Where are we with dengue vaccines?

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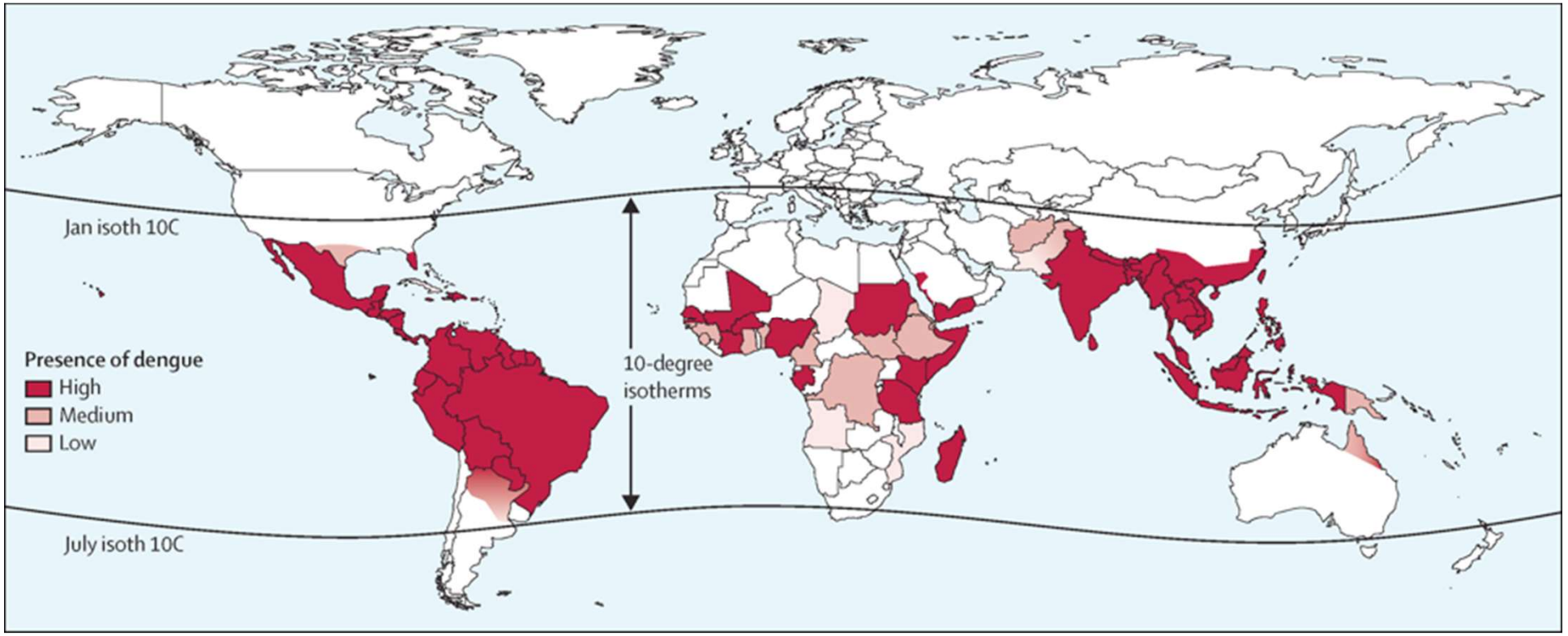
DENGUE VACCINE INITIATIVE

Dengue infections



Global burden of dengue

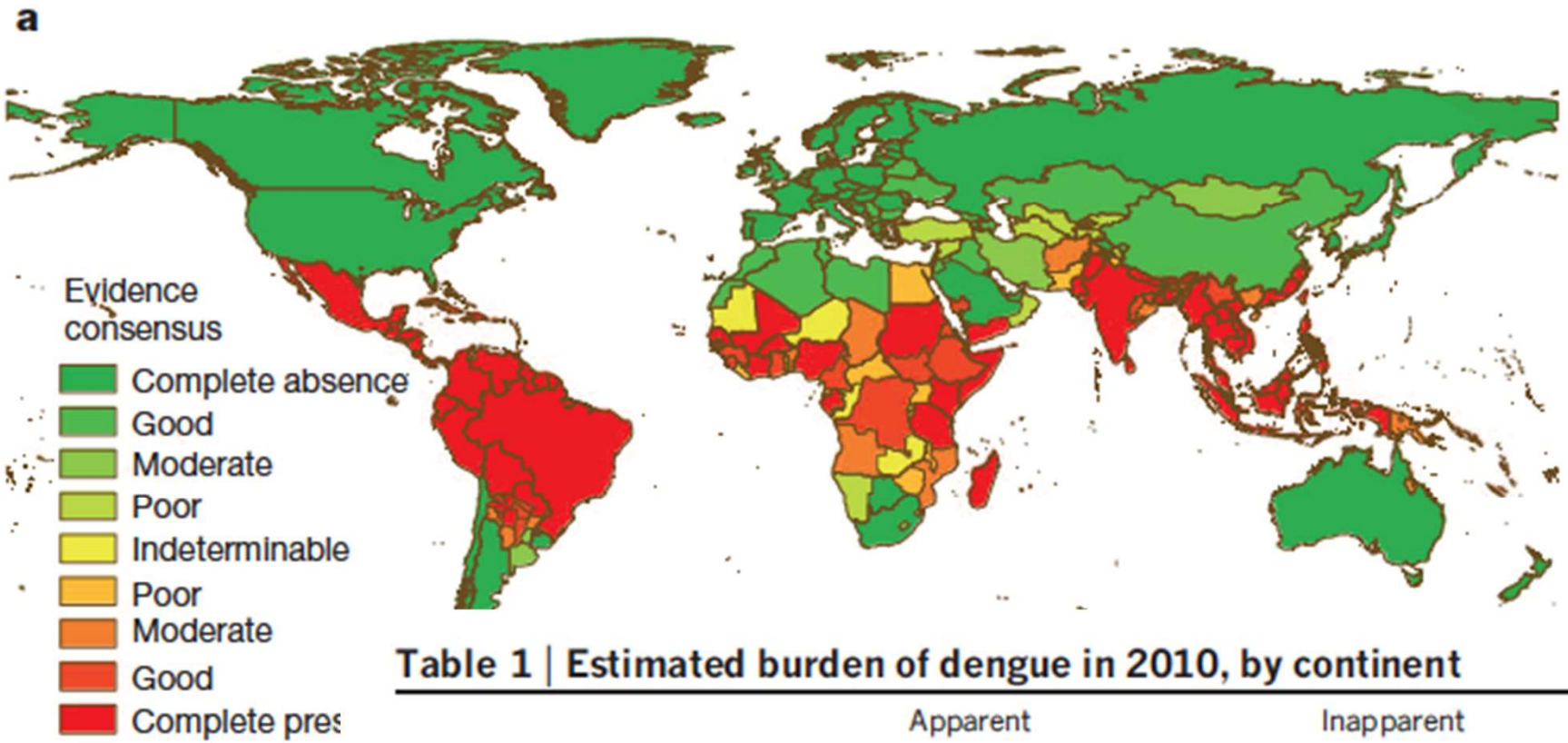
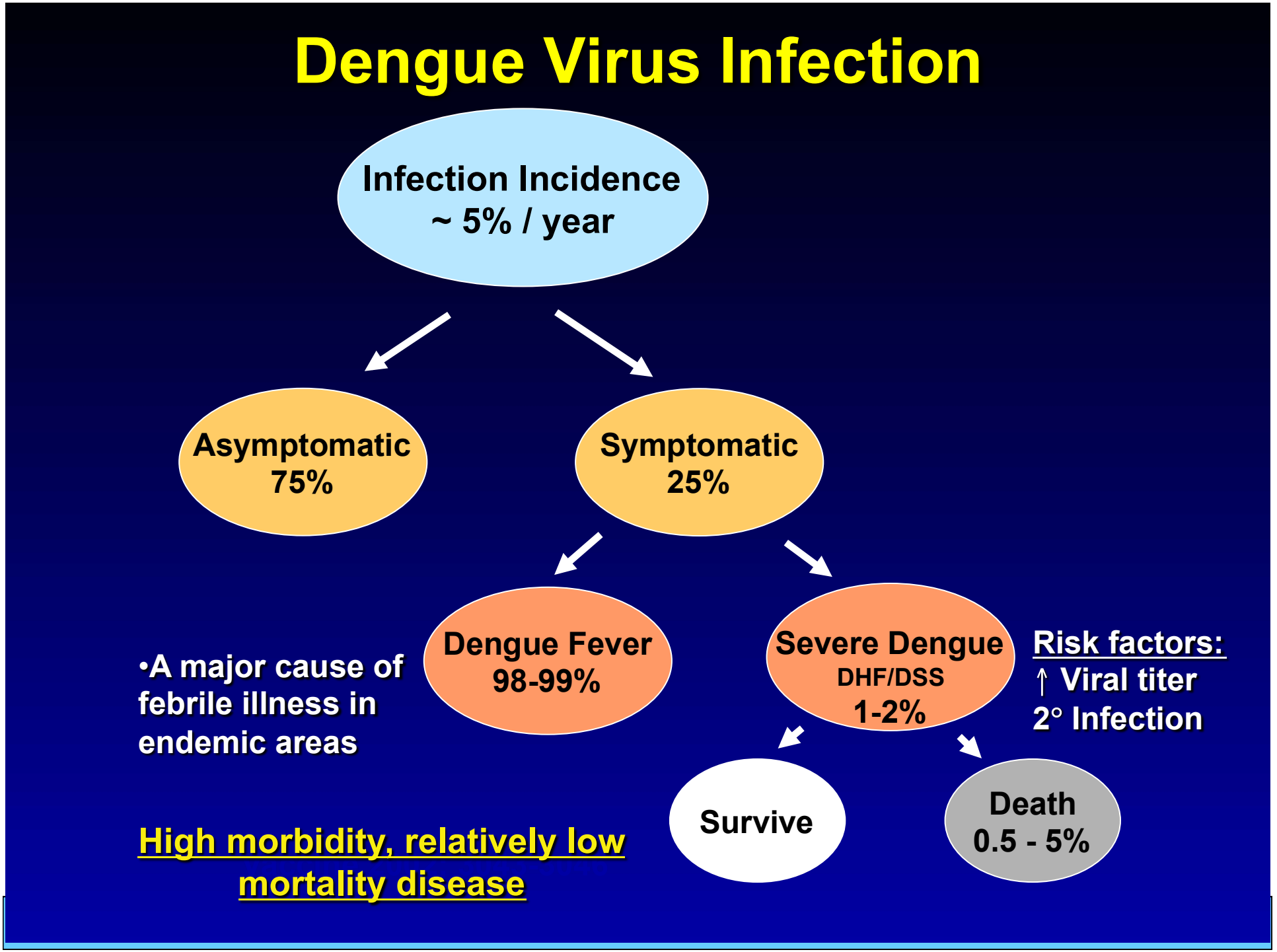


Table 1 | Estimated burden of dengue in 2010, by continent

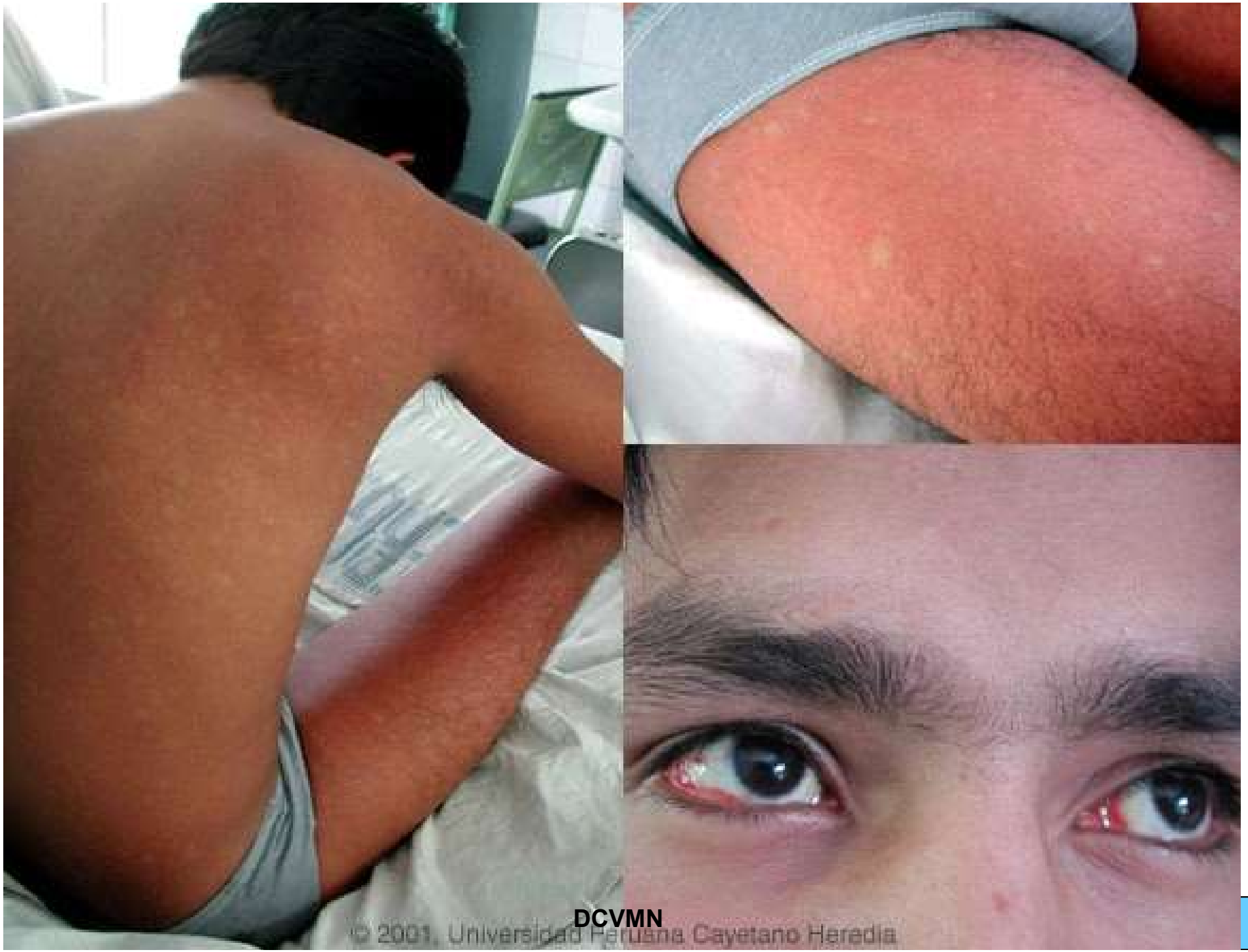
	Apparent	Inapparent
	Millions (credible interval)	Millions (credible interval)
Africa	15.7 (10.5–22.5)	48.4 (34.3–65.2)
Asia	66.8 (47.0–94.4)	204.4 (151.8–273.0)
Americas	13.3 (9.5–18.5)	40.5 (30.5–53.3)
Oceania	0.18 (0.11–0.28)	0.55 (0.35–0.82)
Global	96 (67.1–135.6)	293.9 (217.0–392.3)

Dengue Virus Infection



Dengue Hemorrhagic Fever

DCVMN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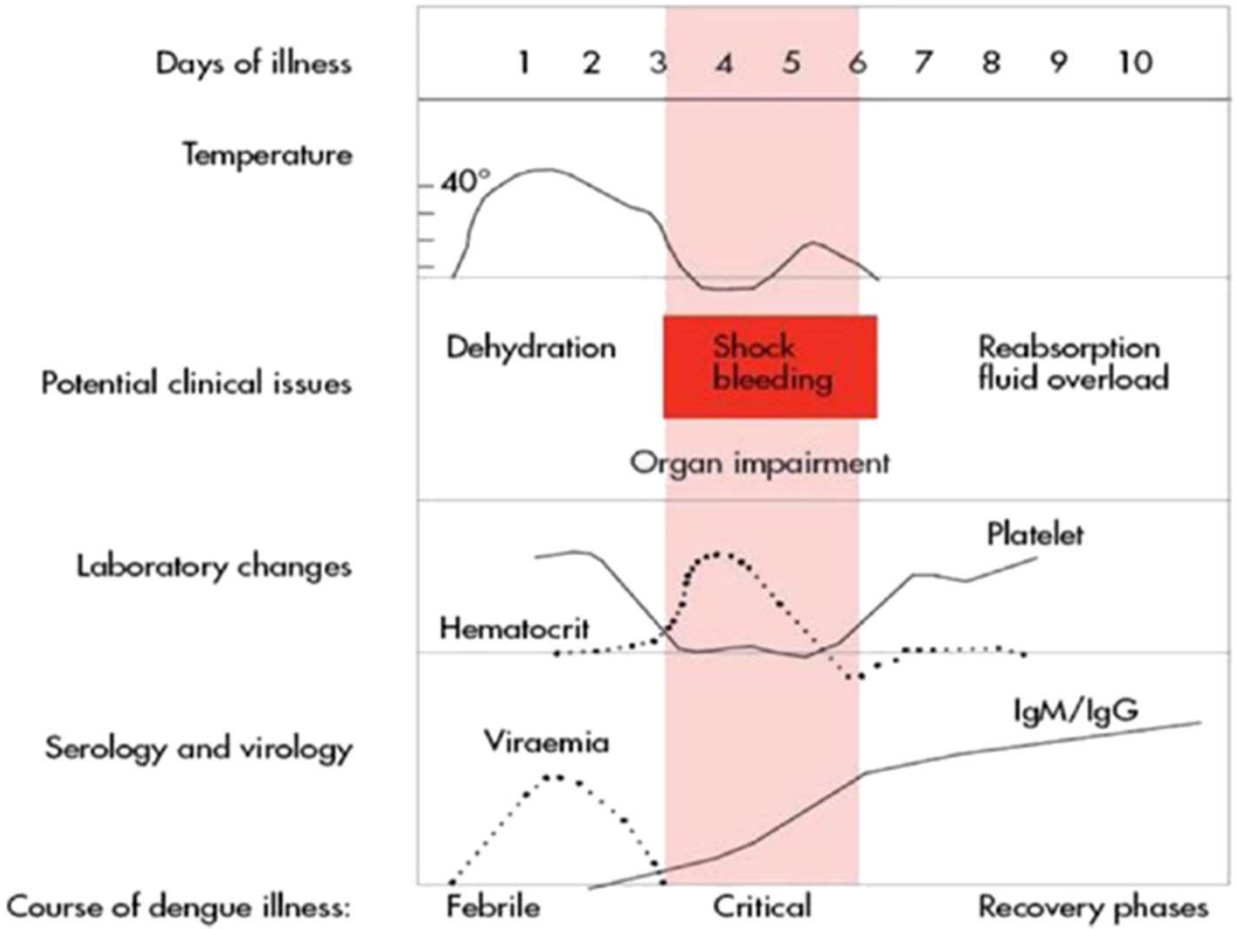
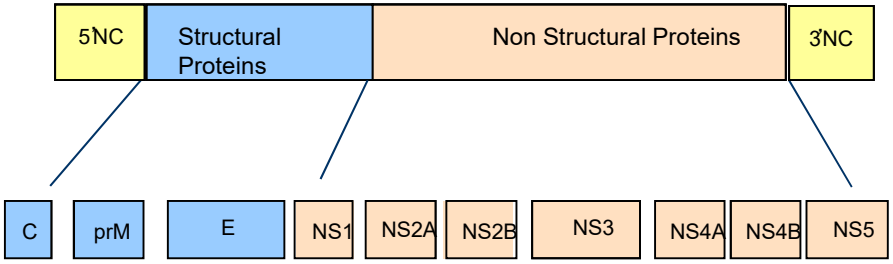
Time course


Days of illness
1 2 3 4 5 6 7 8 9 10
Temperature
40°
Potential clinical issues
Dehydration
Shock bleeding
Reabsorption fluid overload
Organ impairment
Laboratory changes
Platelet
Hematocrit
Serology and virology
Viraemia
IgM/IgG
Course of dengue illness:
Febrile
Critical
Recovery phases

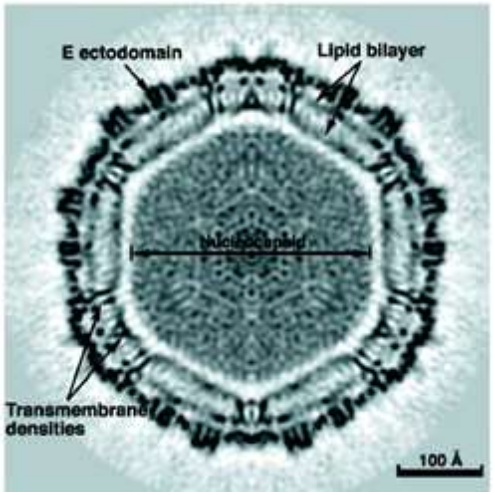
Dengue Virus

- Flavivirus (YF, JE, TBE, WN)
- RNA Virus: 3 structural proteins & 7 non-structural proteins

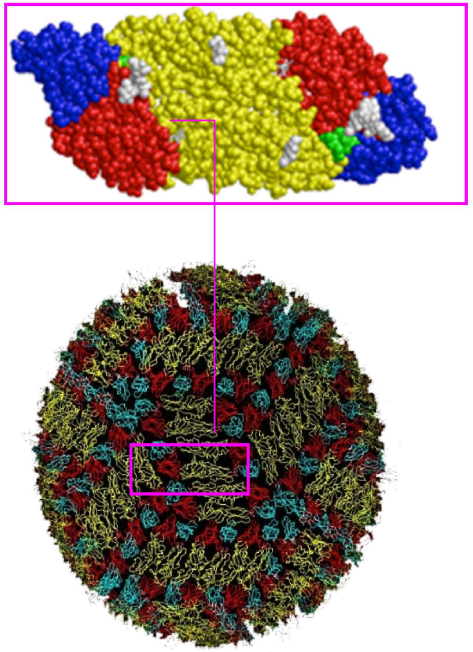


- 4 close but genetically different serotypes

DEN-1
DEN-2
DEN-3
DEN-4

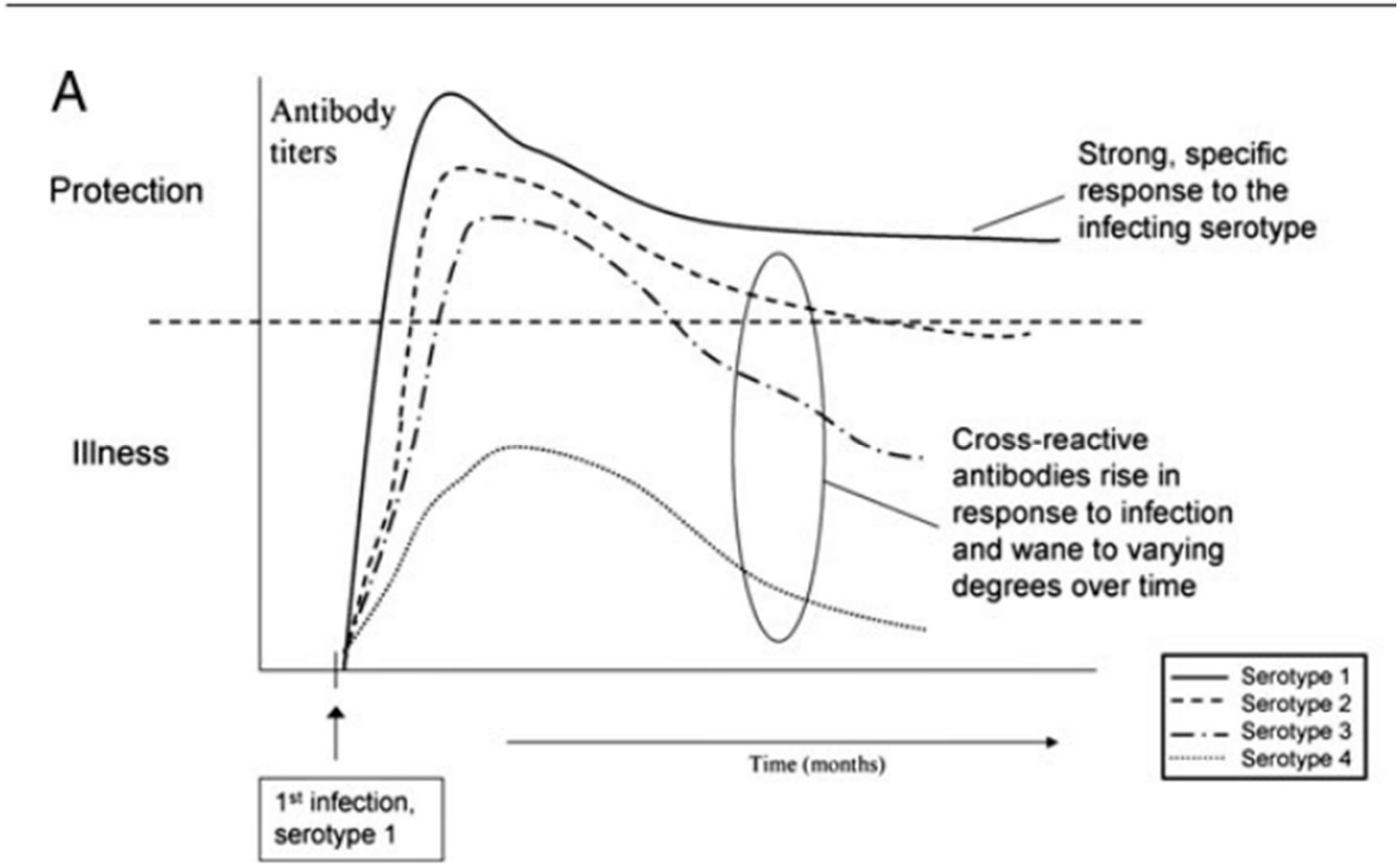


Zhang et al., 2003,



Cell 108, 717-725

Antibodies can be protective or destructive



Immunity

- **Monotypic immunity**
- **Heterotypic immunity**
- **Multitypic immunity**

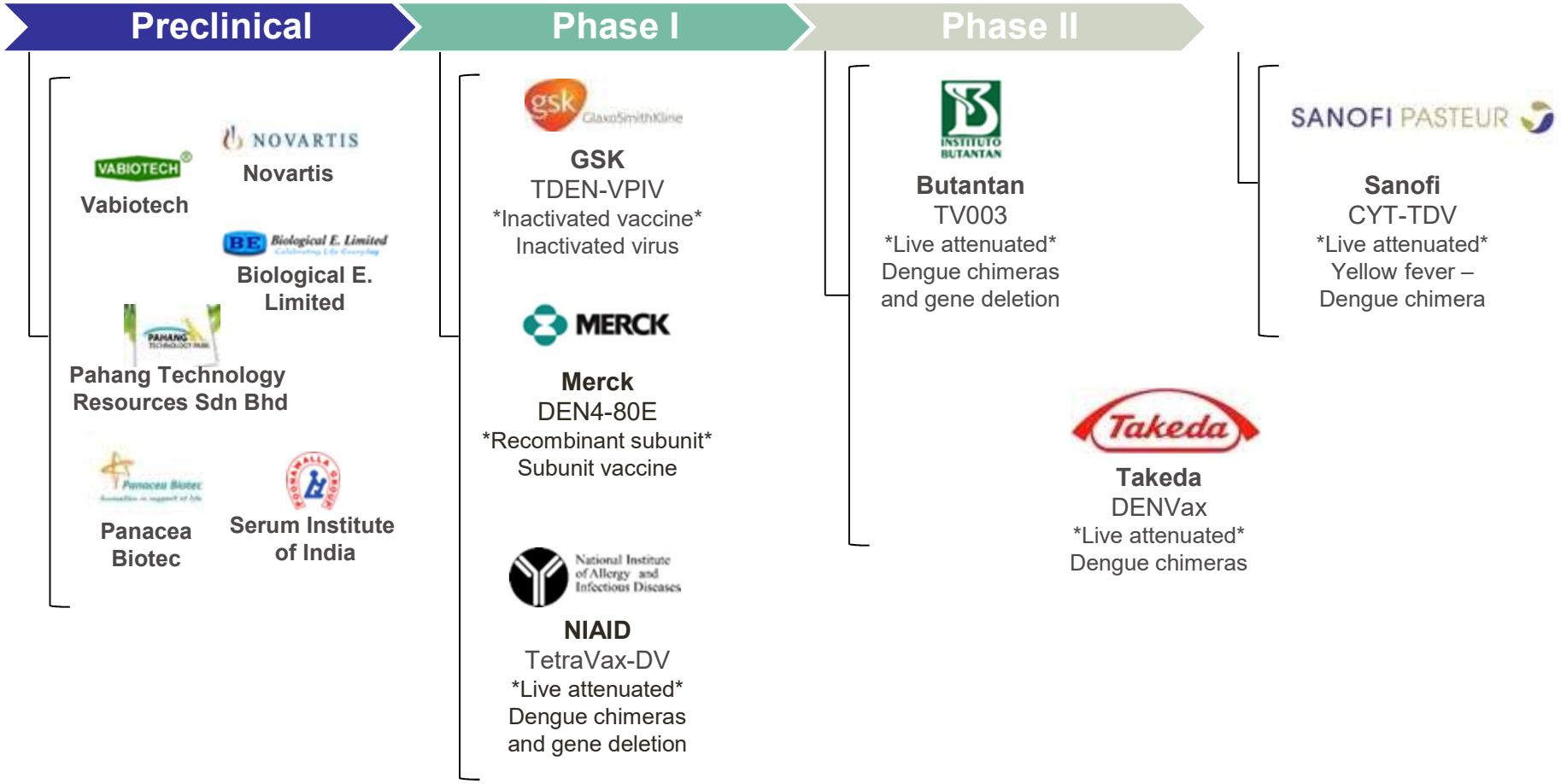
Additional hurdles

- Animal model
- True correlate of protection
  - Neutralizing antibody appears to be poor predictor
- Overcoming viral interference with a tetravalent vaccine (live)
- Role of cellular immunity

Dengue Vaccine

- High level country interest in a vaccine
- 30 year of development
- Robust vaccine pipeline
- First Phase 3 efficacy results in 2014
- First vaccine licensed in 2015

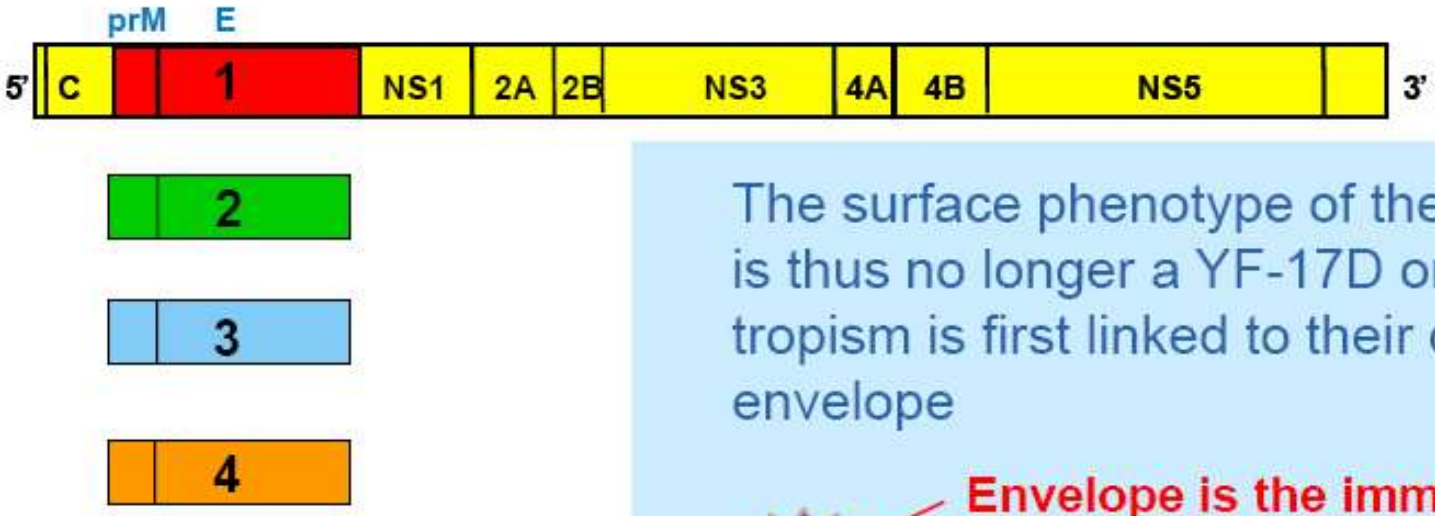
Competitive landscape, different stages



DCVMN

Live chimeric vaccine (SP)

Live attenuated CYD vaccinal viruses express the pre-membrane (prM) and envelope (E) proteins of each dengue serotype, which genes have been inserted in place of the corresponding genes of the YF 17D vaccine



The surface phenotype of these vaccines is thus no longer a YF-17D one, and their tropism is first linked to their dengue envelope

Envelope is the immunizing Ag from an heterologous virus

RNA replication engine is from YF17D

Phase II randomized controlled trial in Singapore

Yee Sin Leo,[1] Annelies Wilder-Smith,[2,3] Sophia Archuleta,[2,3] Lynette P. Shek,[4] Chia Yin Chong,[5] Hoe Nam Leong,[6] Chian Yong Low,[6] May-Lin Helen Oh,[7] Alain Bouckenooghe,[8] T. Anh Wartel[8,*] and Denis Crevat[10]

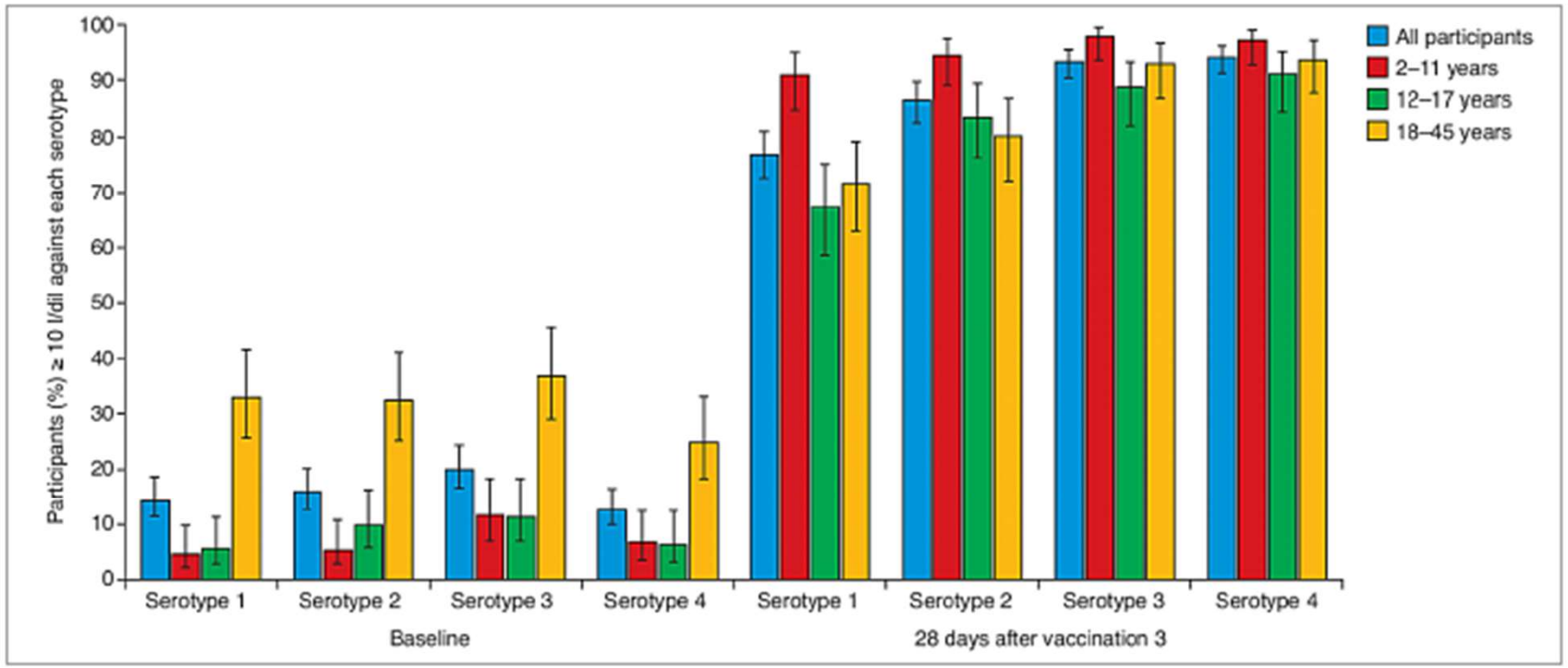
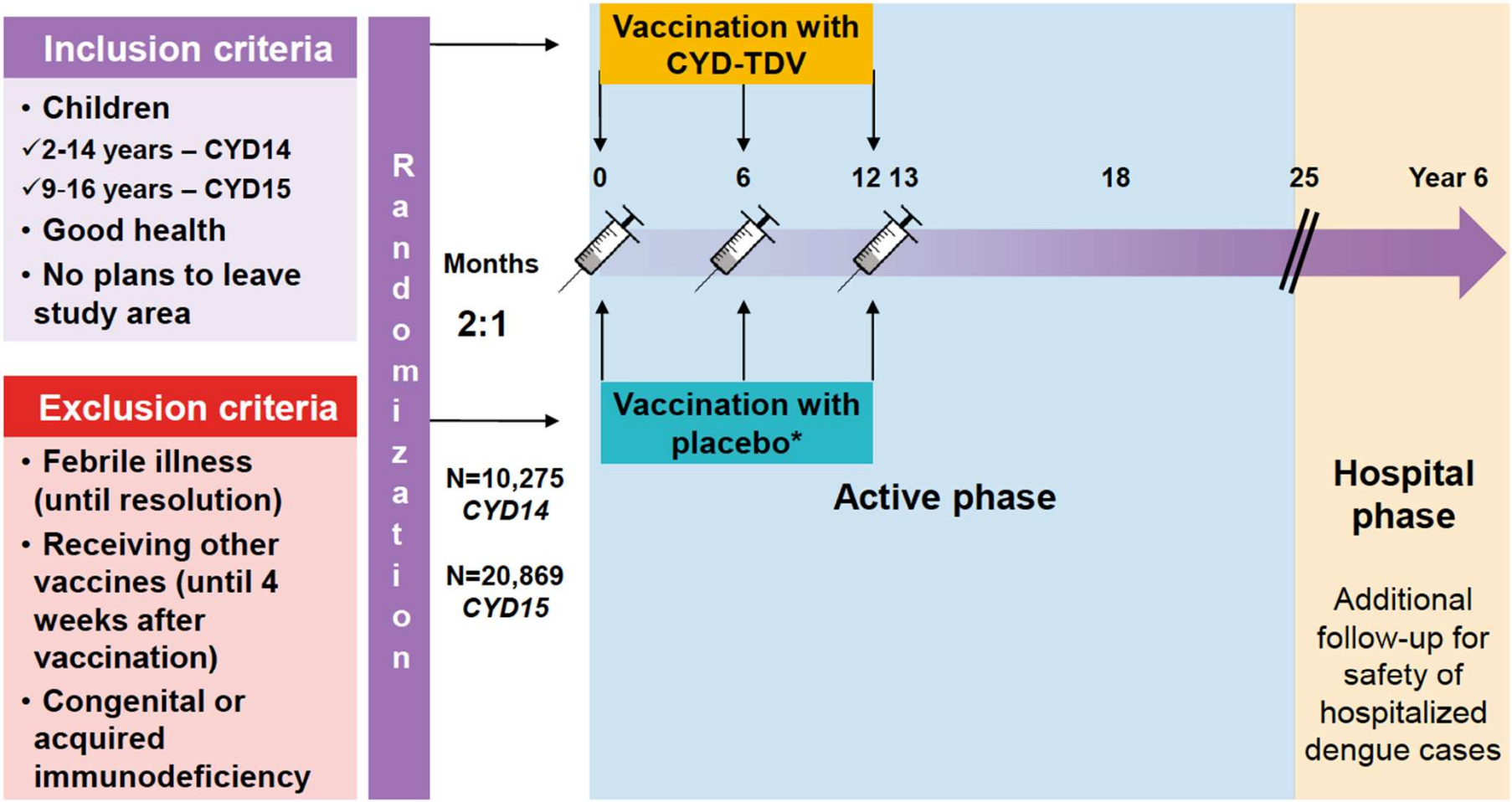


Figure 3. Seropositivity rates (percentage of participants $PRNT_{50}$ titer ≥ 10 1/dil) against each of the four dengue virus serotypes (1, 2, 3 and 4) at baseline and 28 d after the third vaccination in all participants and in each of the three age groups.

Sites of Phase 3 trials

Study design: Randomized, observer-masked, placebo-controlled, multicenter, phase III trials[1,2,3]



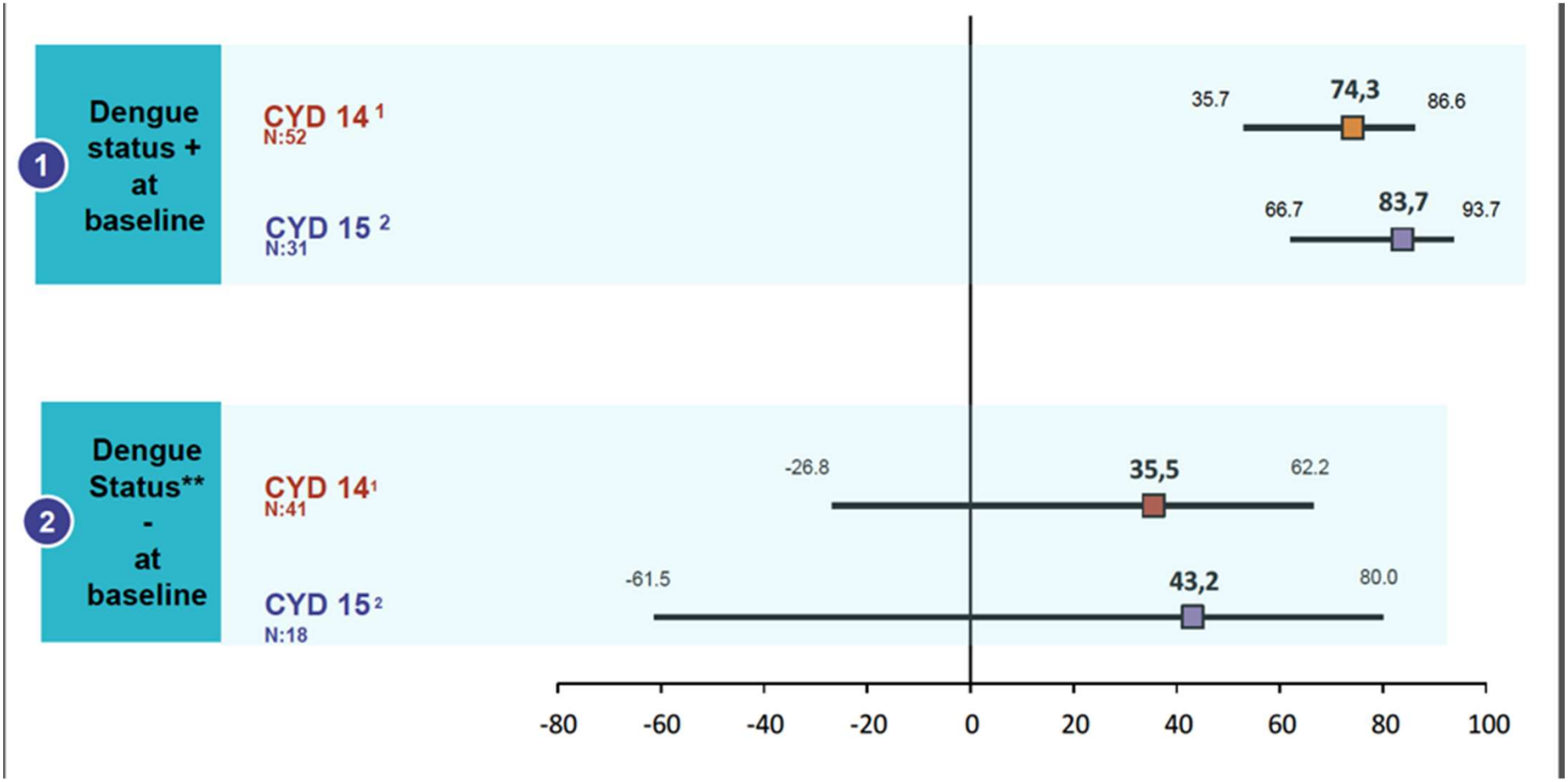
1 Capeding, 2014, Lancet.
ClinicalTrials.gov, 2014, NCT01374516.
2 Villar, 2014, N Engl J Med.
3 Villar, 2014, N Engl J Med (Supplementary Appendix)

SANOFI PASTEUR

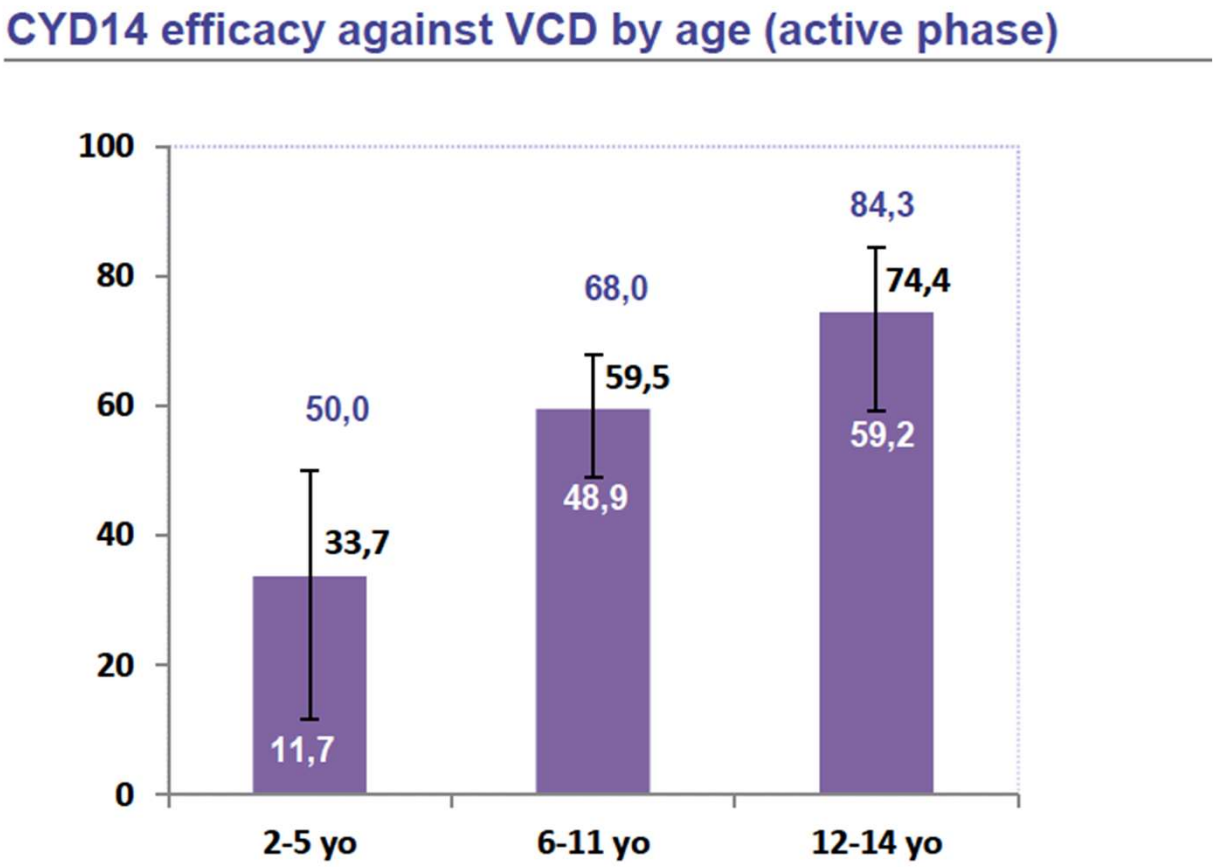
Vaccine efficacy

	Latin American Trial (N= 20869)	Asian Trial (N= 10275)
Overall Efficacy • Per Protocol	60.8% (52.0-68.0)	56.5 (43.8-66.4)
Serotype Specific Efficacy (Per Protocol) • DEN-1 • DEN-2 • DEN-3 • DEN-4	 50.3 (29.1-65.2) 42.3 (14.0-61.1) 74.0 (61.9-82.4) 77.7 (60.2-88.0)	 50.0 (24.6-66.8) 35.0 (-9.2-61.0) 78.4 (52.9-90.8) 75.3 (54.5-87.0)

Efficacy by flavivirus baseline status



Efficacy by Age



Vaccine efficacy against severe disease

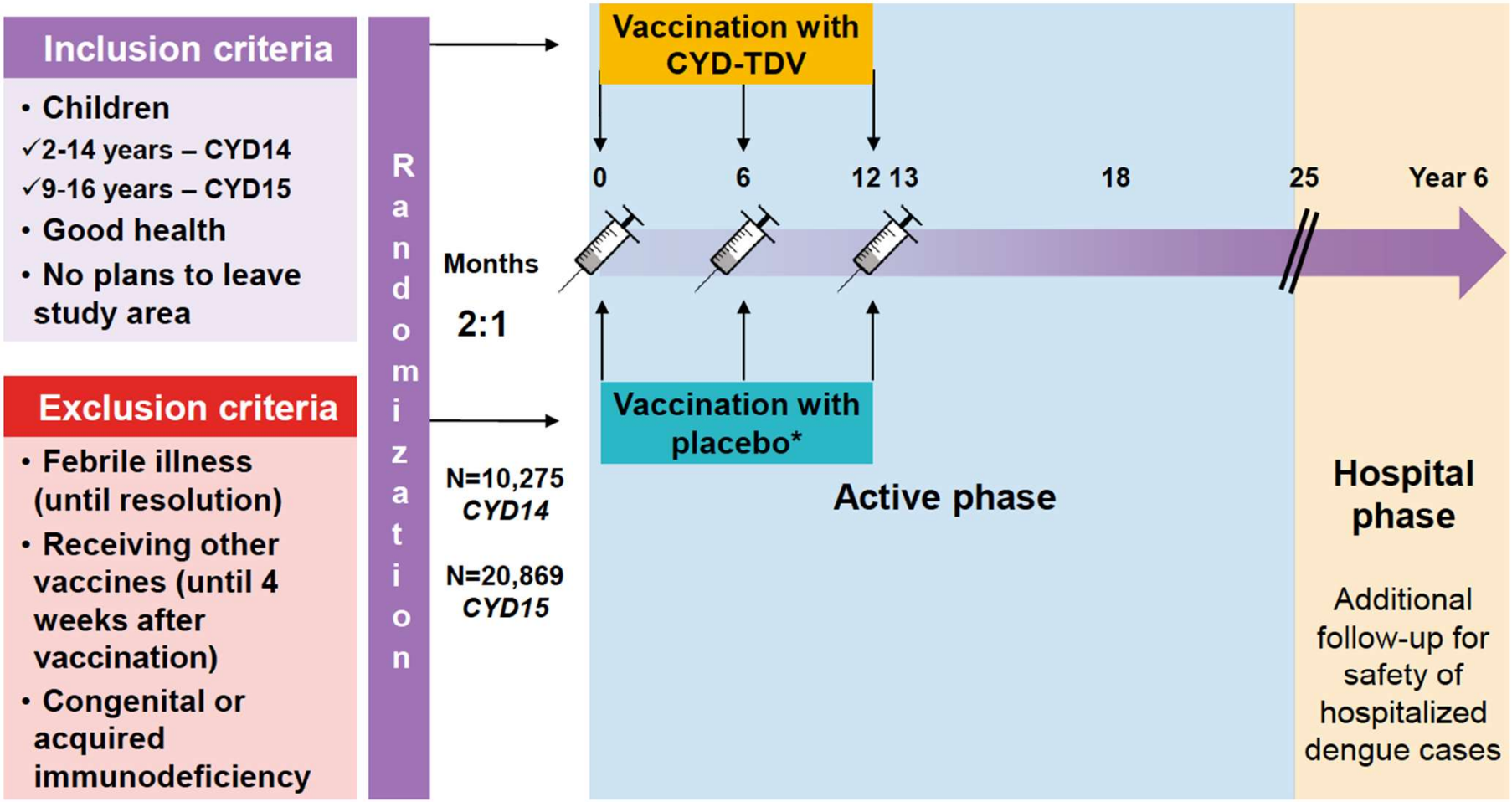
	Latin American Trial (N= 20869)	Asian Trial (N= 10275)
Efficacy against		
• Hospitalization	80.3 (64.7-89.5)	67.2 (50.3-78.6)
• Severe Dengue	91.7 (31.4-99.8)	80.8 (42·7–94·7)
• DHF	90 (10.7-99.8)	88.5 (58·2–97·9)

Vaccine efficacy- intermediate summary

- Age
- Seropositivity
- Serotype

- Efficacy against severity of disease > against incidence

Study design: Randomized, observer-masked, placebo-controlled, multicenter, phase III trials[1,2,3]



1 Capeding, 2014, Lancet.
ClinicalTrials.gov, 2014, NCT01374516.
2 Villar, 2014, N Engl J Med.
3 Villar, 2014, N Engl J Med (Supplementary Appendix)

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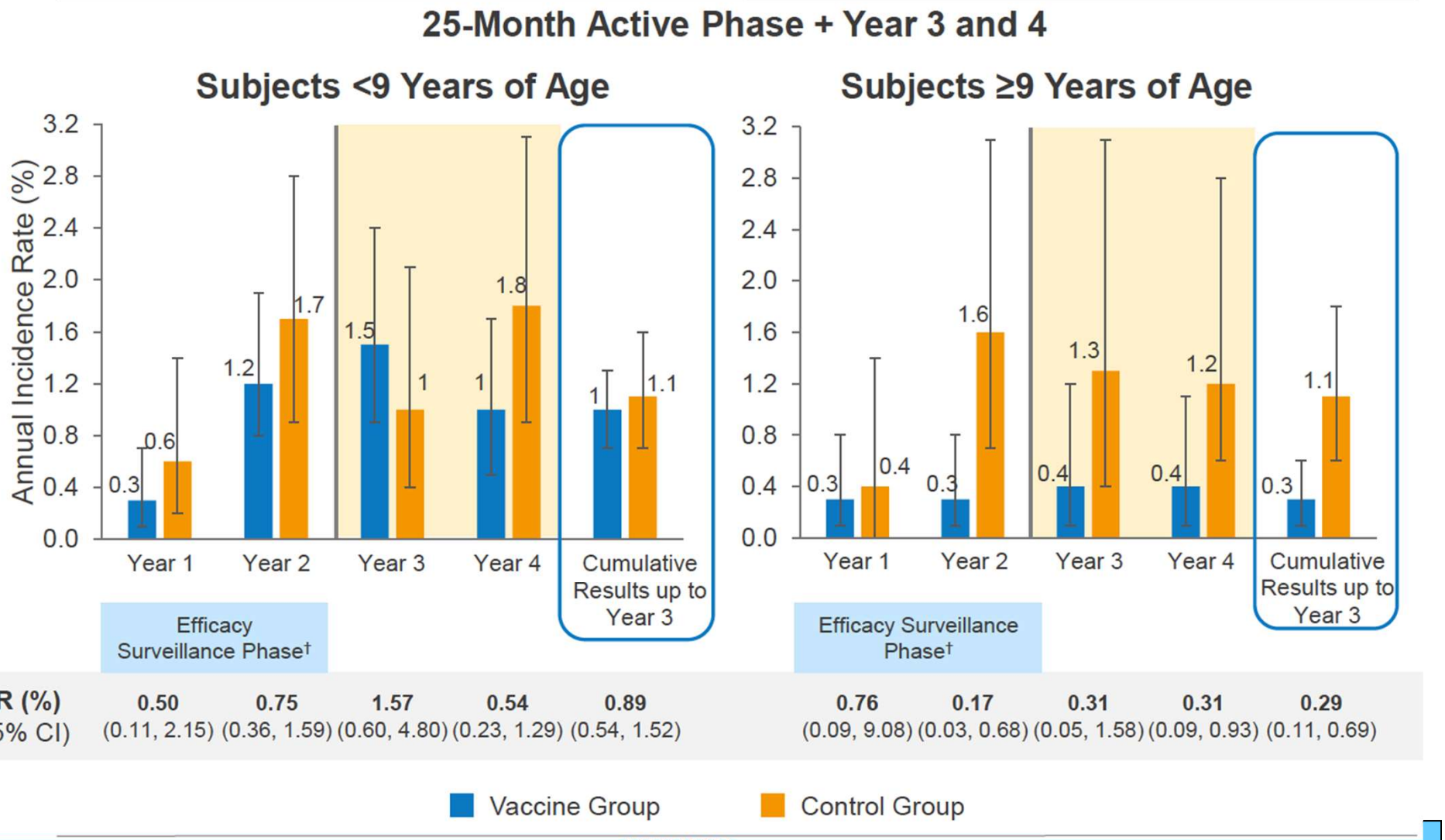
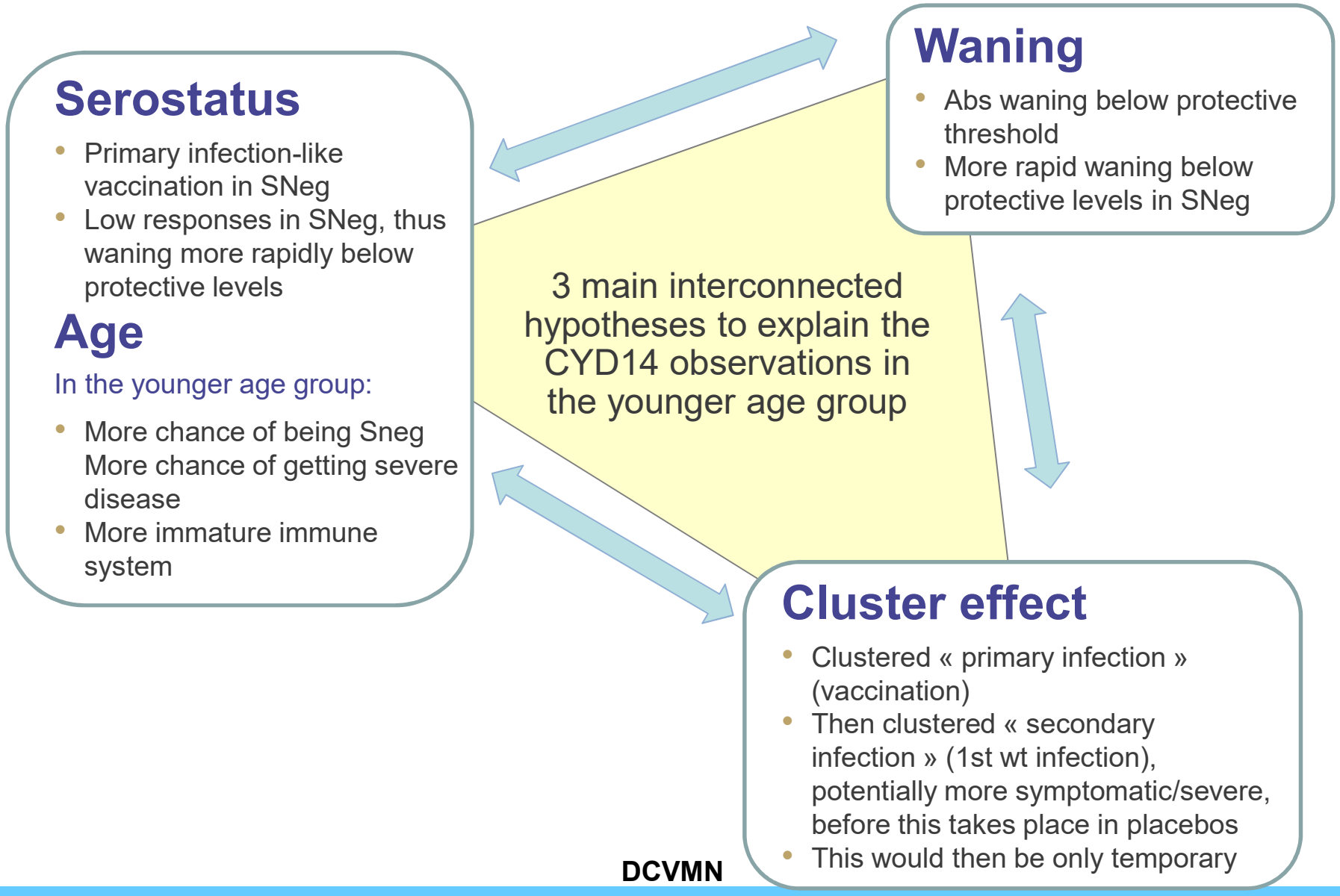
HOSPITALIZED VCD (ANY SEVERITY) IN SUBJECTS 4–11 YEARS OF AGE BY AGE GROUP (CYD23/57)[1]*



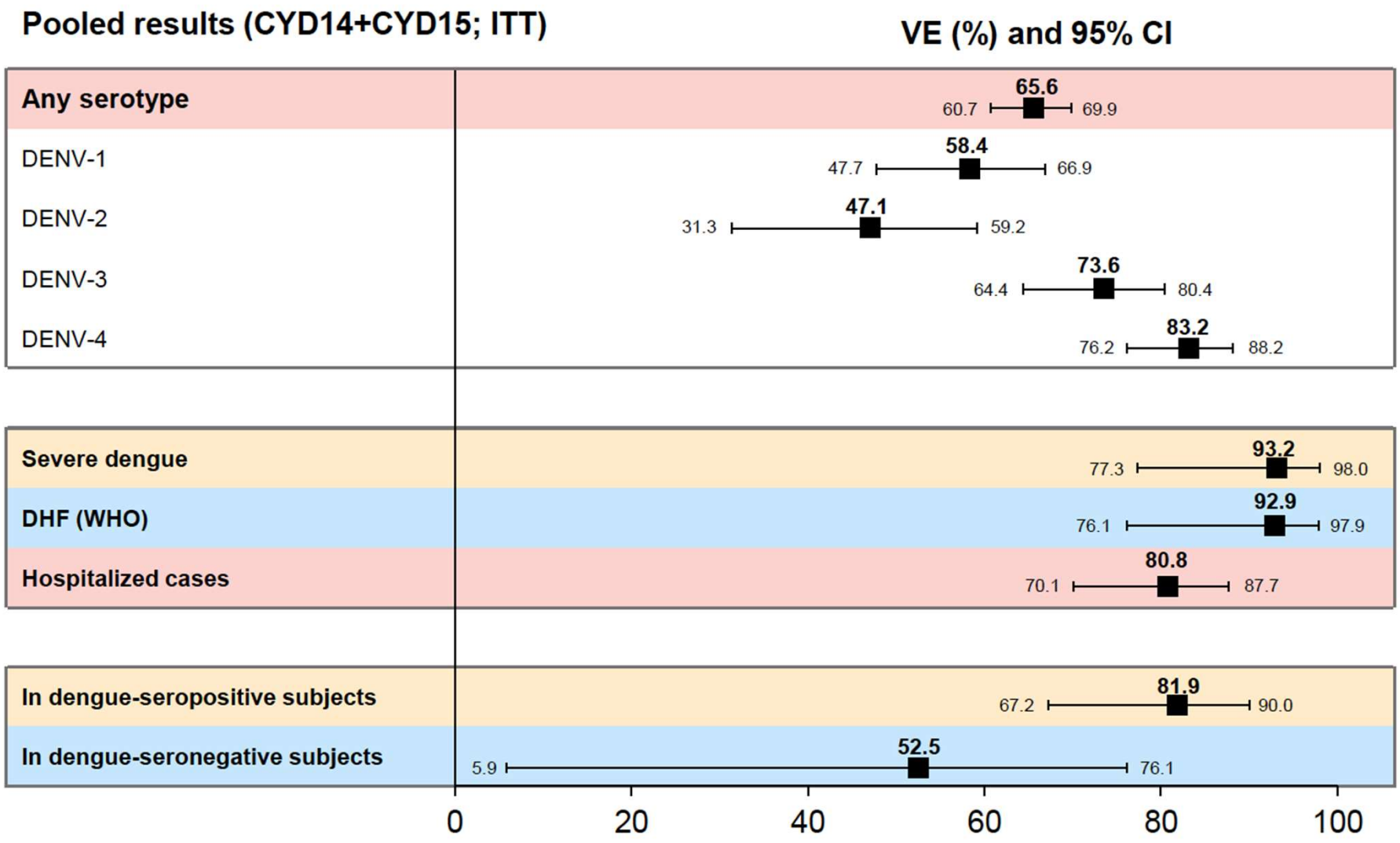
Hospital Phase / CYD14

Hypotheses to explain the observations in the younger age group



Licensure filed for age 9 and above

SUMMARY OF POOLED EFFICACY: VE WAS CONSISTENTLY DEMONSTRATED FOR THE CANDIDATE DENGUE VACCINE IN SUBJECTS AGED 9–16 YEARS IN THE 25-MONTH ACTIVE PHASE[1]



DENV=dengue virus; DHF=dengue hemorrhagic fever; ITT=intent to treat; VE=vaccine efficacy; WHO=World Health Organization.

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PUBLIC HEALTH

Dengue vaccines at a crossroad

Despite modest efficacy, a newly developed vaccine may be key for controlling dengue

By **Annelies Wilder-Smith**[1] *and* **Duane J. Gubler**[2]

through direct and indirect protection, which is particularly pertinent for diseases that are of high public health importance.

bly death. Patients with a second infection with a different serotype are thought to be at increased risk for severe disease (*2*), pos-

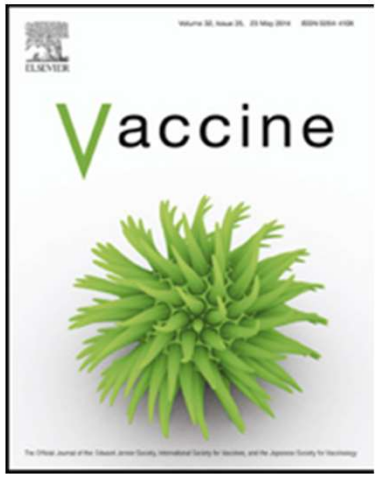
Do we use a vaccine with moderate efficacy, limited to age group 9 and above, with little efficacy in seronegatives subjects?

Estimating the public health importance of the CYD-tetravalent dengue vaccine: Vaccine preventable disease incidence and numbers needed to vaccinate

Bradford D. Gessner[a], Annelies Wilder-Smith[b,c,*]

- **Vaccine preventable disease incidence (VPDI)**

  = Incidence[unvaccinated] X VE



Number needed to vaccinate

=NNV- 1/ARR

		Vaccine efficacy (95% CI)	VPDI	NNV
Dengue (5)*	All virologically confirmed clinical cases	65% (59, 70)	1778	28
	All virologically confirmed hospitalized cases	80% (65, 89)	204	245

World Health Organization

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Immunization, Vaccines and Biologicals

SAGE Working Group on Dengue Vaccines and Vaccination (established March 2015)

Terms of Reference

The Working Group will be asked to review the evidence, identify the information gaps, and formulate proposed recommendations on the use of a licensed dengue vaccine for a SAGE review. This review is tentatively scheduled for April 2016. This will lead to the publication of a WHO position paper on the use of a dengue vaccine.

The Working Group will specifically be asked to review data relating to:

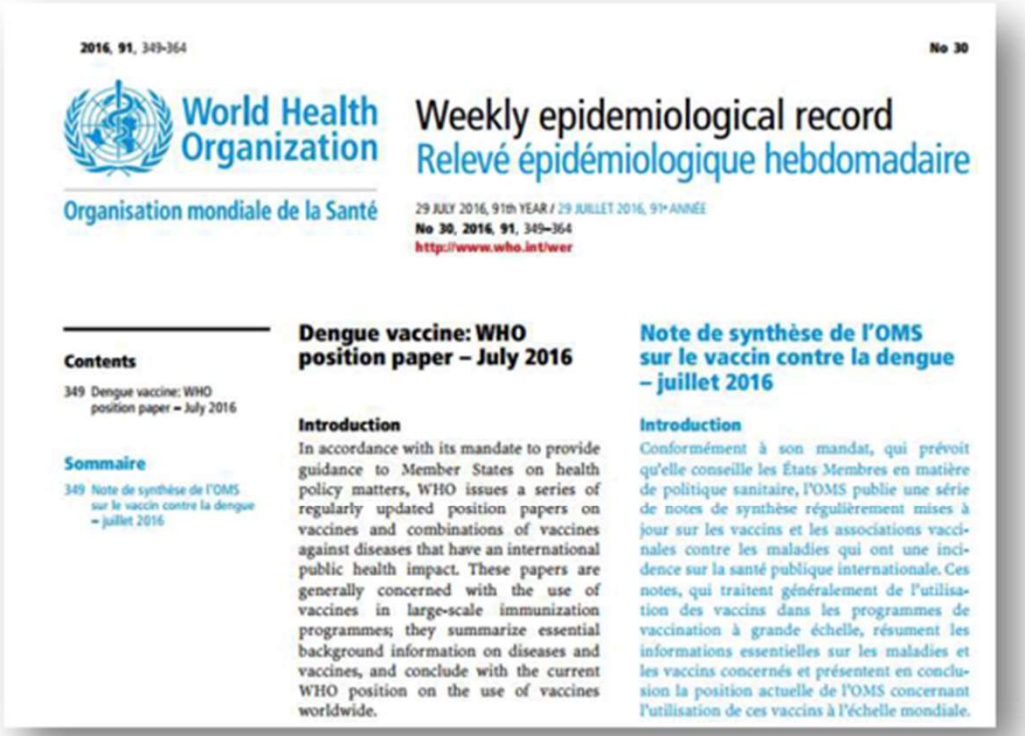
- the global prevalence and burden of disease caused by dengue
- the safety, efficacy, and immunogenicity profile of a licensed dengue vaccine
- the schedule, age of administration, and potential vaccination strategies for a dengue vaccine, including setting-specific attributes that may be important for designing immunization programs
- the disease impact and cost-effectiveness of dengue immunization programs
- identification of key data gaps that may be important for decisions about immunization programs, and recommendations for data collection related to key issues such as long-term safety, duration of protection, etc.
- additional critical issues that need to be considered in drafting proposed recommendations

MEMBERSHIP

- Terry Nolan (Co-Chair), Australia
- Jeremy Farrar (Co-Chair), UK
- Ananda Amarasinghe, Sri Lanka (until 1.3.2016)
- Alan Barrett, USA
- Anna Durbin, USA (until 31.12.2015)
- Elizabeth Ferdinand, Barbados
- Maria Guzman, Cuba
- Maria Novaes, Brazil
- Lee Ching Ng, Singapore
- Amadou Sall, Senegal
- Peter Smith, UK
- Wellington Sun, USA (until 1.2.2016)
- Piyanit Tharmaphornphilas, Thailand
- Stephen Thomas, USA

Key sources for WHO global policy on dengue vaccine

- WHO Vaccine Position Paper (published: 29 July 2016)
  http://www.who.int/wer/2016/wer9130.pdf



2016, 91, 349–364 No 30

World Health Organization

Organisation mondiale de la Santé

Weekly epidemiological record

Relevé épidémiologique hebdomadaire

29 JULY 2016, 91th YEAR / 29 JUILLET 2016, 91e ANNÉE

No 30, 2016, 91, 349–364

http://www.who.int/wer

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Dengue vaccine: WHO position paper – July 2016

Introduction

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are generally concerned with the use of vaccines in large-scale immunization programmes; they summarize essential background information on diseases and vaccines, and conclude with the current WHO position on the use of vaccines worldwide.

Note de synthèse de l'OMS sur le vaccin contre la dengue – juillet 2016

Introduction

Conformément à son mandat, qui prévoit qu'elle conseille les États Membres en matière de politique sanitaire, l'OMS publie une série de notes de synthèse régulièrement mises à jour sur les vaccins et les associations vaccinales contre les maladies qui ont une incidence sur la santé publique internationale. Ces notes, qui traitent généralement de l'utilisation des vaccins dans les programmes de vaccination à grande échelle, résument les informations essentielles sur les maladies et les vaccins concernés et présentent en conclusion la position actuelle de l'OMS concernant l'utilisation de ces vaccins à l'échelle mondiale.

Spanish circulated, to be posted online soon

Summary of Vaccine Efficacy Estimates

(from M0-M25, ITT ≥1 dose, post-hoc, pooled analyses)

- **Vaccine efficacy amongst 9-16 year-olds was 65.6% (CI 60.7-69.9)** (any severity)
- Vaccine efficacy varied by :
  - **serotype** of dengue
    - **DENV-1** 58.4%, **DENV-2** 47.1%, **DENV-3** 73.6%, **DENV-4** 83.2%
  - **serostatus** at time of vaccination
    - **dengue-exposed** 81.9%, **dengue-naive** 52.5%
  - **severity** of disease
    - **severe** dengue 93.2%, **hospitalised** dengue 80.8%

Number of hospitalized and/or severe VCD cases by age group and dengue immune status at baseline

		Active phase cases/N (%)		Hospital phase-SEP† cases/N (%)		Cumulative cases/N (%)	
Age group	**Serostatus**	**CYD group**	**Control group**	**CYD group**	**Control group**	**CYD group**	**Control group**
2-8 years	Seropositive*	2/493 (0.4)	8/240 (3.3)	7/476 (1.5)	3/234 (1.3)	9/481 (1.9)	11/236 (4.7)
	Seronegative*	2/337 (0.6)	2/178 (1.1)	15/326 (4.6)	3/170 (1.8)	17/330 (5.2)	5/173 (2.9)
9-16 years	Seropositive*	0/1605 (0.0)	6/777 (0.8)	7/1508 (0.5)	9/736 (1.2)	7/1546 (0.5)	15/752 (2.0)
	Seronegative*	0/398 (0.0)	2/214 (0.9)	7/372 (1.9)	3/197 (1.5)	7/382 (1.8)	4/204 (2.0)

Pool of CYD14, CYD15, and CYD57. *Includes only subjects from the Full Analysis Set for Immunogenicity; † Includes all subjects from the Safety Analysis Set for Efficacy; SEP: Surveillance Expansion Phase

WHO recommendations (1)

- Countries **should consider** introduction of CYD-TDV **only** in geographic settings (national or subnational) where epidemiological data indicate a **high burden of disease.**
- Seroprevalence should be approximately 70% or greater in the age group targeted for vaccination.
- The vaccine is **not recommended** when seroprevalence is below 50% in the age group targeted for vaccination.

WHO recommendations (2)

- Dengue vaccine introduction should be a part of a **comprehensive dengue control strategy**, including well-executed and sustained vector control, evidence-based best practices or clinical care for all patients with dengue illness, and strong dengue surveillance.

- Decisions about introduction require careful assessment at the **country level**, including consideration of local priorities, national and subnational dengue epidemiology, predicted impact and cost-effectiveness with country-specific inputs, affordability and budget impact.

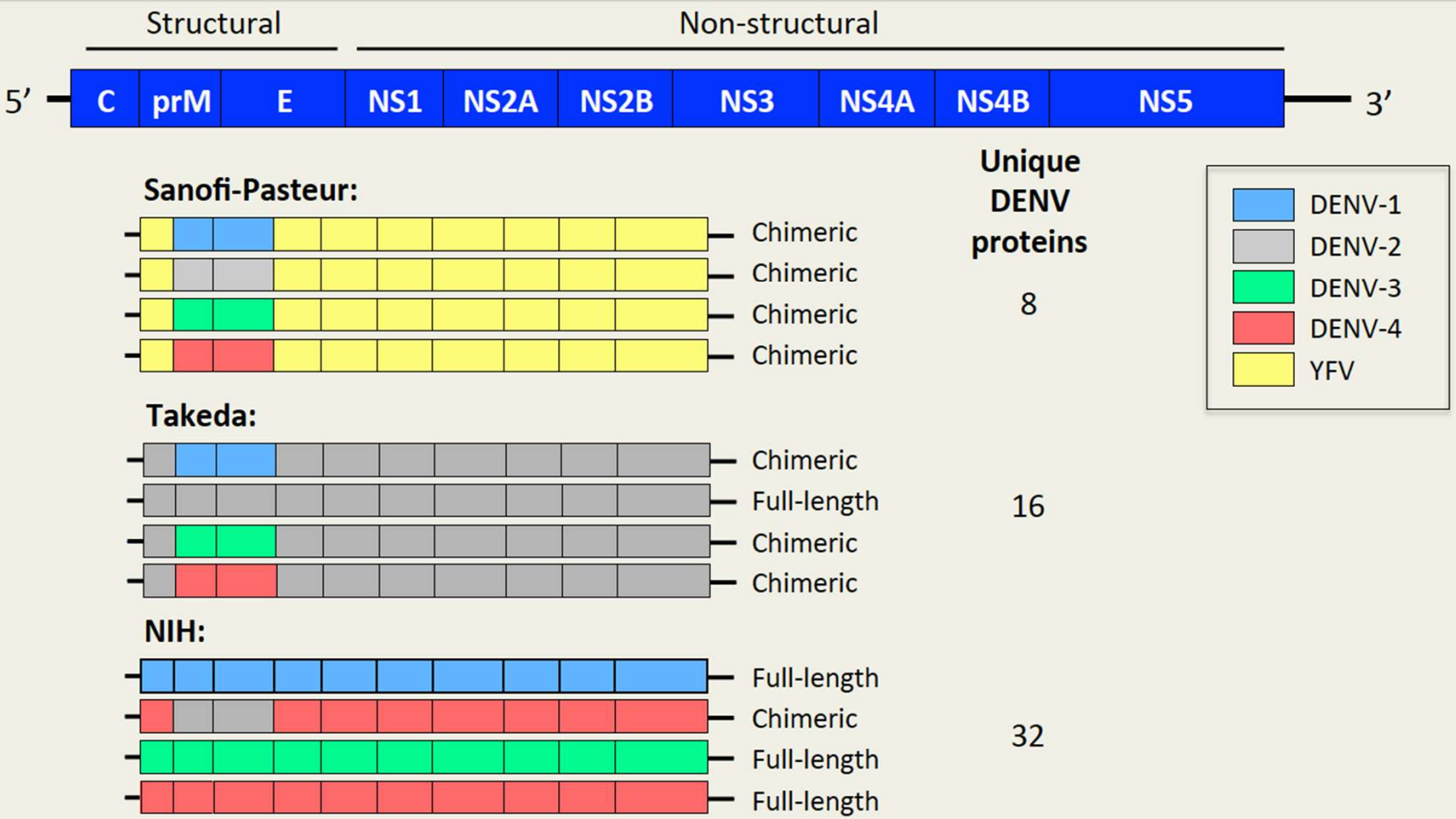
WHO recommendations (3)

- The target age for routine vaccination should be defined by each country based on **maximizing program impact and programmatic feasibility** of targeting particular ages.
  - Modelling predicts vaccinating at different age groups depending on endemicity will maximize the number of cases averted
  - Programmatic factors such as school attendance, co-administration, etc., may also guide decisions about age groups to target
- If CYD-TDV is introduced it should be administered as a **3-dose series** given as a **0/6/12 month** schedule.

Summary

- The CYD-TDV vaccine profile is complex
- SAGE/WHO recommendations are conditional, recommending consideration only in select areas meeting seroprevalence criteria
- Vaccination should be considered as part of a comprehensive dengue control strategy
- If used as recommended in settings fitting the criteria recommended by SAGE, the vaccine could have a substantial public health impact on dengue
- Global recommendations are meant to inform national decision-making for national programs, which should always be done with consideration of the national context

Recombinant live attenuated DENV vaccine strategies



Science Translational Medicine

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] and Anna P. Durbin[3,†]

DCVMN

Summary

- First dengue vaccine (SP) licensed in a few countries
- Efficacy is only partial
- Given the high burden of dengue, even a vaccine with partial efficacy will have a public health impact
- Long-term data on duration of efficacy and safety are needed
- Many other dengue vaccine candidates in the pipeline

DCVMN

Lee Kong Chian School of Medicine

A Joint Medical School by Imperial College London and Nanyang Technological University

Thank you!

dvi

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DengueTools