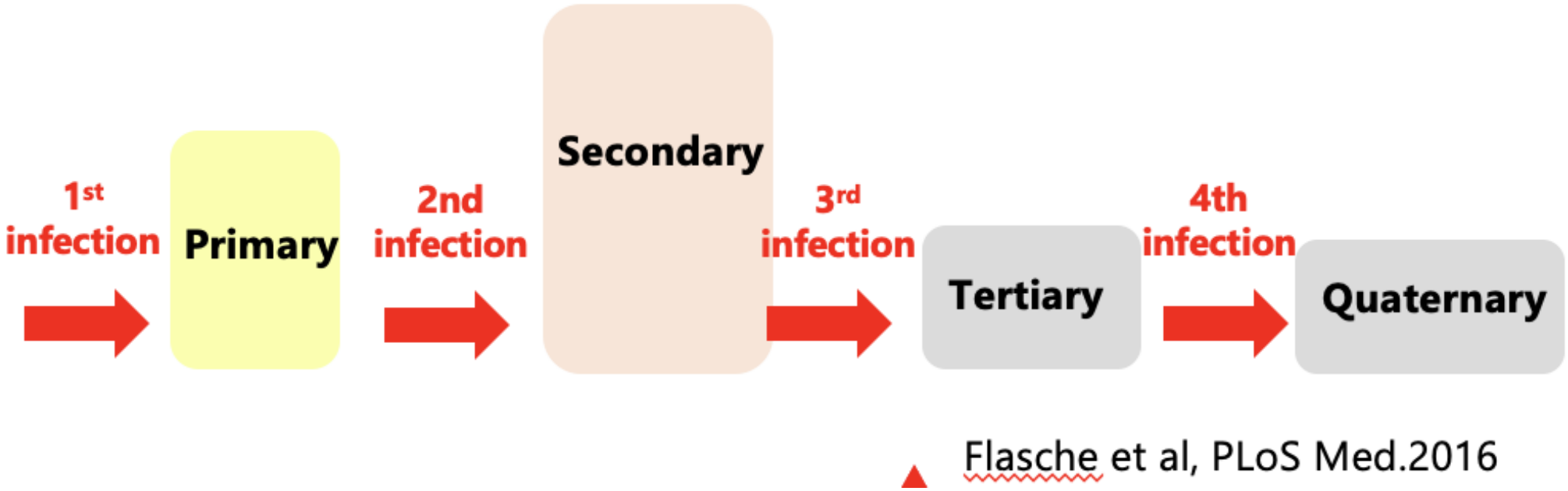


Critical issues for dengue vaccine development

- All four serotypes of DENV are capable of causing the full spectrum of disease -> need for a tetravalent dengue vaccine
- Life-long homotypic protection afforded after infection, but only short term (few months) heterotypic protection is afforded
- Secondary infection with a different serotype is strongly associated with severe disease
- Enhanced risk starts to occur ~ 2 years post 1° infection
- Antibody-mediated enhancement of infection
- Partial immunity to dengue is BAD

Antibody dependent enhancement

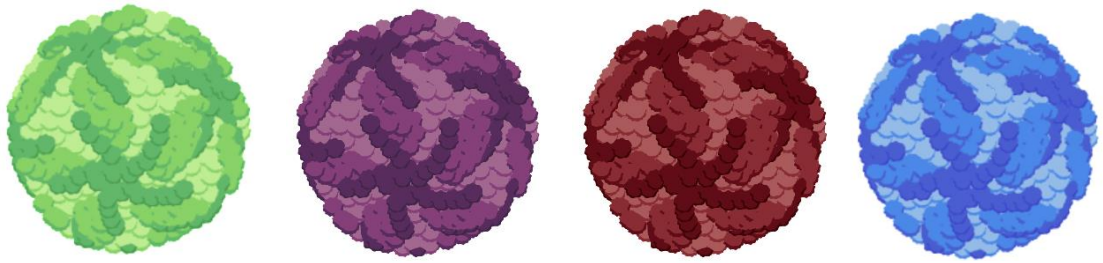




Flasche et al, PLoS Med.2016

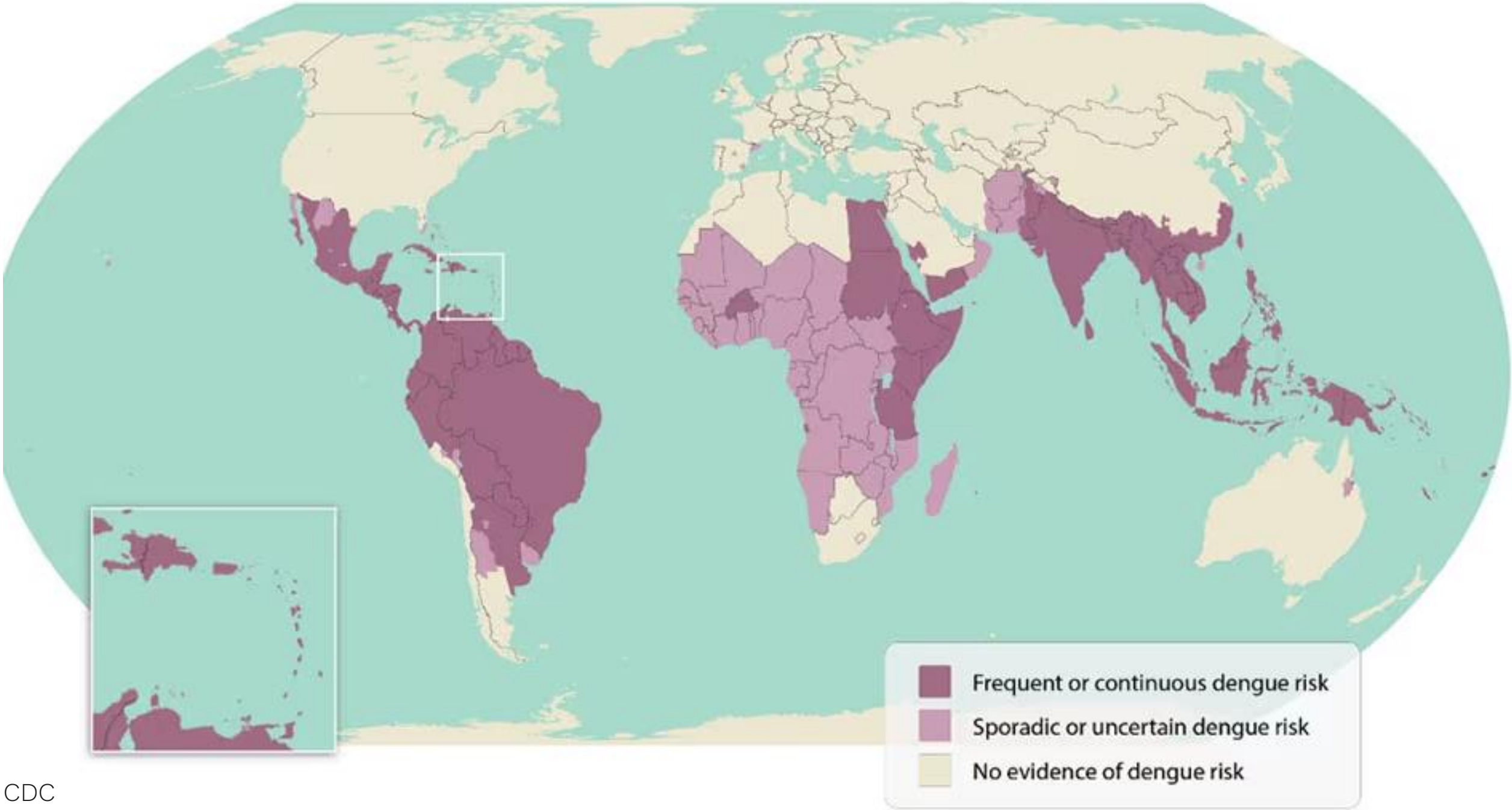
Important considerations for dengue vaccines

- *A dengue vaccine is really 4 vaccines*: must be effective against all 4 DENV serotypes
- Dengue vaccine must protect against all four DENV serotypes
- Neutralizing antibody is the standard measure of immunogenicity but is not predictive of efficacy ie. not a correlate of protection
- Long-term safety follow-up required (~ 5 years)
- 80-90% of CD8 epitopes are located in the NS proteins

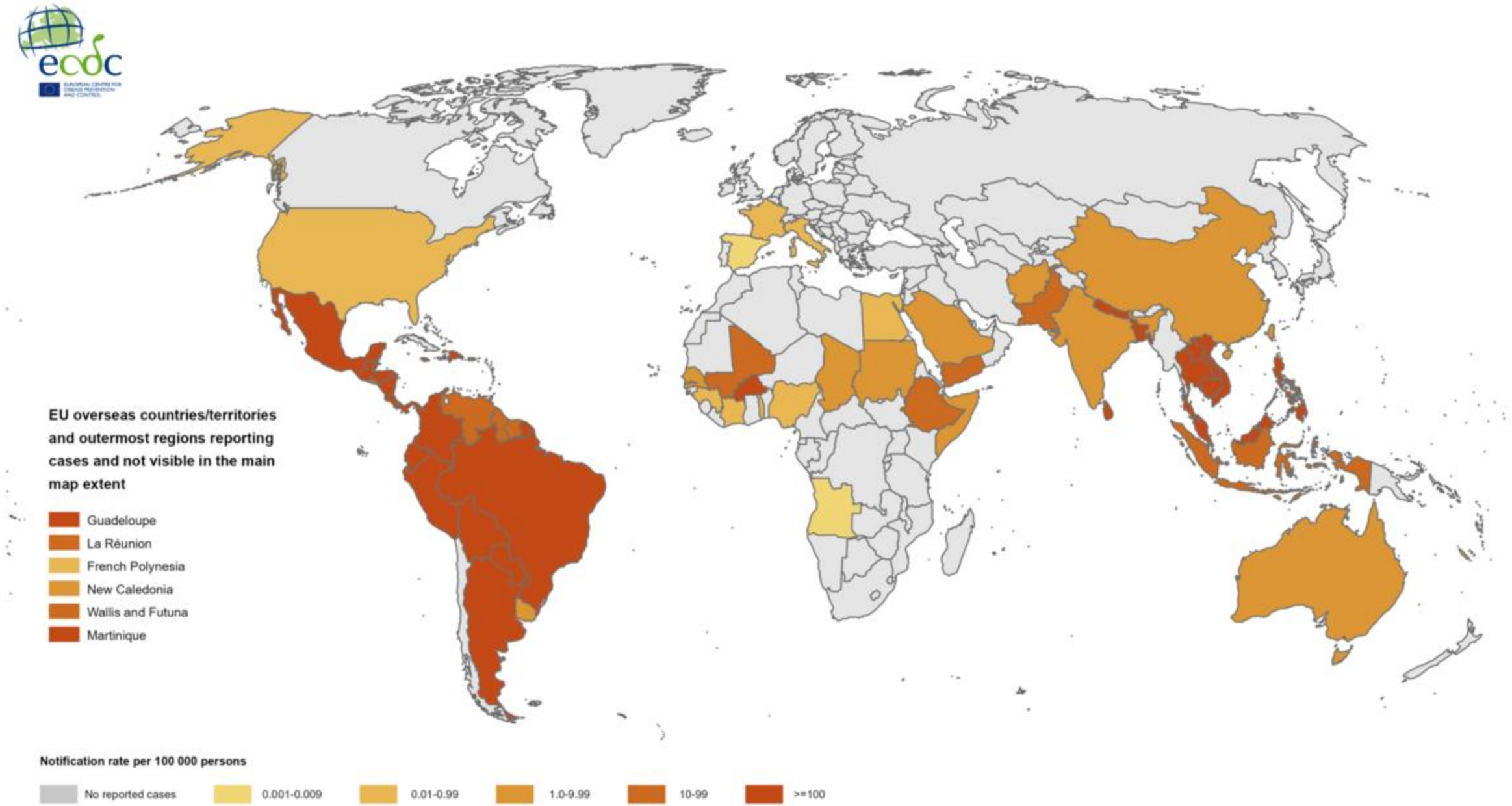


DENV-1 DENV-2 DENV-3 DENV-4

Created with BioRender.com


Frequent or continuous dengue risk
Sporadic or uncertain dengue risk
No evidence of dengue risk

CDC



Note: Data refer to dengue virus cases reported in the last 12 months (January 2023-December 2023) [Data collection: January 2024].Administrative boundaries: © EuroGeographics
The boundaries and names shown on this map do not imply official endorsement or acceptance by the European Union. ECDC. Map produced on 24 January 2024

Journal of Travel Medicine, 2023, 1–14
https://doi.org/10.1093/jtm/taad085
Review

Review

Travel vaccines—priorities determined by incidence and impact

Robert Steffen, MD[1,2,*], Lin H Chen, MD[3,4] and Peter A Leggat, MD, PhD, DrPH[5,6]

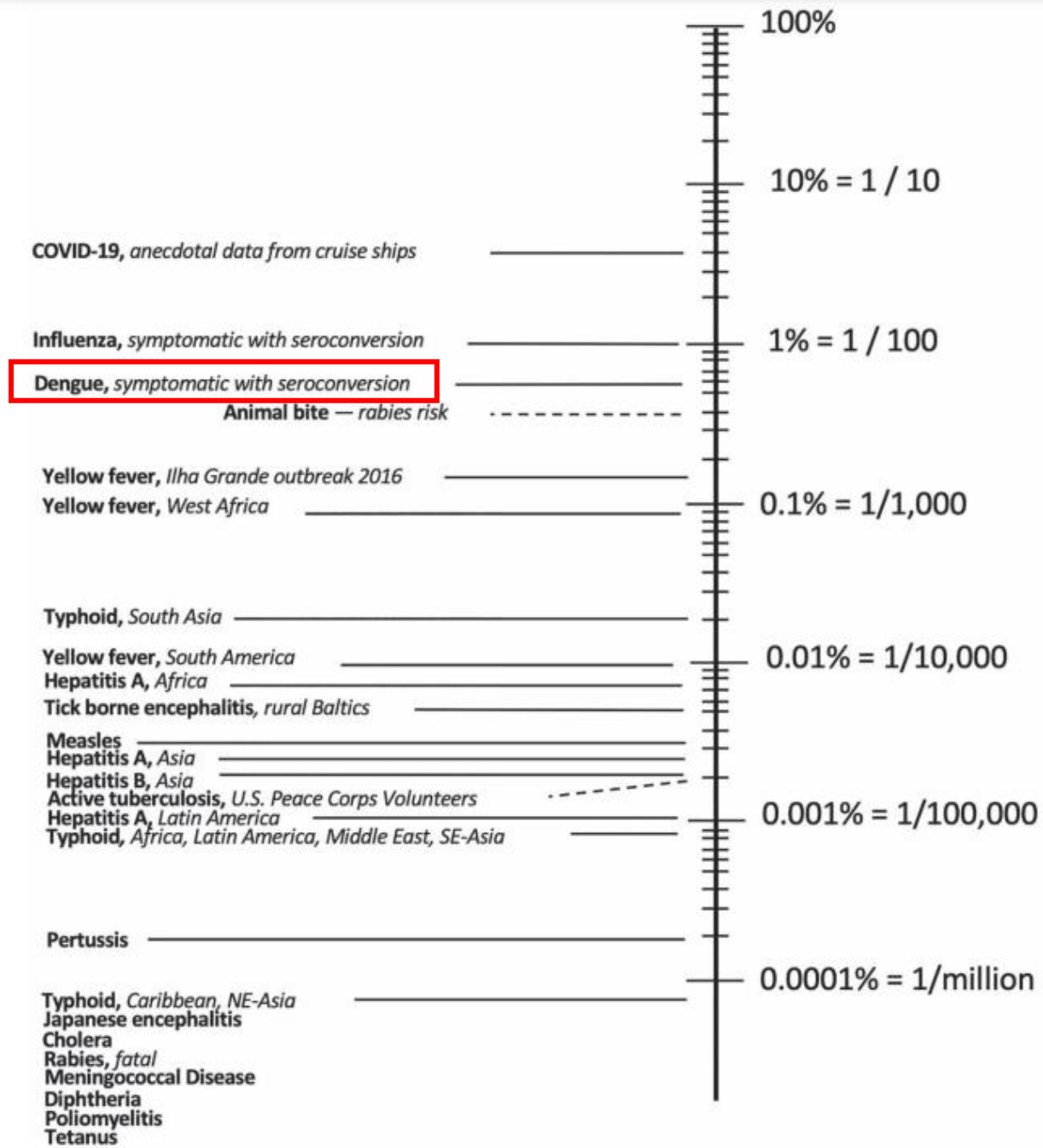
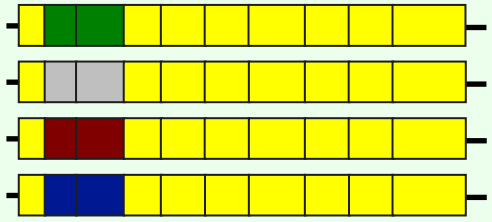
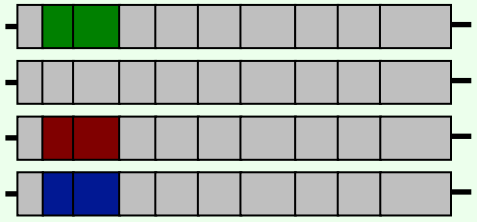
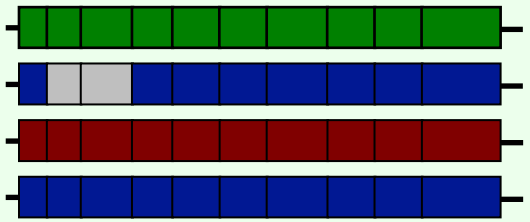


Figure 1. Incidence rate per month of VPDs in travellers; best estimate for non-immunes

Live attenuated dengue vaccines

	Dengvaxia™ (Sanofi Pasteur)	Qdenga™ (TAK-003 -Takeda)	TV003 (multiple manufacturers)
Status	Licensed	Licensed	Phase 3 (Instituto Butantan)
# Doses	**3 doses** over 12 months (0, 6, 12)	**2 doses** (0, 3 months)	**Single dose**
Indicated age	6 – 16 (US) 9-45 (WHO)	Phase 3 (age 4 – 16) Age > 4 (EMA)	Phase 3 age 2 - 59
WHO SAGE	**Documented previous DENV infection**	≥ 6 in areas of high DENV endemicity	?
Construct			
Dengue proteins	8	16	32

Johns Hopkins Bloomberg School of Public Health

Efficacy[1] of Dengvaxia™ (CYD-TDV) against VCD by serotype

Study	Overall Efficacy	DENV-1	DENV-2	DENV-3	DENV-4
CYD23[2]	30.2 (-13.4-56.6)	**55.6% (-21.6 - 84)**	**9.2% (-75 – 51.3)**	**75.3% (-37.5 – 99.6)**	100% (24.8 – 100)
CYD14[3]	56.5 (43.8-66.4)	50.0% (24.6 – 61.0)	**35.0% (-9.2 – 61.0)**	78.4% (52.9 – 90.8)	75.3% (54.5 – 87.0)
CYD15[4]	60.8 (52.0-68.0)	50.3% (29.1 – 65.2)	42.3% (14.0 – 61.1)	74.0% (61.9 – 82.4)	77.7% (60.2 – 88.0)

1. Per Protocol analysis
2. Sabchareon, The Lancet, 2012 - Thailand
3. Capeding et al, The Lancet, 2014 – South East Asia
4. Villar et al, NEJM, 2014 – Latin America

Efficacy[1] of Dengvaxia™ (CYD-TDV) against VCD by serostatus

Trial	Region	Vaccine recipients enrolled	Age	Efficacy in seropositive at baseline	Efficacy in seronegative at baseline
CYD23[2]	Thailand	2,669	4-11	Not reported	Not reported
CYD14[3]	SE Asia	6,851	2-14	**74.3 (53.2-86.3)**	**35.5 (-26.8-66.7)**
CYD15[4]	Latin America	13,920	9-16	**83.7 (62.2-93.7)**	**43.2 (-61.5-80)**

1. Per protocol analysis. Period of primary efficacy evaluation was > 28 days after the third dose to month 25 (12-month period)
2. Sabchareon, The Lancet, 2012
3. Capeding et al, The Lancet, 2014
4. Villar et al, NEJM, 2014

NEWS

Filtered By: Topstorie

FILIPINO CHILDREN'S LIVES AT RISK

DOJ orders NBI to investigate P3.5-B dengue vaccine scandal

By VIRGIL LOPEZ, GMA News

Published December 4, 2017 10:45am
Updated December 4, 2017 3:12pm

Justice Secretary Vitaliano Aguirre II ordered the National Bureau of Investigation (NBI) on Monday to investigate the P3.5-billion dengue vaccination program of the Department of Health (DOH) that put the lives of more than 733,000 public school children at risk.

DENGVAXIA & VAED RISK

Children 2 – 5 years of age at the time of vaccination had a 7.45 RR of hospitalized dengue in year 3 if they had received vaccine compared with placebo

Absolute risk of VAED among those Dengvaxia -vaccinated, seronegatives was very small during the 5 years of follow up = 4,5 hospitalization / 1 000 seronegative vaccinated children
Relative risk considered significant, i.e. 2,4 x in comparison to those vaccinated while seropositive

thl

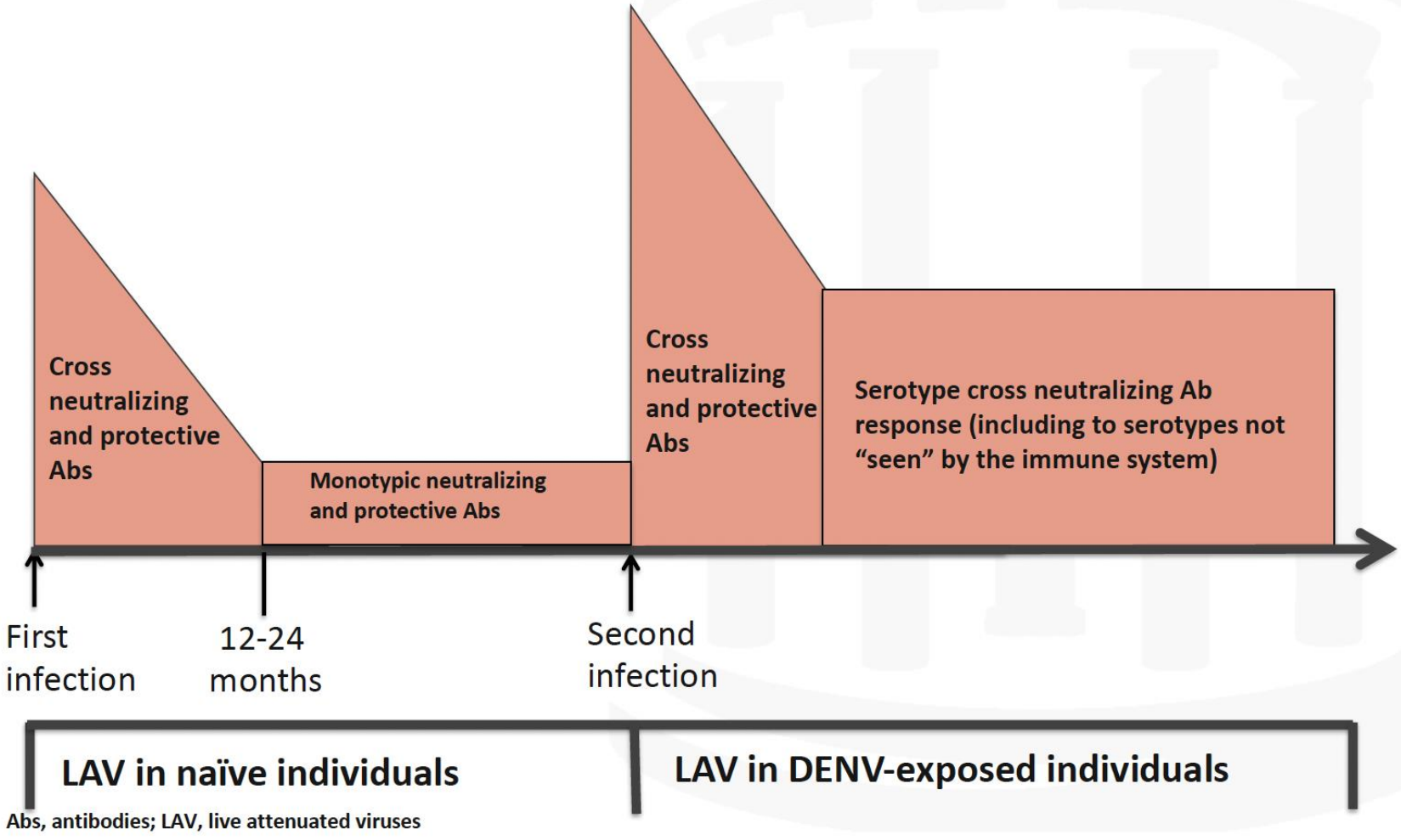
WHO SAGE recommendations on Dengvaxia™

- Initially recommended for children ≥ 9 in areas of high endemicity
- Further studies identified seronegative at baseline as risk for more severe DENV disease 2 years following vaccination
- Recommendations changed to vaccinate only those ≥ 9 who have already had documented dengue
  - There is no point of care diagnostic
  - Uptake of vaccine has been very low and the company is discontinuing production

Putting Qdenga™ (TAK-003) in the context of Dengvaxia™

Dengue vaccine	Data available	Results
Dengvaxia 2016	Aggregate data only; subset with serostatus stratification had inconclusive results	Data did not identify a risk. WHO acknowledged a theoretical risk
Dengvaxia 2018	Retrospectively stratified by baseline serostatus	Serostatus-driven vaccine performance: excess risk for severe dengue in baseline seronegative vaccinated persons
TAK-003 Qdenga 2023	Rigorously conducted RCT prospectively stratified by serostatus and serotype (*but unfortunately little circulation of DENV3 and DENV4 in trial sites*)	No serostatus-driven performance IN THE SETTING of the trial (mainly serotypes 1 and 2 circulating). Serotype-stratified analysis: absence of VE for DENV3 and 4 (with negative point estimates and wide CI intervals) Underpowered to rule in or rule out a risk in a subset of seronegatives.

Neutralizing/protective antibody responses following DENV infection and vaccination



Abs, antibodies; LAV, live attenuated viruses

TAK-003 Phase 3 results during each time period & through year 3 (36 months)

	Efficacy against VCD		Efficacy against hospitalized dengue	
	Seropositive	**Seronegative**	**Seropositive**	**Seronegative**
Year 1[1]	**82.2%** (74.5; 87.6)	**74.9%** (57.0;85.4)	**94.4%** (84.3; 98.0)	**97.2%** (79.1; 99.6)
Year 2[2]	60.3% (44.7; 71.5)	45.3% (9.9; 66.8)	90.0% (81.9; 94.5)	87.0 (70.1; 94.3)[2]
Year 3[3]	48.3% (34.2; 59.3)	35.5% (7.3;55.1)	78.4% (57.1; 89.1)	45.0% (**-42.6**; 78.8)
36 mo[3]	65% (58.9; 70.1)	54.3% (41.9; 64.1)	86% (78.4; 91)	77.1% (58.6; 87.3)

1. Biswal, S et al NEJM 2019
2. Lopez-Medina et al JID 2020. Hospitalized cases in year 1 43/58 were DENV-2; year 2 7/33 were DENV-2
3. Rivera, L et al CID 2021

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Vaccine efficacy against VCD over time

	DENV-1		DENV-2		DENV-3		DENV-4	
	Seropos	Seroneg	Seropos	Seroneg	Seropos	Seroneg	Seropos	Seroneg
Year 1[1]	79.8% (51.3;91.6)	67.2% (23.2;86.0)	**96.5% (88.7;98.8)**	**100%**	71.4% (54.3;82.1)	**-38.7% (-335;55.8)**	**63.8% (-61.8;91.9)**	n/a
Year 2[2]	59.1% (31.1;75.7)	60.7% (22.1;80.2	**75.5% (49.5;88.1)**	**70.5% (23.4;93.0)**	44.9% (1.6;69.1)	**-18.5% (-236.2;58.3)**	**69.0% (-85.8;94.8)**	**-47.6% (-1319;84.6)**
Year 3[3]	45.4% (24.5;60.6)	**17.2% (-31.8;47.9)**	**72.1% (51.6;84.0)**	**84.9 (58.7;94.5)**	**15.2% (-46.1;50.8)**	**9.5% (-144.7;66.5)**	**61.9% (-24.9;88.4)**	**-99.0% (-1681;77.8)**

1. Biswal, S et al NEJM 2019
2. Lopez-Medina et al JID 2020.
3. Rivera, L et al CID 2021

thl

Vaccine efficacy against VCD by serostatus through 57 months after first dose

	Placebo n=6687	TAK-003 n=13,380	VE (95% CI)
VCD (per 100 person-yrs)			
Seropositive			
DENV-1	151 (0.7)	133 (0.3)	**56.1 (44.6, 65.2)**
DENV-2	135 (0.6)	54 (0.1)	**80.4 (73.1, 86.7)**
DENV-3	97 (0.4)	96 (0.2)	**52.3 (36.6, 64.0)**
DENV-4	20 (<0.1)	12 (<0.1)	**70.6 (39.9, 85.6)**
Seronegative			
DENV-1	79 (1.0	89 (0.5)	**45.4 (26.1, 59.7)**
DENV-2	58 (0.7)	14 (<0.1)	**88.1 (78.6, 93.3)**
DENV-3	16 (0.2)	36 (0.2)	**-15.5 (-108.2, 35.9)**
DENV-4	3 (<0.1)	12 (0.1)	**-105.6 (-628.7, 42.0)**

SAGE, Tricou 2024

Vaccine efficacy against hospitalized VCD by serostatus through 57 months after first dose

	Placebo n=6687	TAK-003 n=13,380	VE (95% CI)
VCD (per 100 person-yrs)			
Seropositive			
DENV-1	24 (0.1)	16 (<0.1)	**66.8 (37.4, 82.3)**
DENV-2	59 (0.3)	5 (<0.1)	**95.8 (89.6, 98.3)**
DENV-3	15 (<0.1)	8 (<0.1)	**74.0(38.6, 89.0)**
DENV-4	3 (<0.1)	0 (<0.1)	**100 (NE)**
Seronegative			
DENV-1	14 (0.2)	6 (<0.1)	**78.4 (43.9, 91.7)**
DENV-2	23 (0.3)	0 (0.0)	**100 (NE, NE)**
DENV-3	**3 (<0.1)**	**11 (<0.1)**	**-87.9 (-573, 47.6)**
DENV-4	1 (<0.1)	0 (0.0)	**100 (NE, NE)**

SAGE, Tricou 2024

SAGE Recommendations for the use of TAK-003 dengue vaccine

World Health Organization

WHO SAGE WG considerations presented in SAGE October 2023

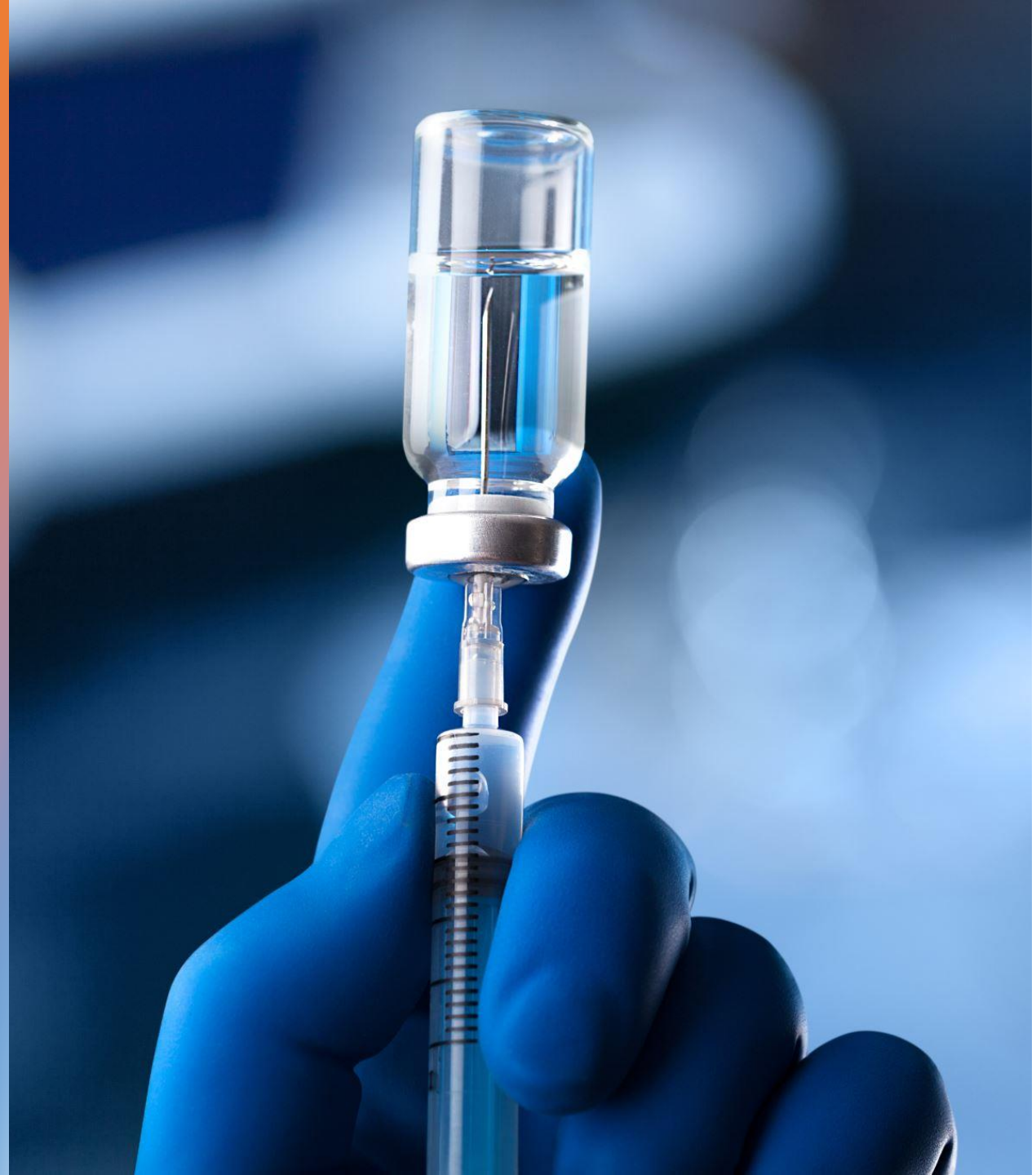
The SAGE position paper came out in Weekly Epidemiologic Record 3 May 2024

Communication of an uncertain risk is difficult.

The public is sensitized to the potential risk due to the Dengvaxia story.

Transparency is needed.

SAGE WG considered a full range of policy options and narrowed down the options to recommending the use in high dengue transmission settings only, without pre-vaccination screening



Rationale for use in high dengue transmission settings only, as defined as 60% seroprevalence by age 9

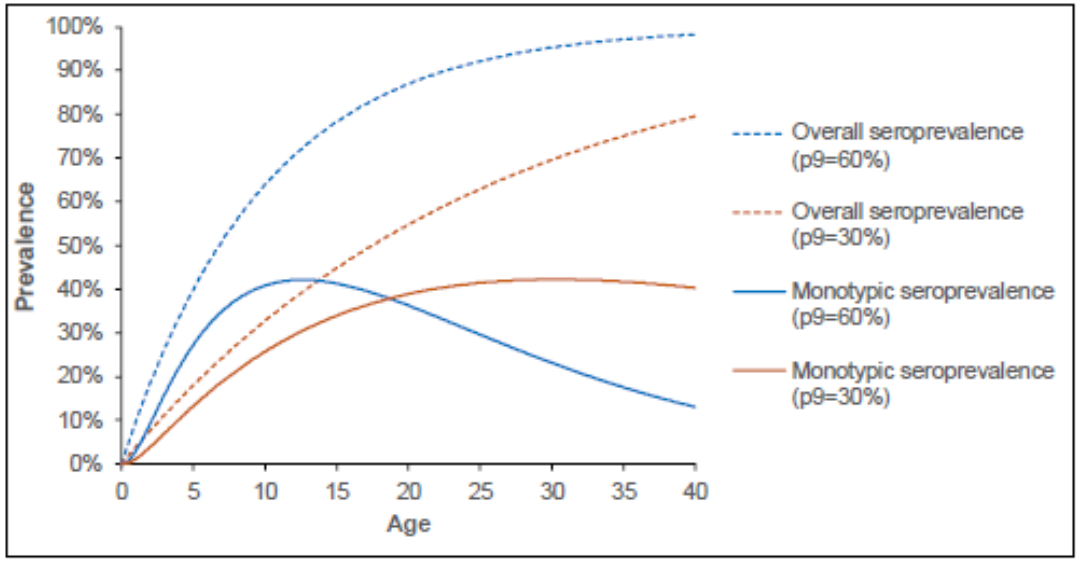
- Highest public health impact
- Mitigate any potential individual risk
- Most cost-effective use of finite vaccine supplies
- Targeted roll-out allows time for communication strategies and advocacy
- Will enable more precise risk estimates in seronegative persons, thereby enabling a broader recommendation in the near future

Why seroprevalence ?

- Proportion of dengue seropositive persons in the population
- Vaccine impact is highest in monotypic seropositive individuals
- Seroprevalence is correlated with force of infection
- The higher the force of infection, the younger the mean age of peak incidence
- Seroprevalence by a certain age is therefore not just the proportion of seropositive persons; it reflects the transmission intensity and therefore the interval between infections
- Seroprevalence of 60% and above by age 9 is a proxy for high dengue transmission intensity

Target age for programmatic use of TAK-003 in dengue endemic countries

- WHO recommends that the vaccine is introduced for children aged 6 to 16 years in settings with high dengue transmission intensity.
- Within this age range, the vaccine should optimally be introduced about 1-2 years prior to the age-specific peak incidence of dengue related hospital admissions, but considerations such as programmatic alignment with the administration of other school-based vaccination strategies (i.e. HPV vaccines) can also be taken into account.
- Catch-up programmes can be considered for other age groups within the age range of 6 to 16 years.



- Until the efficacy-risk profile in seronegative persons for DENV3 and DENV4 has been more precisely assessed, WHO does not recommend the programmatic use of this vaccine in low to moderate dengue transmission settings

So what about travellers as most travellers are adults and seronegative?

Dengue in Travelers

- Dengue is the most frequent cause of fever in travelers returning from South East Asia: GeoSentinel analysis
- The proportion of dengue amongst ill-returned travelers is increasing
- Prospective seroconversion studies:
  - 2.4% after 1 month travel
  - 6.9% after 6 month travel
- Travelers who had a primary infection fear severe dengue if returning to dengue endemic countries
- Dengue rarely causes deaths in travelers
- But dengue disrupts travel, adds out-of-pocket costs and may lead to evacuation back home

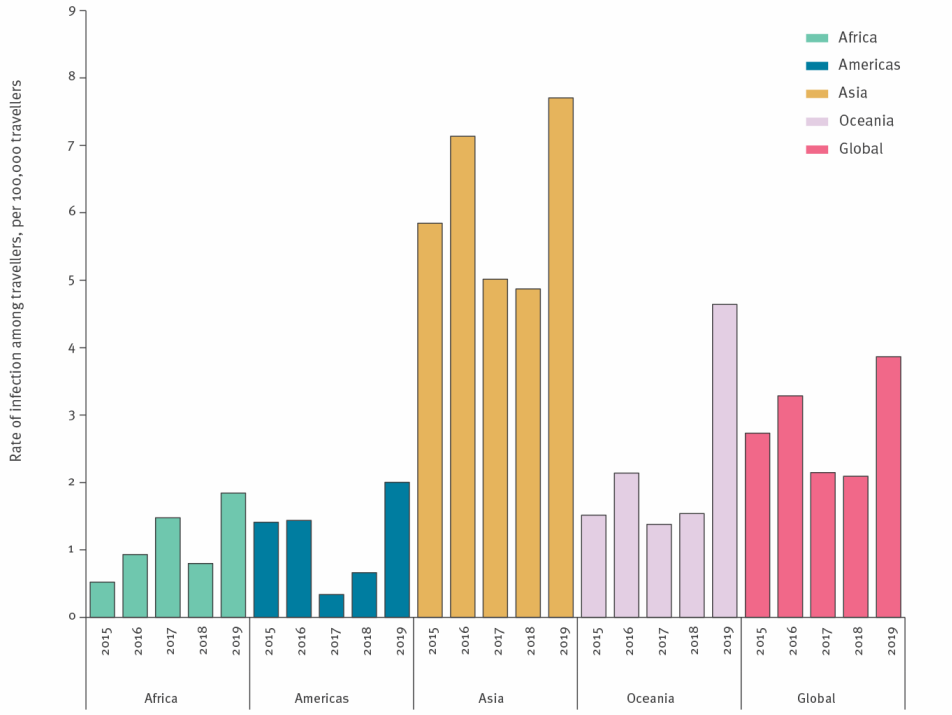
- Halstead, Wilder-Smith. Risk of severe dengue in travelers. J Travel Med 2019
- Wilder-Smith, Schwartz. Dengue in travelers. NEJM 2005
- O'Brien et al. Fever in returned travelers: review of hospital admissions. Clin Infect Dis 2001
- Schwartz et al. Dengue fever among travelers. A, J Med 1996
- Freedman et al. Spectrum of disease and relation to place of exposure in ill-returned travelers. NEJM 2006
- Schwartz et al, Changing epidemiology of dengue fever in travelers to Thailand. Eur J Clin Microbiol Infect Dis 2000
- Cobelens et al, Incidence and risk factors of dengue among Dutch travellers to Asia. Trop Med Int Health 2002
- Potasman et al, Dengue serconversion among Israeli travelers to tropical countrires. Emerg Infect Dis 1999
- Tozan, et al. **A Prospective Study on the Impact and Out-of-Pocket Costs of Dengue Illness in International Travelers,** *The American Journal of Tropical Medicine and Hygiene*, *100*(6**)**, 1525-1533

Surveillance

Dengue virus infections among European travellers, 2015 to 2019

Check for updates

Céline M Gossner[1], Nelly Fournet[2], Christina Frank[3], Beatriz Fernández-Martínez[4], Martina Del Manso[5], Joana Gomes Dias[1], Henriette de Valk[2]



Country	Cases	Cases/100 000 travellers
Thailand	2956	20
Indonesia	1139	29
Cambodia	278	46
India	1347	9
Brazil	299	3
Paraguay	75	24
Mexico	303	3
Somalia	34	17
Kenya	76	4
Burkina Faso	48	15

The risk of dengue among travellers from Finland to popular destinations

Table 1. Overall crude attack rates (AR/100,000) for dengue infections in common destinations, 2016–2019.

Destination	Number of arrivals[a]	Number of infections[b]	AR (95% CI)
Asia			
Thailand	137,351	18.5	13.5 (8.3–20.7)
Indonesia	22,739	4.75	20.9 (7.1–45.0)
Maldives	3147	1.75	55.6 (7.7–176.9)
Vietnam	17,095	1.75	10.2 (1.4–32.6)
Sri Lanka	6742	1.25	18.5 (3.6–82.6)
India	19,378	1.0	5.2 (1.3–28.6)
Philippines	6638	1.0	15.1 (3.7–83.9)

[a]Average of 2016–2017.
[b]Average of 2016–2019.

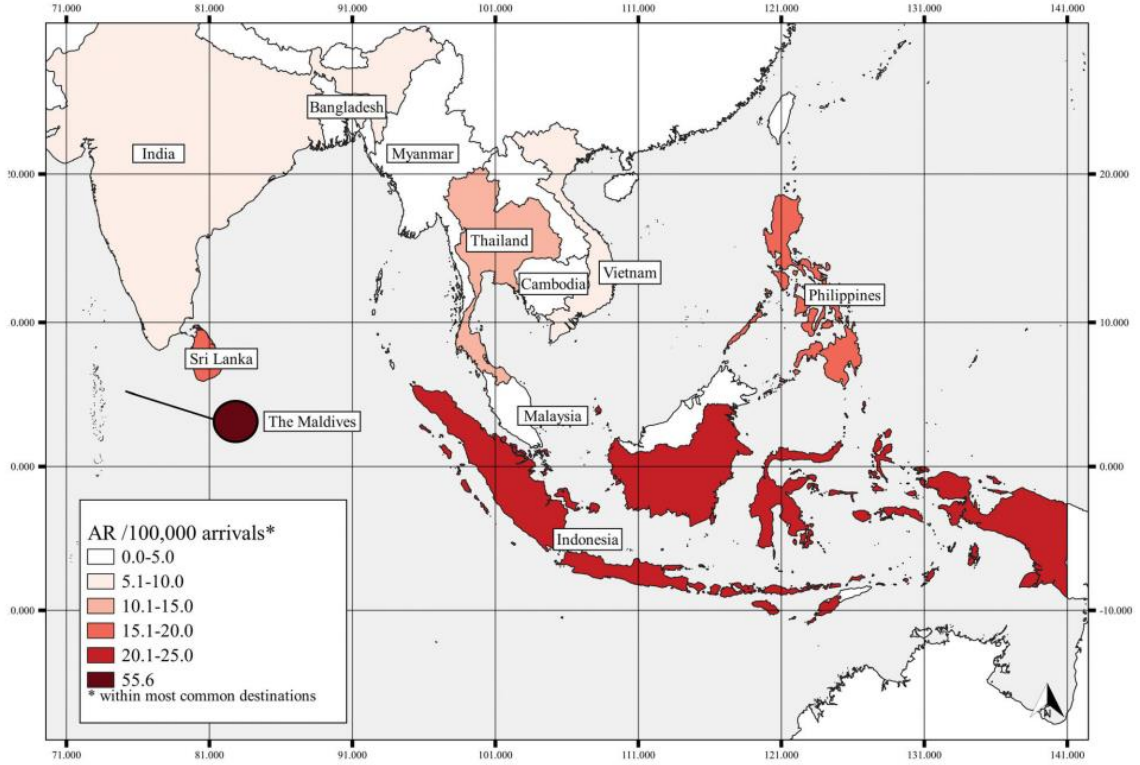


Figure 2. Crude attack rates for dengue in most popular destinations in Finnish travellers, January 2016–May 2019.

Mäkelä 2020

Travellers, history of dengue, and what can be expected from TAK-003

Seropositive

- Clear benefit

Seronegative

- Lower benefit (DENV 1-2)
- No benefit (DENV 3-4)
- Possibly increased risk

- Pre-vaccination screening was not considered to remain consistent with the logic applied to endemic populations, BUT could be considered on an individual level

WHO SAGE Dengue vaccine position paper, WER 3.5.2024

Position on travellers (1)

- Persons living in non-endemic countries who have previously been infected with any of the 4 dengue virus serotypes … may benefit from TAK-003 vaccination to prevent a second (and hence potentially more severe) dengue infection when travelling again to an endemic country.
- The benefits of vaccination with TAK-003 are lower for travellers who have never experienced dengue infection… compared to travellers who are seropositive.
- Travellers need to be informed that the vaccine may not confer protection against DENV3 and DENV4 if they are seronegative, and that there is a potential risk of severe dengue if seronegative individuals are exposed to DENV3 and DENV4.
- Although pre-vaccination screening to determine serostatus is not required, where available its use could be considered to inform the assessment of risks and benefits.

https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers/dengue

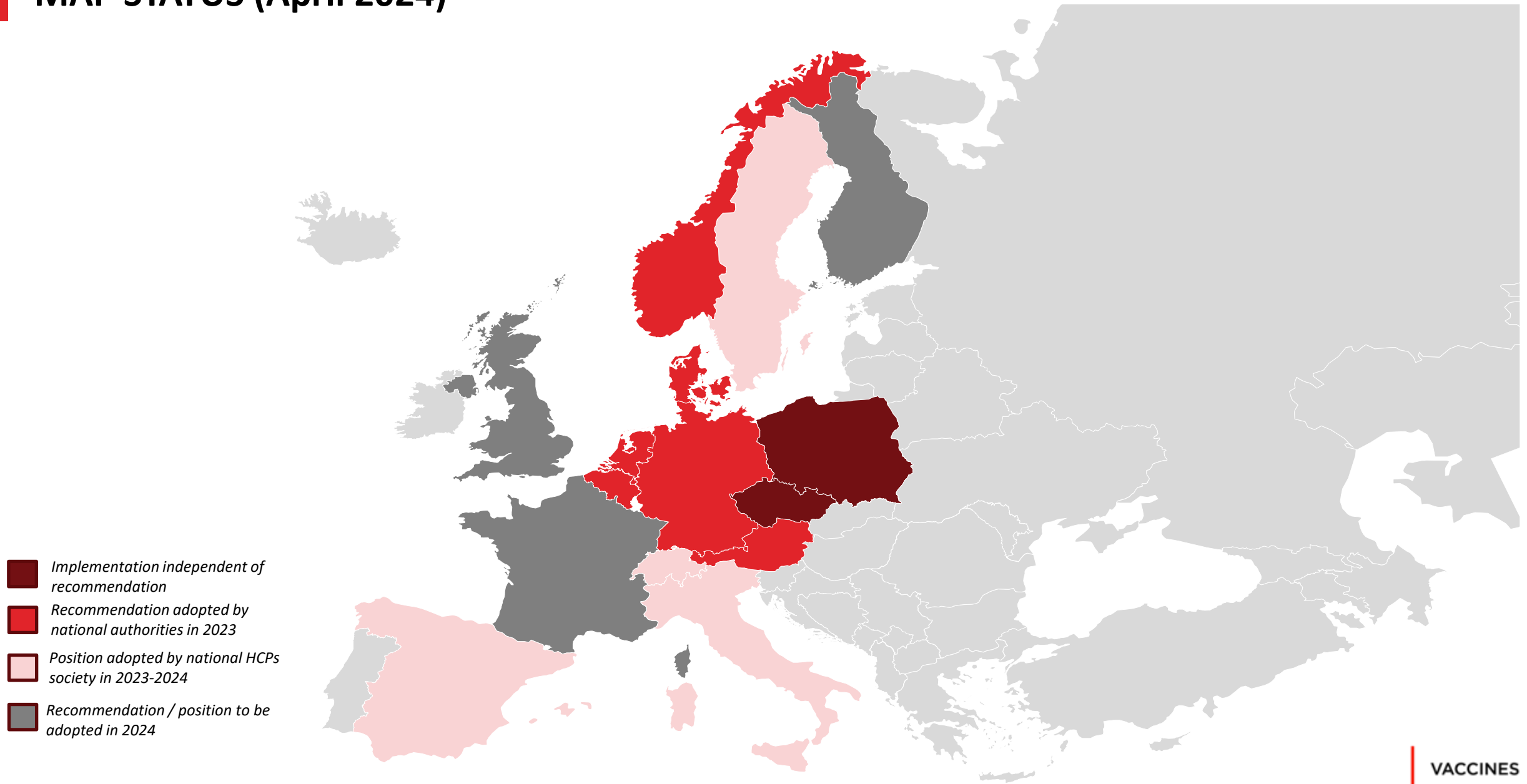
WHO SAGE Dengue vaccine position paper, WER 3.5.2024

Position on travellers (2)

- Coadministration with Yellow fever vaccine and Hepatitis A vaccine does not interfere with dengue vaccine response
- Protection starts 14 days after the first dose and has been demonstrated between the first and second dose; hence, the first dose can be given up to 14 days before travel to a dengue-endemic country.
- To ensure the durability of the protection, a second dose is needed after a minimum interval of 3 months
- Until more data become available on efficacy-safety profile, WHO recommends a lower age limit of 6 years and upper age limit of 60 years for travellers

https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers/dengue

QDENGA TRAVEL VACCINATION RECOMMENDATIONS IN EUROPE: MAP STATUS (April 2024)



VACCINES

What do different ”like minded” countries / bodies recommend on TAK-003

	Responsible for making recommendation	Reference
Sweden	Vaccine Expert group of the Swedish Society for Infectious Diseases Physicians	https://doi.org/10.1016/j.tmaid.2023.102598
Denmark	Statens Serum Institut (SSI)	https://en.ssi.dk/news/epi-news/2023/no-14---2023
Germany	STIKO, Robert Koch Institut	https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2023/Ausgaben/48_23.pdf?__blob=publicationFile
Belgium	Superior Health Council	https://www.health.belgium.be/en/report-9739-vaccination-against-dengue

What do different ”like-minded” countries / bodies recommend on TAK-003

	Age in years	How many doses before travel ?	Is pretravel status of dengue infection required?	Duration of travel ?
Sweden	4-60	2	Yes, self reported	> 6 weeks to South East Asia
Denmark	> 4	2	No stand on this	> 4 weeks to endemic area
Germany	> 4	2	Yes, laboratory confirmed	Long trip or epidemic area
Belgium	> 4	2	Yes	> 4 weeks to high risk area

What to do with those without dengue history ?

How to assess individual risk ?

Terveyden ja hyvinvoinnin laitos

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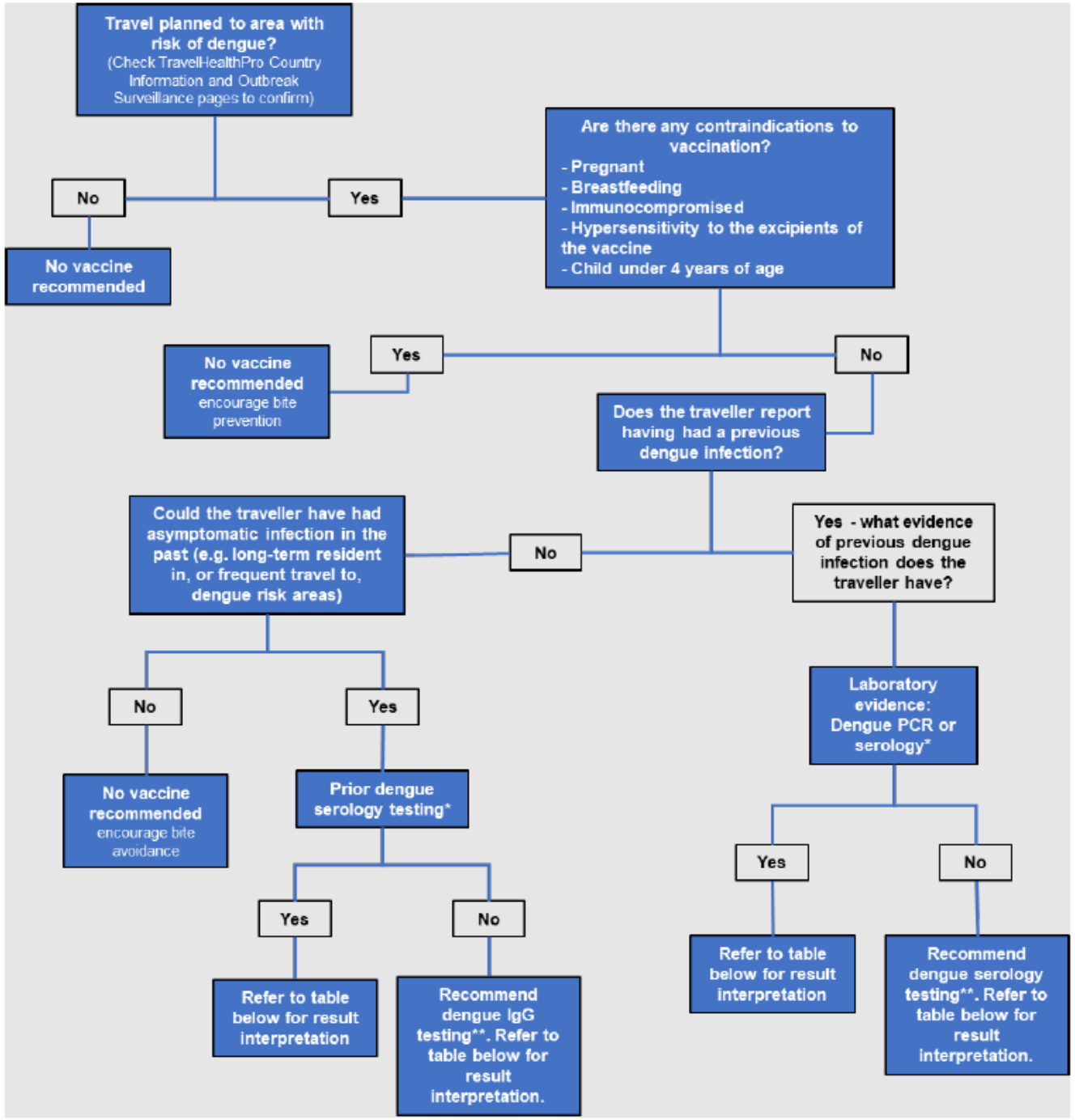

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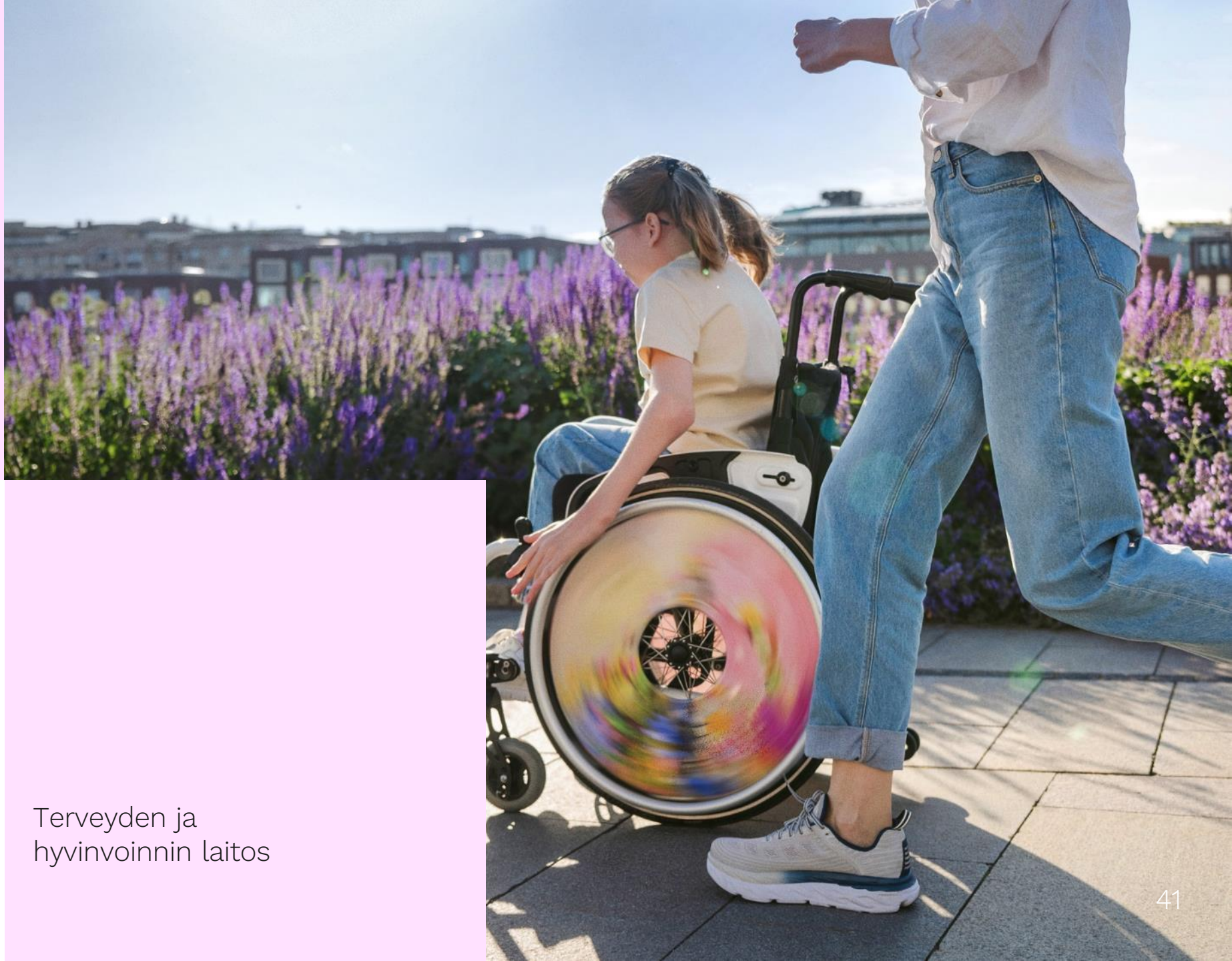
Appendix 2: Consideration of eligibility for vaccination

	No compatible travel, no compatible illness	Compatible illness, no compatible travel	Compatible travel, no compatible illness	Compatible travel, compatible illness
IgM negative, IgG negative on any blood sample taken ≥4 weeks after last compatible illness	Vaccination not recommended	Vaccination not recommended	Vaccination not recommended	Vaccination not recommended
IgM positive, IgG and PCR negative on any blood sample taken <4 weeks after travel	Vaccination not recommended	Vaccination not recommended	Test for IgG >4 weeks after leaving endemic area	Test for IgG >4 weeks after compatible illness
IgM negative, IgG positive on any blood sample taken >4 weeks after travel or illness	Vaccination not recommended	Vaccination not recommended	Consider vaccination* in light of other reasons for IgG†	Consider vaccination* in light of other reasons for IgG†
IgM and IgG positive on any blood sample taken >4 weeks and <6 months after travel	Vaccination not recommended	Vaccination not recommended	Consider vaccination**	Consider vaccination**
PCR positive on any sample	This should be discussed with RIPL	This should be discussed with RIPL	Consider vaccination**	Consider vaccination**

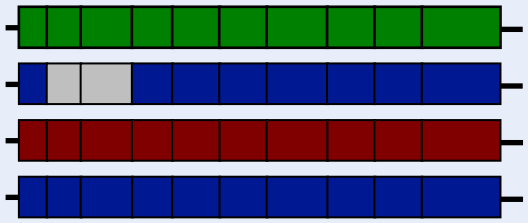
thl



Terveyden ja
hyvinvoinnin laitos

Clinical development of the NIH LATV vaccine

- Components of tetravalent vaccine first evaluated as monovalent vaccines in flavivirus-naïve volunteers
  - Several tetravalent admixtures evaluated for infectivity, safety, and immunogenicity
- **Single dose vaccine**
- Phase 3 trial conducted by Instituto Butantan in Brazil
  - **47% vaccine recipients were seronaive**
- Interim results through 2 years post vaccination published

	TV003 (multiple manufacturers)
Status	Phase 3 (Instituto Butantan)
# Doses	**Single dose**
Indicated age	Phase 3 age 2 - 59
Other	?
Construct	
Dengue proteins	32 (NS proteins of DENV-1, DENV-3, & DENV-4)

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Live, Attenuated, Tetravalent Butantan–Dengue Vaccine in Children and Adults

E.G. Kallás, M.A.T. Cintra, J.A. Moreira, E.G. Patiño, P.E. Braga, J.C.V. Tenório, V. Infante, R. Palacios, M.V.G. de Lacerda, D.B. Pereira, A.J. da Fonseca, R.Q. Gurgel, I.C.-B. Coelho, C.J.F. Fontes, E.T.A. Marques, G.A.S. Romero, M.M. Teixeira, A.M. Siqueira, A.M.P. Barral, V.S. Boaventura, F. Ramos, E. Elias Júnior, J. Cassio de Moraes, D.T. Covas, J. Kalil, A.R. Precioso, S.S. Whitehead, A. Esteves-Jaramillo, T. Shekar, J.-J. Lee, J. Macey, S.G. Kelner, B.-A.G. Coller, F.C. Boulos, and M.L. Nogueira

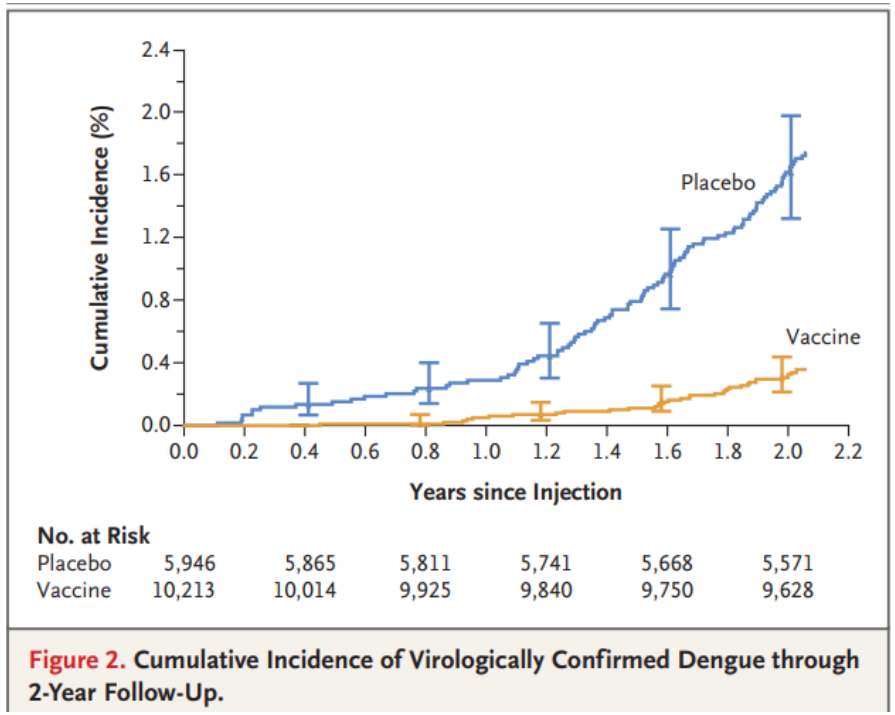

Figure 2. Cumulative Incidence of Virologically Confirmed Dengue through 2-Year Follow-Up.

- Double-blind trial in Brazil, 16235 participants, one dose Butantan-DB
- Vaccine efficacy against any serotype, no previous dengue exposure 73.6% (57.6 – 83.7)
- Vaccine efficacy aganist any serotype, evidence of previous dengue exposure 89.2% (77.6 – 95.5)
- Limitations
  - No cases with serotypes DENV-3 and DENV-4
  - Low incidence of severe dengue

5 year follow up ends in 6/2024
Expecting licensure early 2025
Presently Brazil facing major serotype 3 and 4
Epidemic -> data on VE and safety is being monitored further

Tackar !

Thank you to Annelies Wilder-Smith, Ann Durbin, Ville Holmberg