A Dengue Controlled Human Infection Model in Vietnam?

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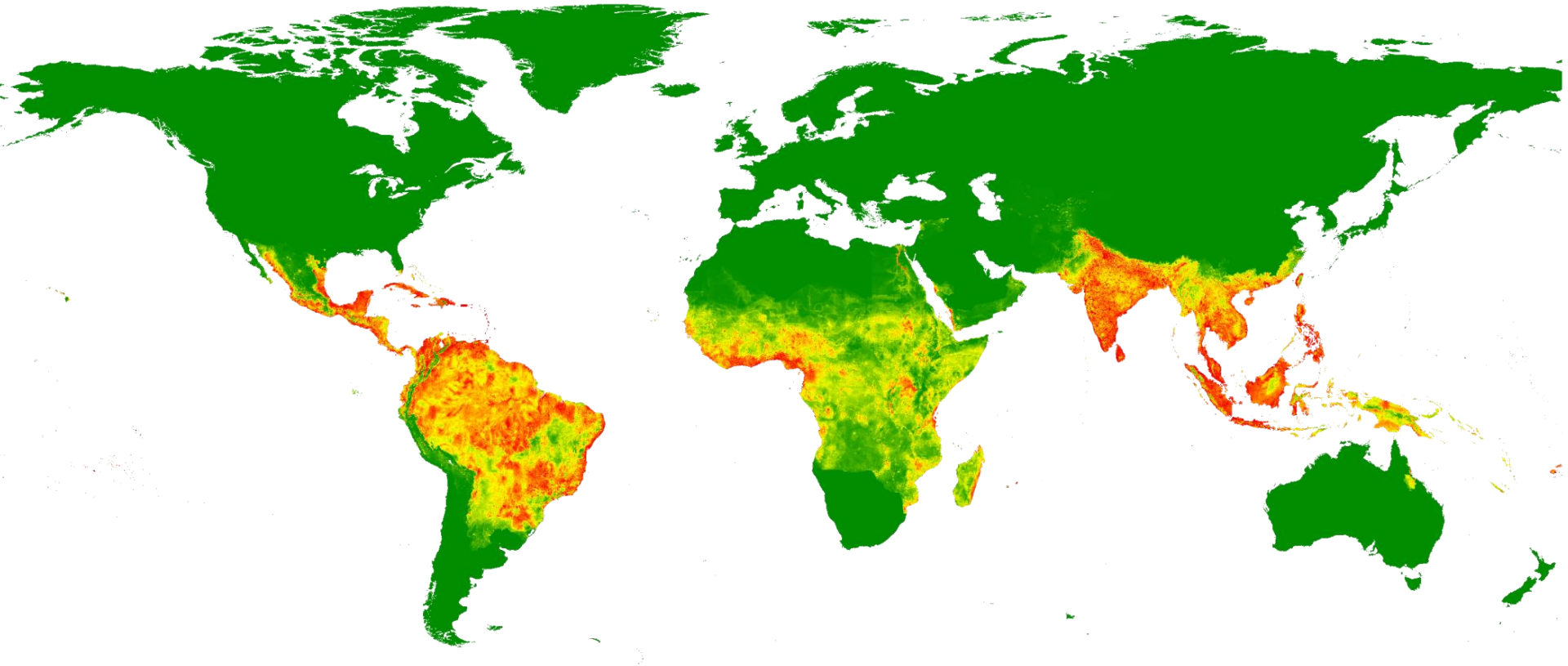

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LETTER

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The global distribution and burden of dengue

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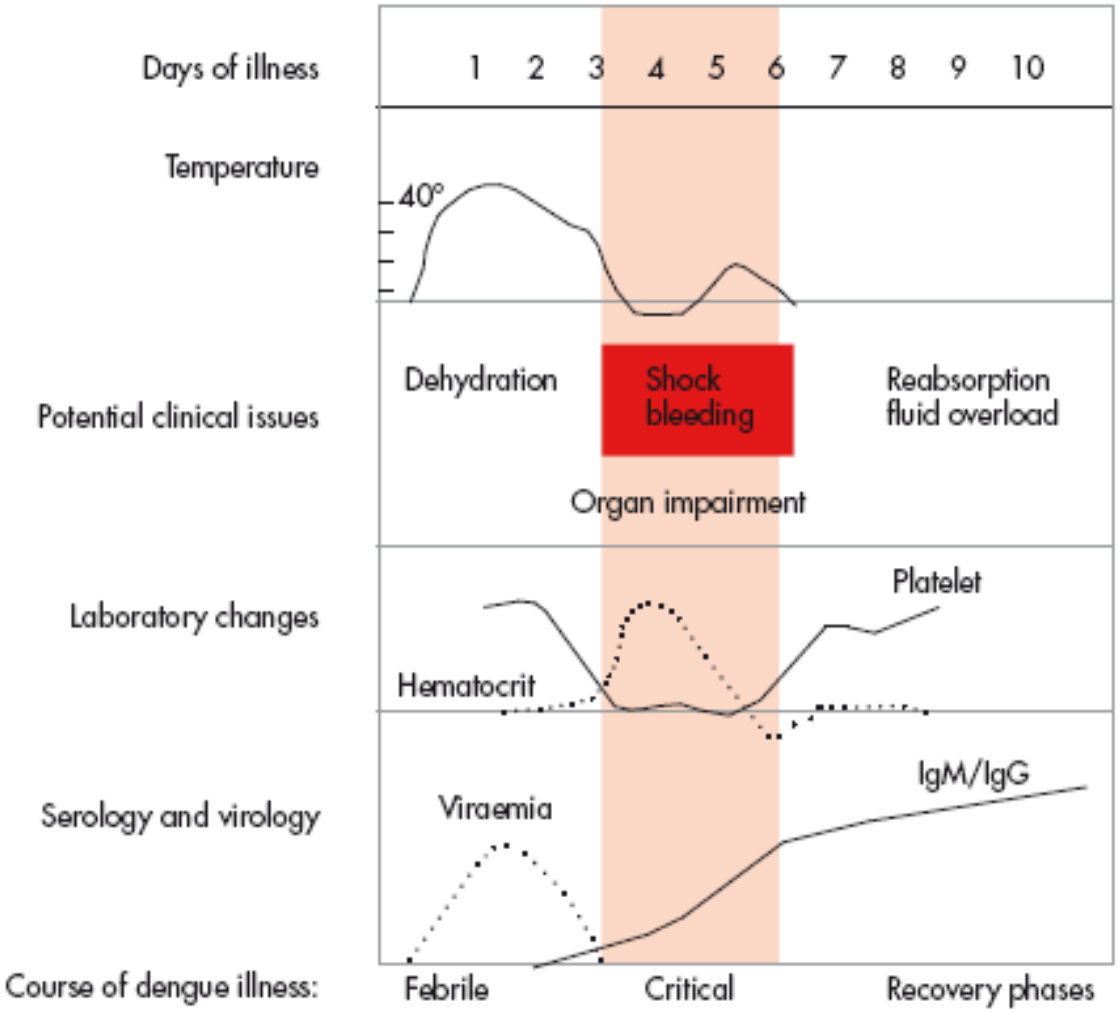
The clinical evolution of dengue – WHO 2009



Major clinical features of severe dengue

- Intravascular volume depletion secondary to increased systemic vascular permeability, potentially leading to DSS

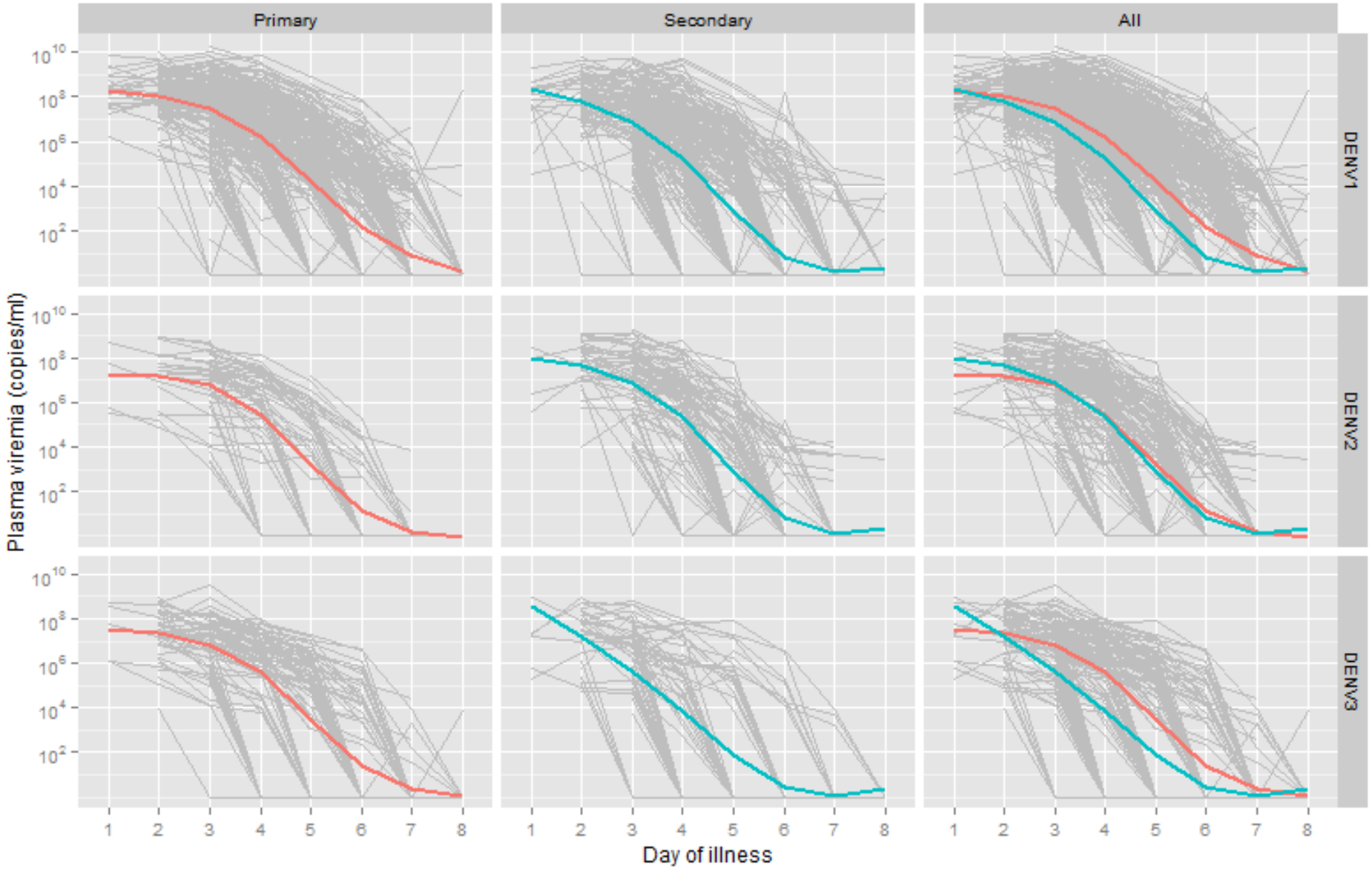
- A variety of haemorrhagic manifestations due to the combined effects of -
    - Thrombocytopenia
    - Deranged haemostasis

- Severe organ impairment -
    - Usually secondary
    - May be idiosyncratic

Risk factors associated with development of severe dengue

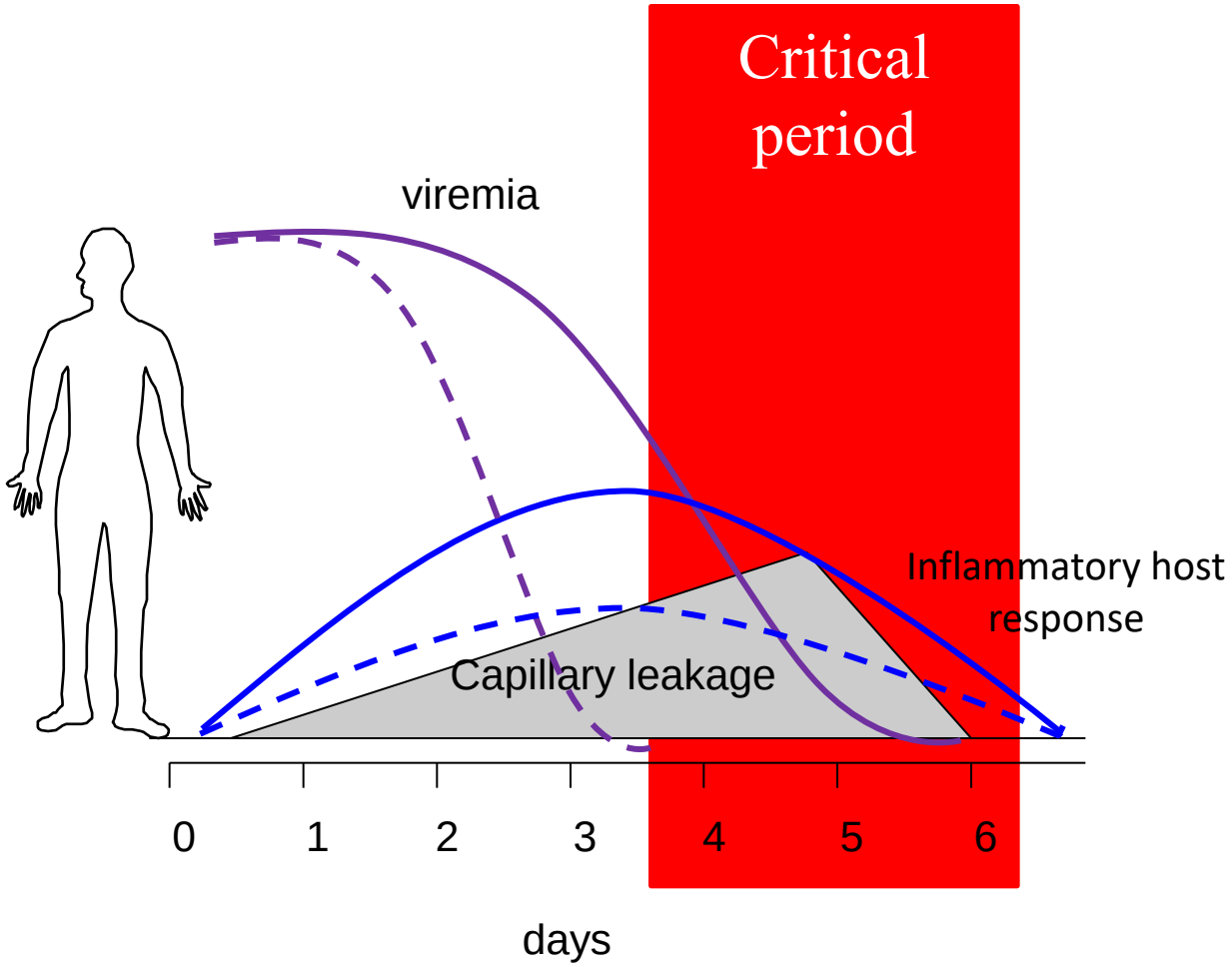
- Pre-existing immunity to a heterotypic DENV serotype during a “secondary infection” – resulting in antibody dependent enhancement (ADE)
- Viremia? Immunopathogenic cascade?
- Virus characteristics? Specific serotypes? DENV-2 and DENV-3?
- Age, Sex, Host Genetics
- Underlying diseases, co-morbidities

Viremia kinetics

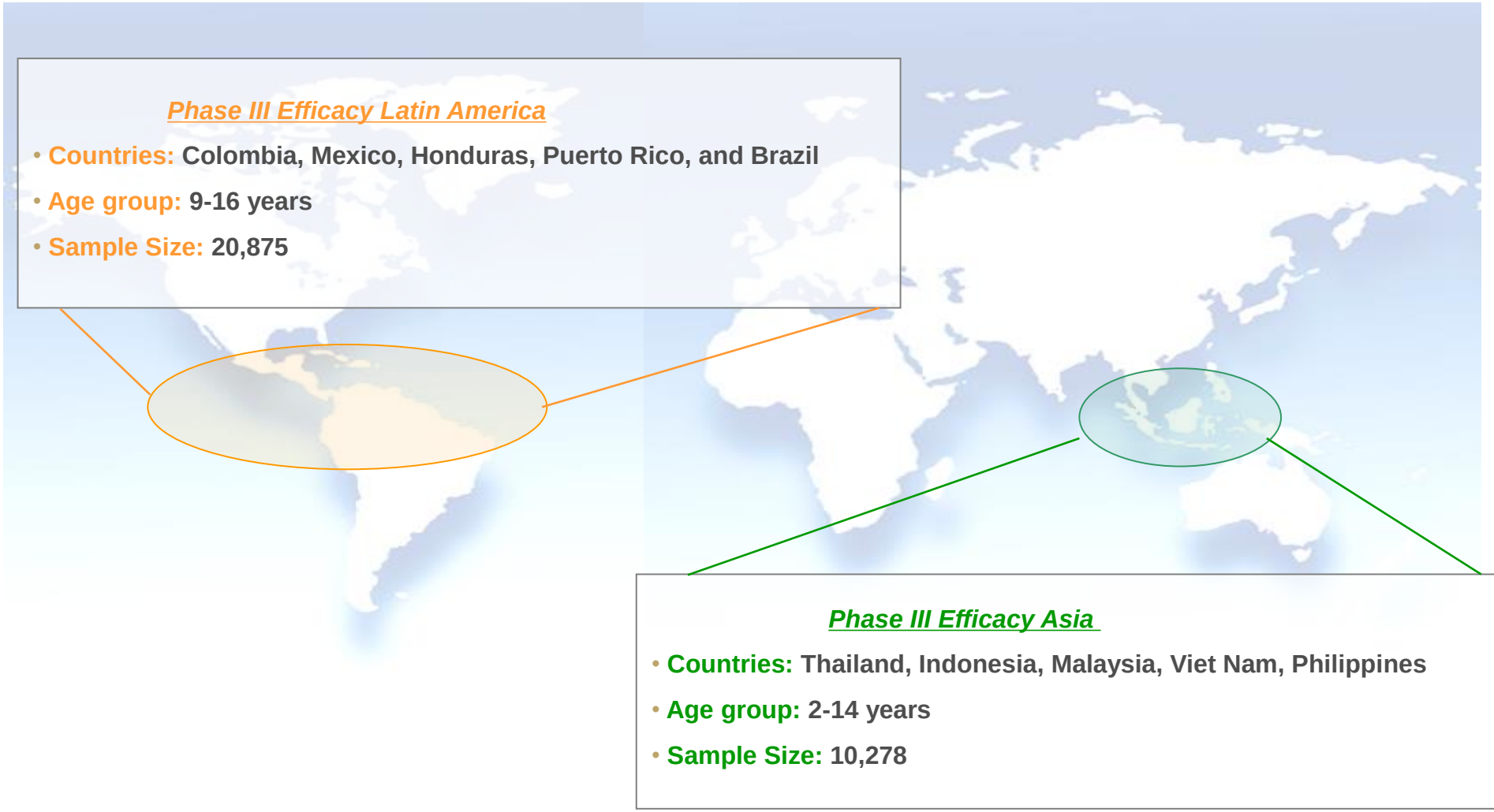


Duyen et al, J Infect Dis. 2011

Therapeutic interventions?



Large-scale CYD-TDV Safety & Efficacy Trials



Phase III Efficacy Latin America

- **Countries:** Colombia, Mexico, Honduras, Puerto Rico, and Brazil
- **Age group:** 9-16 years
- **Sample Size:** 20,875

Phase III Efficacy Asia

- **Countries:** Thailand, Indonesia, Malaysia, Viet Nam, Philippines
- **Age group:** 2-14 years
- **Sample Size:** 10,278

Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial

*Maria Rosario Capeding, Ngoc Huu Tran, Sri Rezeki S Hadinegoro, Hussain Imam HJ Muhammad Ismail, Tawee Chotpitayasunondh, Mary Noreen Chua, Chan Quang Luong, Kusnandi Rusmil, Dewa Nyoman Wirawan, Revathy Nallusamy, Punnee Pitisuttithum, Usa Thisyakorn, In-Kyu Yoon, Diane van der Vliet, Edith Langevin, Thelma Laot, Yanee Hutagalung, Carina Frago, Mark Boaz, T Anh Wartel, Nadia G Tornieporth, Melanie Saville, Alain Bouckenooghe, and the CYD14 Study Group**

Summary

Background An estimated 100 million people have symptomatic dengue infection every year. This is the first report of a phase 3 vaccine efficacy trial of a candidate dengue vaccine. We aimed to assess the efficacy of the CYD dengue vaccine against symptomatic, virologically confirmed dengue in children.

Methods We did an observer-masked, randomised controlled, multicentre, phase 3 trial in five countries in the Asia-Pacific region. Between June 3, and Dec 1, 2011, healthy children aged 2–14 years were randomly assigned (2:1), by computer-generated permuted blocks of six with an interactive voice or web response system, to receive three injections of a recombinant, live, attenuated, tetravalent dengue vaccine (CYD-TDV), or placebo, at months 0, 6, and 12. Randomisation was stratified by age and site. Participants were followed up until month 25. Trial staff responsible for the preparation and administration of injections were unmasked to group allocation, but were not included in the follow-up of the participants; allocation was concealed from the study sponsor, investigators, and parents and guardians. Our primary objective was to assess protective efficacy against symptomatic, virologically confirmed dengue, irrespective of disease severity or serotype, that took place more than 28 days after the third injection. The primary endpoint was for the lower bound of the 95% CI of vaccine efficacy to be greater than 25%. Analysis was by intention to treat and per procotol. This trial is registered with ClinicalTrials.gov, number NCT01373281.

Findings We randomly assigned 10 275 children to receive either vaccine (n=6851) or placebo (n=3424), of whom 6710 (98%) and 3350 (98%), respectively, were included in the primary analysis. 250 cases of virologically confirmed dengue took place more than 28 days after the third injection (117 [47%] in the vaccine group and 133 [53%] in the control group). The primary endpoint was achieved with 56·5% (95% CI 43·8–66·4) efficacy. We recorded 647 serious adverse events (402 [62%] in the vaccine group and 245 [38%] in the control group). 54 (1%) children in the vaccine group and 33 (1%) of those in the control group had serious adverse events that happened within 28 days of vaccination. Serious adverse events were consistent with medical disorders in this age group and were mainly infections and injuries.

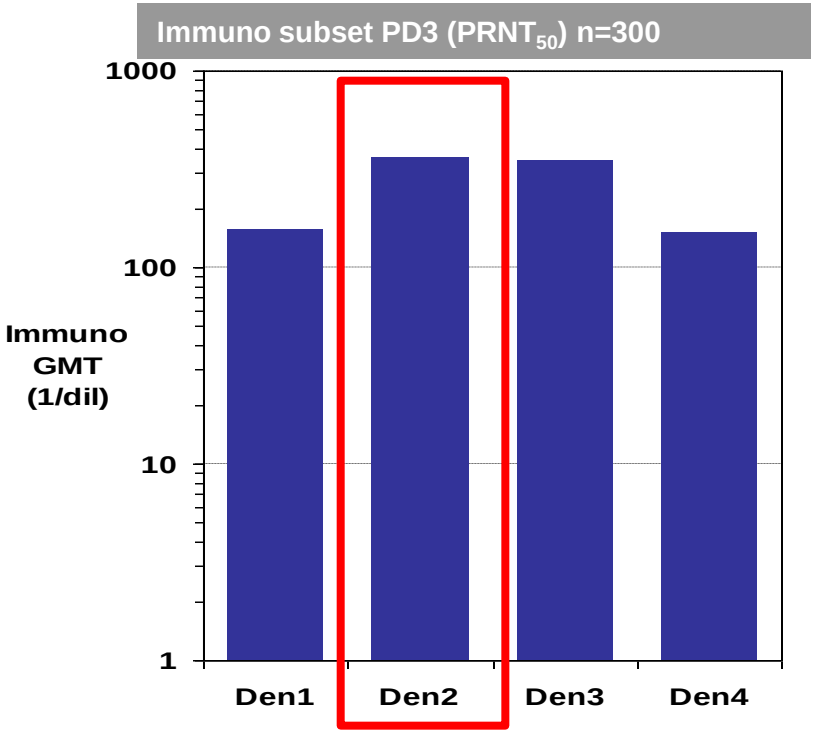
Interpretation Our findings show that dengue vaccine is efficacious when given as three injections at months 0, 6, and 12 to children aged 2–14 years in endemic areas in Asia, and has a good safety profile. Vaccination could reduce the incidence of symptomatic infection and hospital admission and has the potential to provide an important public health benefit.

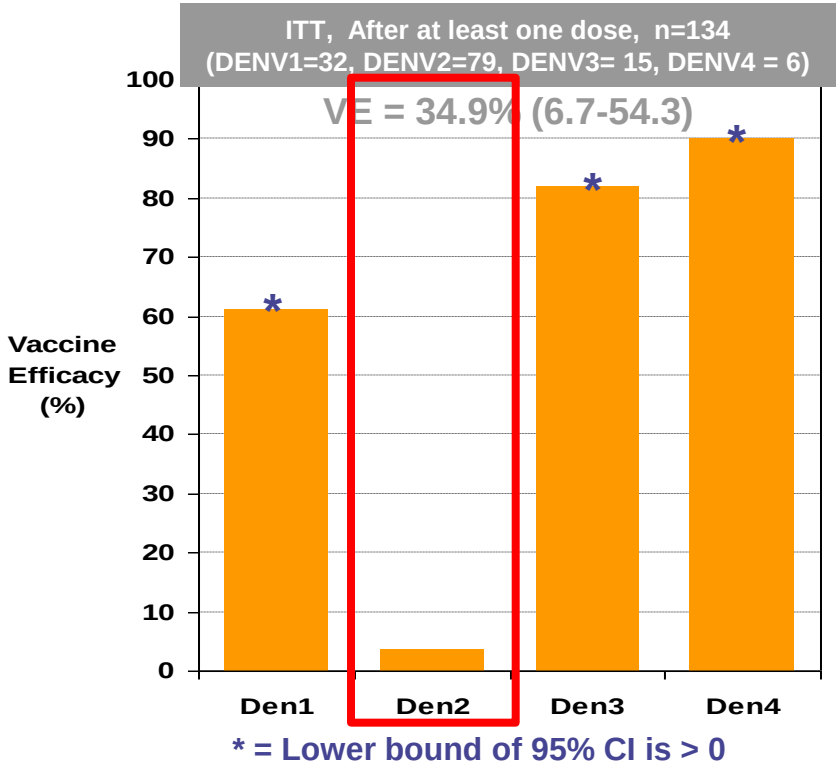
- "The primary endpoint was achieved with 56·5% (95% CI 43·8-66·4) efficacy."
- Serotype dependent: poor efficacy against DENV-2 (35%)
- Poor efficacy in young children (~34%)
- Weak correlation between Nt ab titres and protection

Capeding et al, Lancet 2014

Phase IIb results – 0, 6, 12 month regimen

Immunogenicity vs vaccine efficacy- intention to treat (ITT)





Where to go from here??

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RESULTS OBTAINED IN THE TRANSMISSION OF DENGUE FEVER *

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WASHINGTON, D. C.

The Medical Department Research Board of the United States Army and other workers closely associated therewith are investigating a number of the unsolved problems relating to dengue fever, including its etiology, mechanism of transmission by insects, duration of immunity following an attack, and clinical characteristics. The results will be reported fully at a later date, and published in the *Philippine Journal of Science*, Bureau of Science, Manila, P. I.

It is our purpose in this summary to present briefly the results of a fairly large series of experiments relating to the transmission of dengue fever by mosquitoes. This work has been done in Manila, during the last few months, from July, 1924, to January, 1925, inclusive.

A total of forty-two American soldiers volunteered for these experiments. Eighty-three biting experiments have been made with potentially infected female *Culex quinquefasciatus* (*C. fatigans*) and *Aedes egypti* (*Stegomyia fasciata*), and dengue fever has been transmitted experimentally by mosquitoes in twenty-five instances.

PREVIOUS EXPERIMENTAL WORK

Cleland and Bradley,[3] working in Sydney, Australia, in 1916, report the production of dengue experimentally in four volunteers by subjecting them to the bites of infected female *Aedes egypti*. The mosquitoes used by them were a mixed lot, consisting of laboratory bred insects that were allowed to bite dengue patients in various stages of the disease, and wild mosquitoes caught in infected houses. They demonstrated quite definitely that *A. egypti* was a transmitter. Their investigations throw no light on the developmental period of the virus in the mosquito.

UNSOLVED PROBLEMS COVERED BY THE EXPERIMENTAL WORK OF THIS BOARD

The experimental work incorporated in this report covers the following points:

1. Confirmation of the results obtained by Cleland and Bradley relative to the transmission of dengue by *A. egypti*.
2. Time interval after the appearance of the initial symptoms, during which the dengue patient continues to be infective to mosquitoes.
3. Length of time the dengue virus must remain in the infected mosquito before transmission becomes possible.
4. Length of time infected mosquitoes are capable of transmitting dengue.
5. Incrimination or elimination of *C. quinquefasciatus* as a possible transmitting agent.
6. Incubation period of dengue in the human subject; number of mosquitoes used in each experiment; immunity to dengue.

GENERAL PLANS ADOPTED IN CARRYING OUT EXPERIMENTS

The experimental work was carried out at Manila in the laboratories of the Research Board in the Bureau

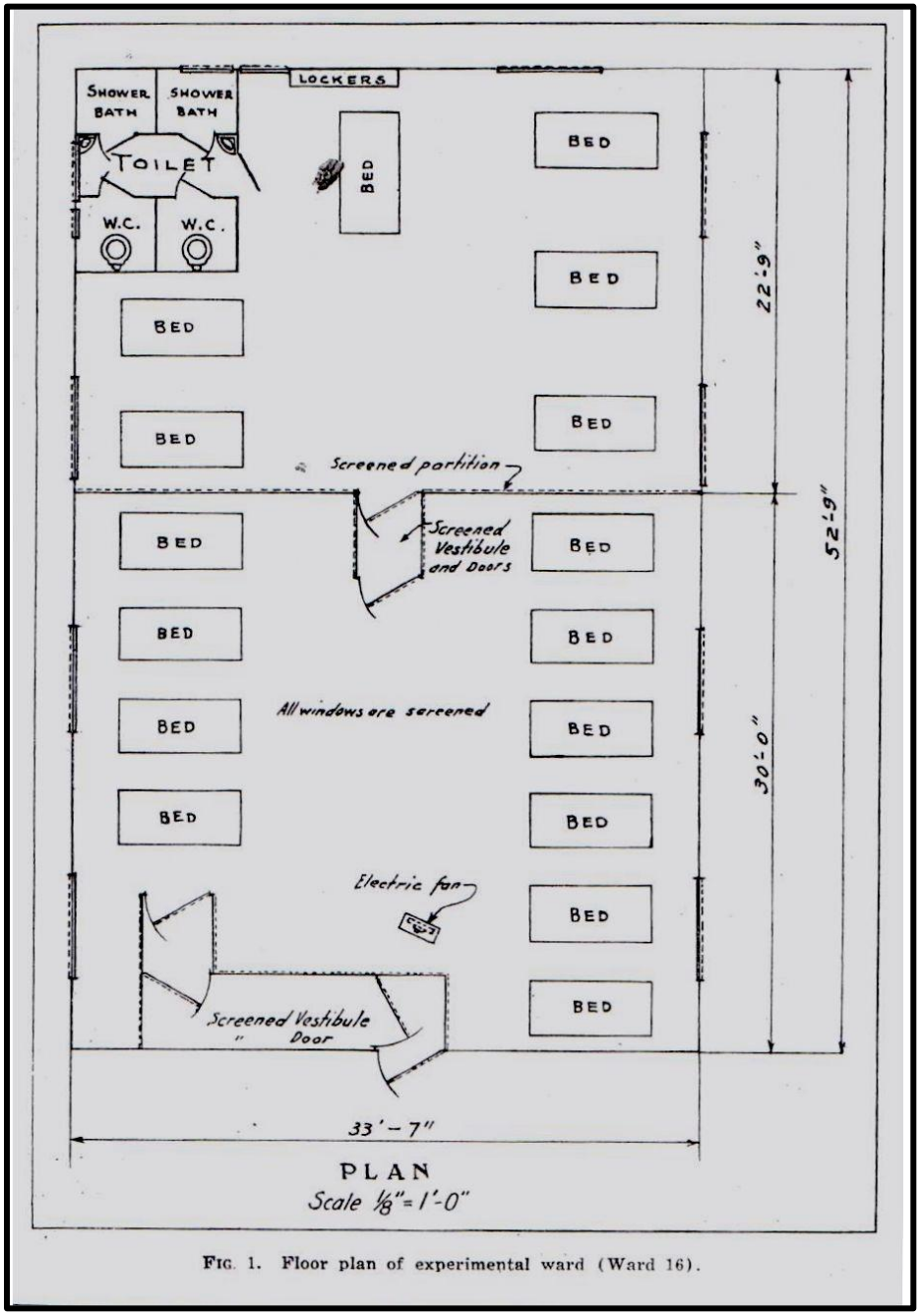

FIG. 1. Floor plan of experimental ward (Ward 16).

Positive experimental infections

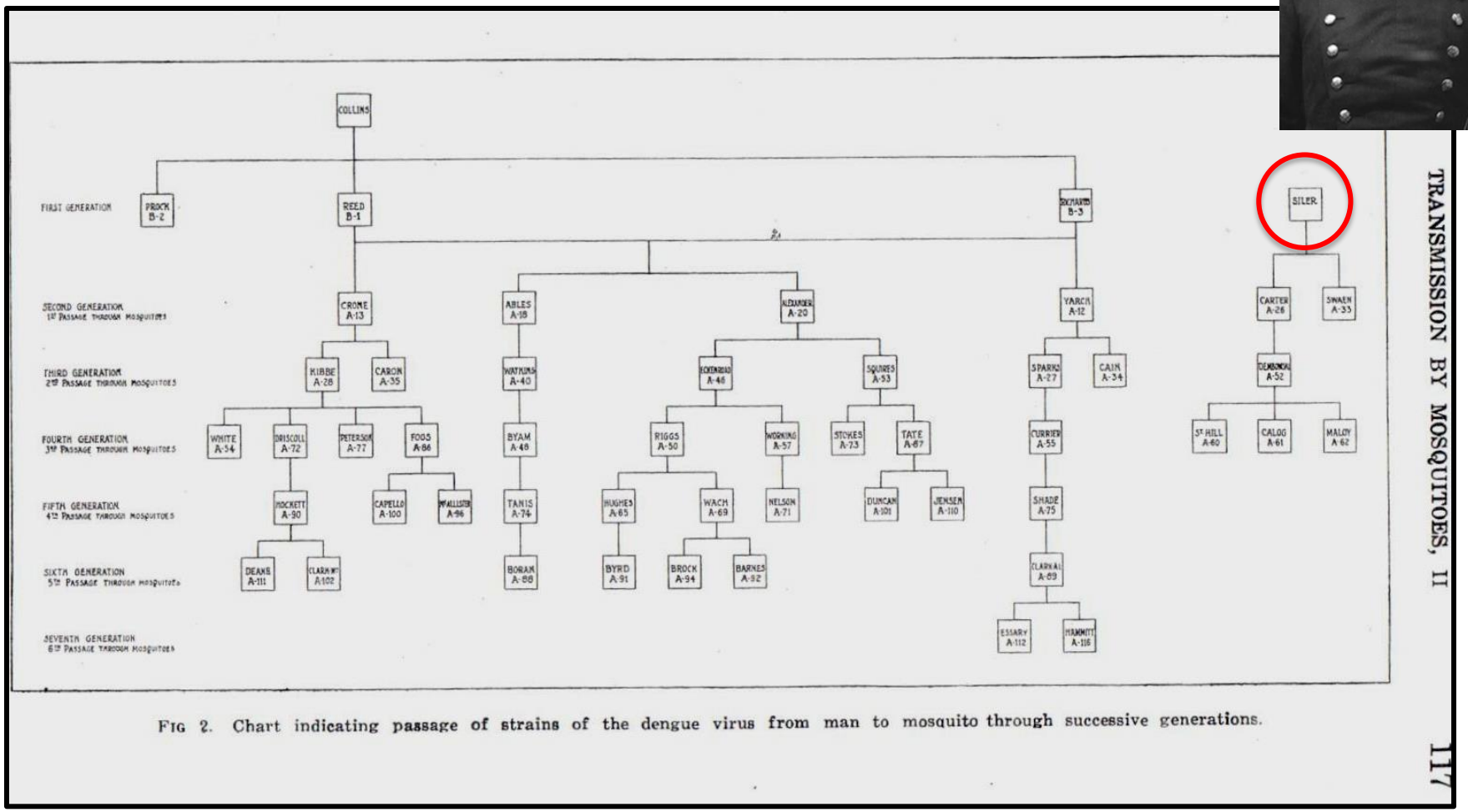

FIG 2. Chart indicating passage of strains of the dengue virus from man to mosquito through successive generations.

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117

Method of infection:

A = Aedes B = Blood C = Culex

1974: virus determined to be DENV-4

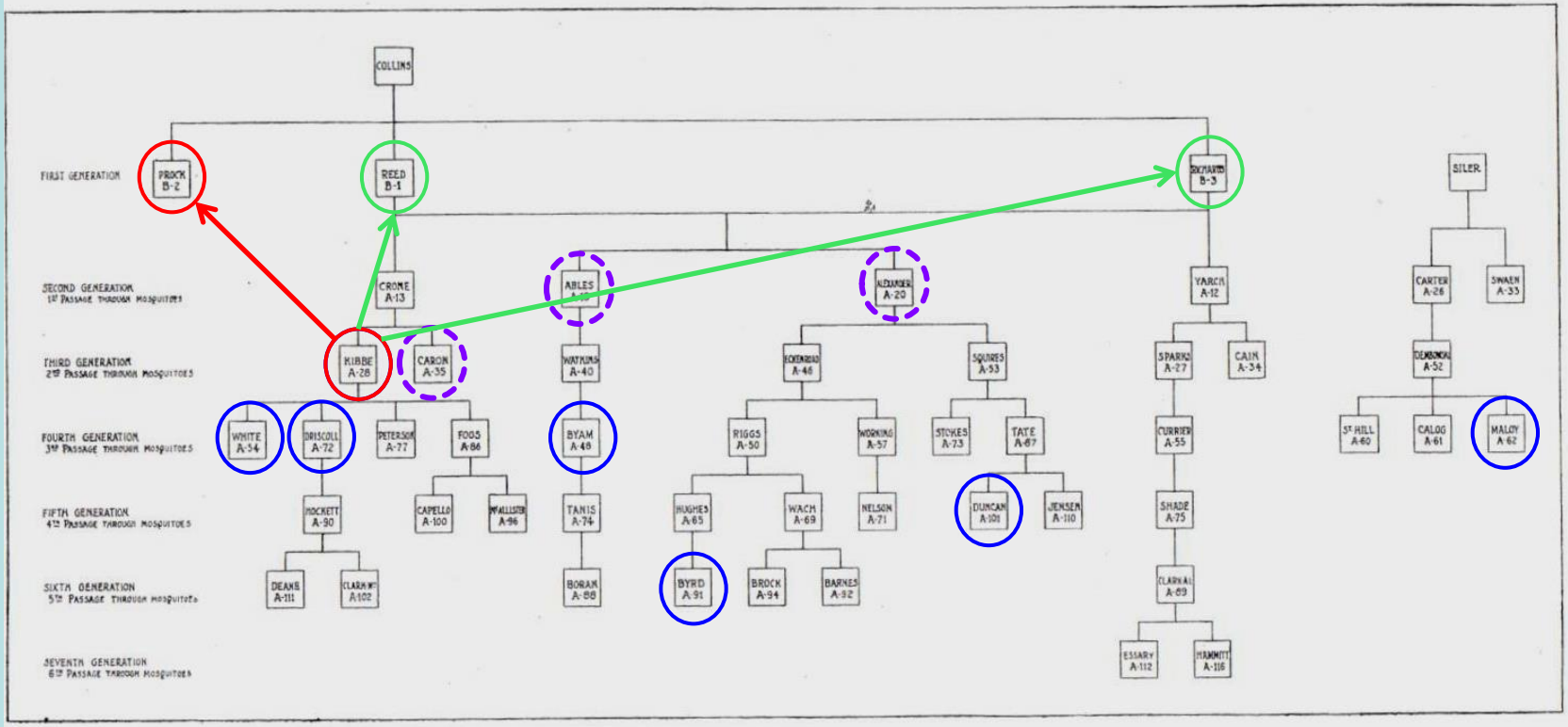

FIG 2. Chart indicating passage of strains of the dengue virus from man to mosquito through successive generations.

TRANSMISSION BY MOSQUITOES, II 117

◯ = used as donors in immunity challenges

◯ = PRNT to determine serotype

What could we learn from a dengue CHIM?

- Evaluation of of candidate dengue vaccines
  - Downselection
  - Dose/schedule refinements
  - Performance in endemic settings
- Evaluation of potential therapeutic drug candidates
  - Efficacy/safety
  - Dose finding
  - Therapeutic window
- Understanding immunity and correlates of protection
  - Homotypic challenge
  - Heterotypic challenge?
  - Drug probe studies – monoclonals, small molecule inhibitors

Consider the bioethical issues

- Explore perceived risks of priming healthy individuals for more severe disease in challenge studies
- Support local / national IRBs with external independent advice to understand the complex scientific concepts
- Establish guidelines for fully competent informed consent. Determine appropriate age and educational level of participants
- Determine an appropriate reimbursement sum for this LMIC setting, avoiding undue influence
- Determine the duration and feasibility of long-term follow up schemes
- Community engagement

Development of a cohort of potential participants for the Dengue-CHIM studies

- 1000+ new medical/science students at Universities in HCMC, from widespread locations across Vietnam with widely varying dengue endemicity.
- Potential study subjects able to understand the complex issues involved, who can be followed for several years during their student residence in HCMC?
- Series of lectures, seminars and focus group interviews to inform and debate the issues around Dengue-CHIM studies. Obtain student feedback on research concepts, ethics, remuneration, long-term follow up etc., and assess comprehension through quizzes, periodic questionnaires.

Development of the necessary clinical infrastructure/logistics

- A comfortable screened “hotel suite” on the HTD site
- Logistics and operational aspects for detailed clinical observational and sampling protocols, safety assessments, pharmacy procedures etc. etc.
- Preparation, shipment and storage of GMP compliant challenge strains and investigational products
- Technology transfer / assay harmonisation / validation - PRNTs, viral culture, viral PCR and sequencing, PBMCs, FACS protocols, mosquito transmission studies.

Proof of Concept Study

- Expose 10-20 multi-typically immune students to the DENV-2 challenge strain. Expect sterile immunity.
- If no safety signals and no viremia, proceed to expose 10-20 naïve individuals (PRNT negative to all relevant flaviviruses), with the capacity to transfer immediately to HTD if any clinical concerns arise.
- Expose participants to sterile mosquitoes during the potentially viremic period in accordance with our standard mosquito transmission protocols.
- Discuss vaccination with all naïve individuals after challenge, using the most effective vaccine available at the time, and arrange annual follow up.