Epidemiological, clinical and immunological risk factors of severe dengue

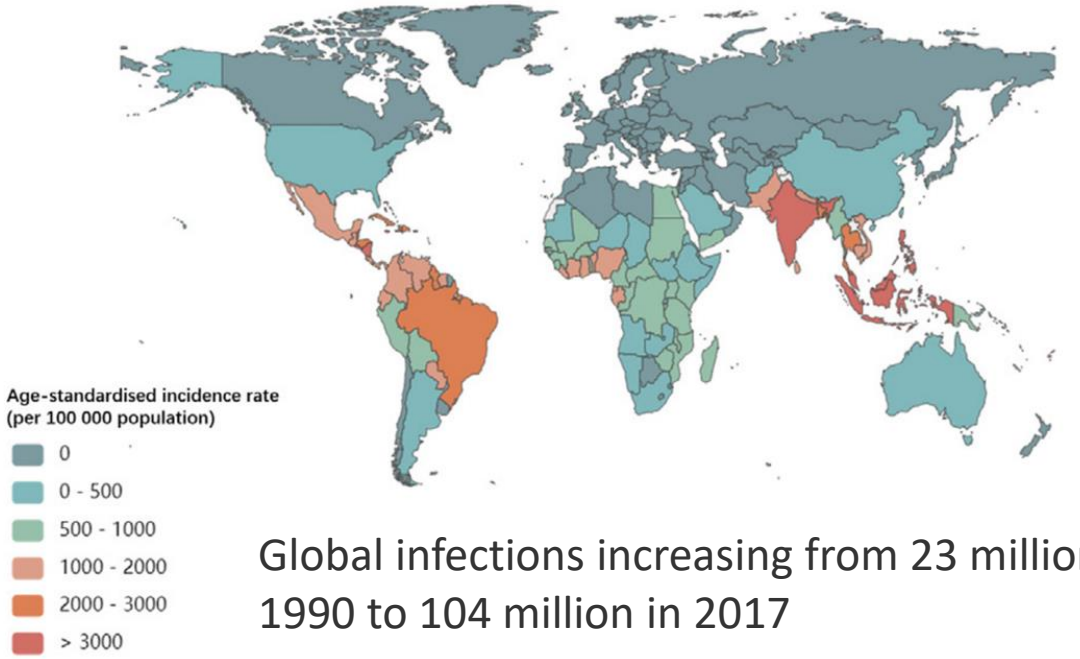
Neelika Malavige

Head, Dengue Global Program and Scientific Affairs (India), DNDi

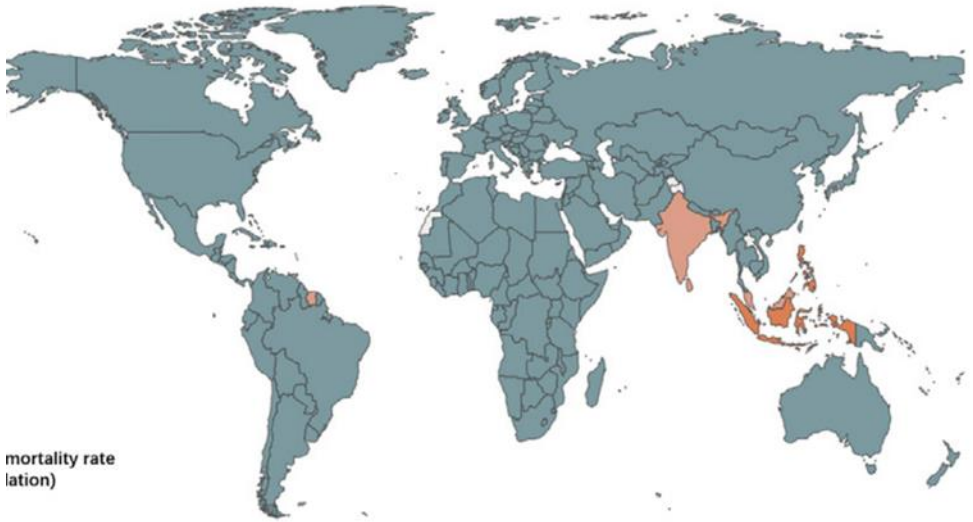
DNDi
Drugs for Neglected Diseases *initiative*

Global, regional, and national dengue burden from 1990 to 2017: A systematic analysis based on the global burden of disease study 2017

Zhilin Zeng [1] • Juan Zhan [1] • Liyuan Chen • Huilong Chen • Sheng Cheng • Show footnotes



Global infections increasing from 23 million in 1990 to 104 million in 2017



Although the incidence of dengue is similar in Latin America and Asia, the mortality rates are higher in Asia

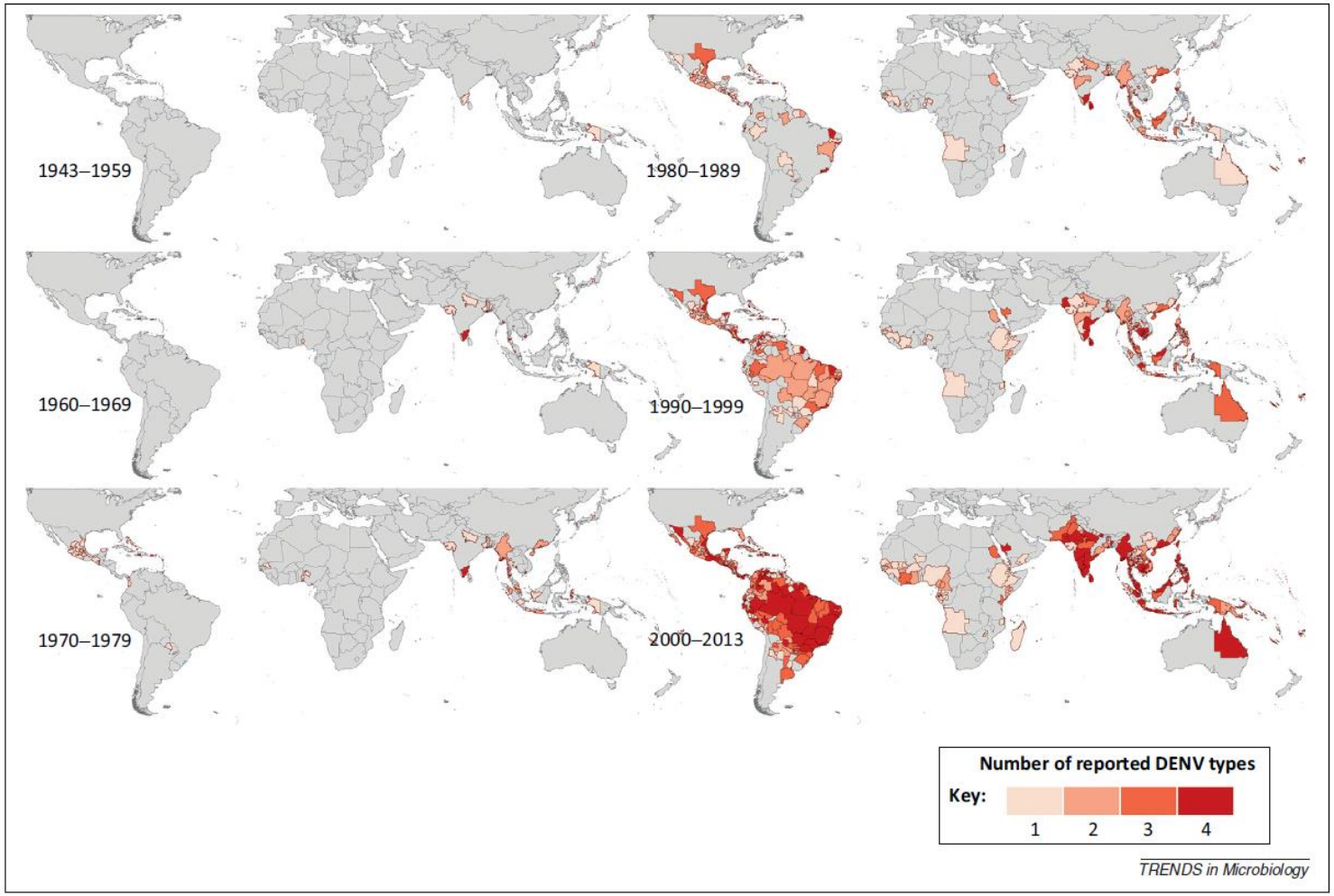
Age stratified deaths and DALYs also increased (DALYS by 109%)

What is causing this increase in dengue?

DNDi
Drugs for Neglected Diseases *initiative*

Global spread of dengue virus types: mapping the 70 year history

Jane P. Messina[1], Oliver J. Brady[1], Thomas W. Scott[2,3], Chenting Zou[1], David M. Pigott[1], Kirsten A. Duda[1], Samir Bhatt[1], Leah Katzelnick[4], Rosalind E. Howes[1], Katherine E. Battle[1], Cameron P. Simmons[5,6,7], and Simon I. Hay[1,3]



Trends in Microbiology March 2014, Vol. 22, No. 3

The first instance where a disease similar to dengue was recorded was in in a Chinese medical encyclopaedia in 992.

First DENV isolated in 1943 in Japan.

With time the four antigenically distinct DENVs spread globally, with the spread of *Aede aegypti*.

Sporadic outbreaks were reported, since 1950s in many countries.

The first known epidemic of DHF occurred in Manila, Philippines, in 1953 to 1954 (Gubler, Clin Micro Rev, 1998)

Dengue Haemorrhagic Fever in Thailand

By

Wiwat Rojanapithayakorn

Dengue Bulletin – Vol 22, 1998

Different phases	Case fatality rates (CFRs)
1st phase (1958-1967)	>10% at beginning dropped to 3% at end
2nd phase (1968-1977)	1% to 4%
3rd phase (1978-1987)	2.45% at the beginning and dropped to 0.58%
4th phase (1988-1997)	0.3 to 0.6%

Age-group	Number of cases	%
0–4 yrs	19 205	15.20
5–9 yrs	46 787	37.03
10–14 yrs	35 403	28.02
15 yrs and over	24 953	19.75
Total	126 348	100.0

Dengue was a predominantly child hood infection.

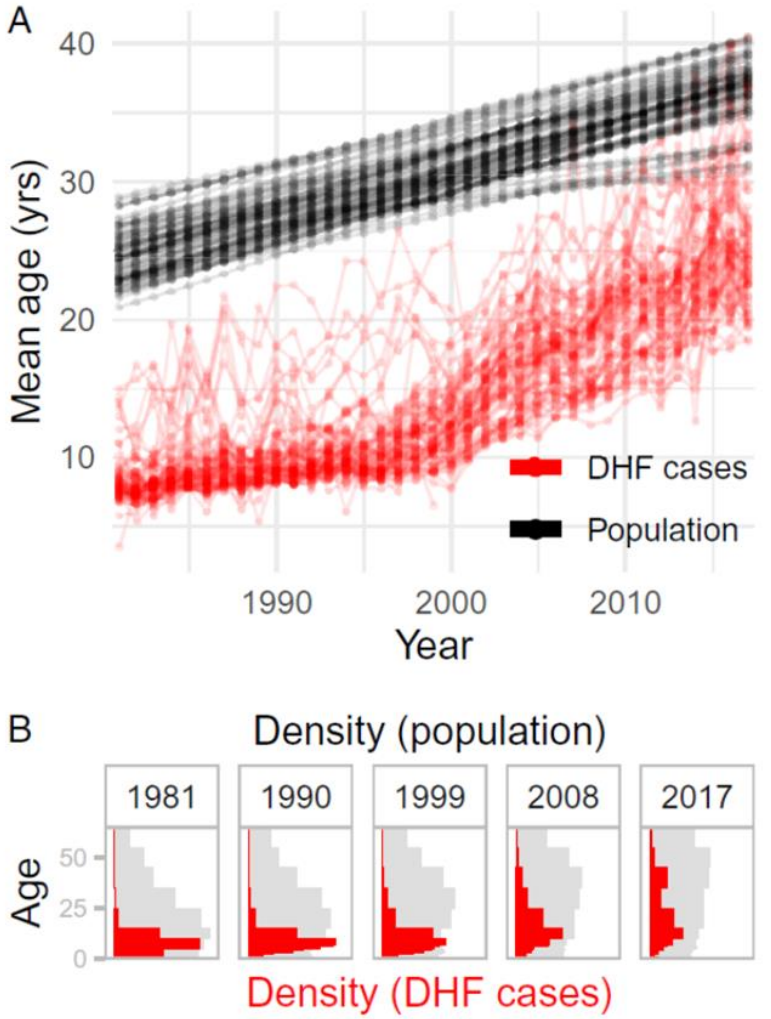


Fig. 1. The increase in the mean ages of (*A*) the population (black) and of reported cases with DHF (red) from 1981 to 2017 in the 72 provinces of Thailand calculated using midpoints of the age strata. (*B*) Country-level age distribution at 9-y intervals; the underlying population is in gray, and DHF cases are in red. Bin widths reflect the age strata reported for the cases at those times. *SI Appendix*, Fig. S2 shows the age distribution of all years in the dataset.

(Huang et al, PNAS, 2022)

DNDi
Drugs for Neglected Diseases *initiative*

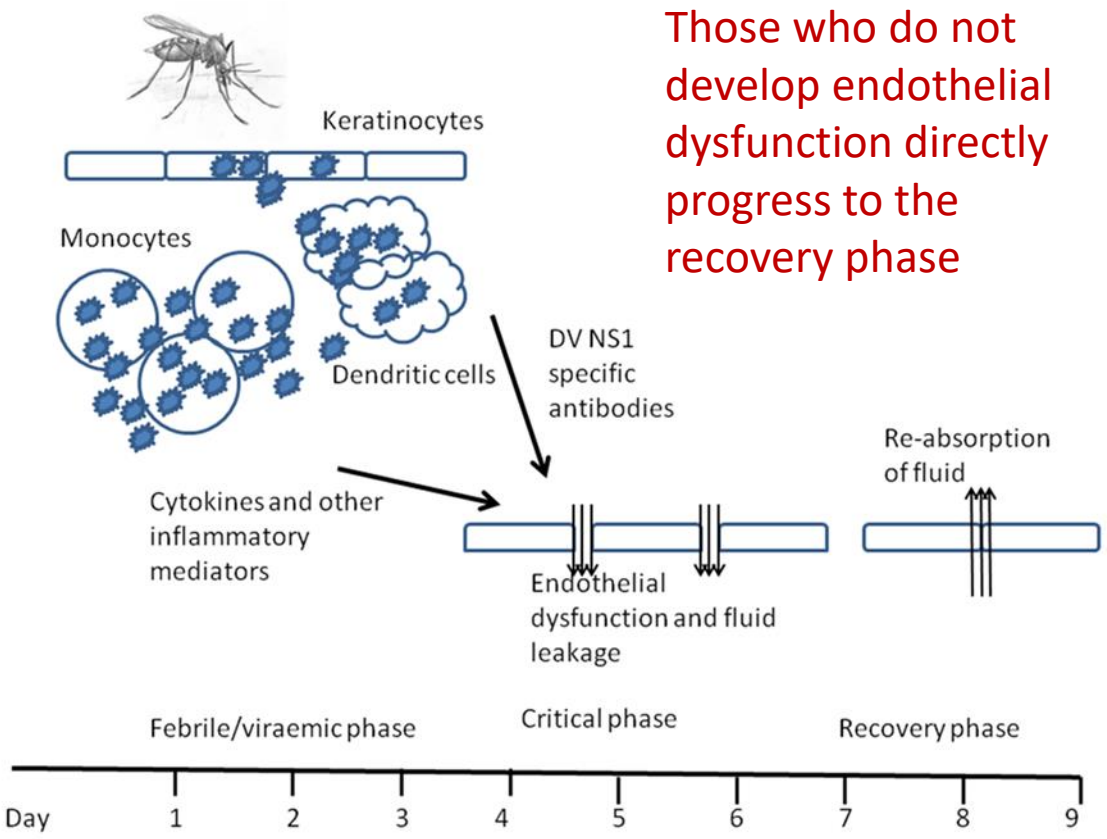
Changing epidemiology in dengue and its significance

Climate change increasing vector competency and geographical expansion of vectors → Increase incidence of dengue in endemic countries and spread to new geographical locations

All four dengue viruses co-circulating in many endemic countries: more intense transmission and many infected with more than one serotype → Increase in disease severity due to more secondary dengue infections

Change in age of infection with the virus: more infections in adults of reproductive age and older age → Dengue in pregnant women and in older adults with co-morbidities leading to severe dengue

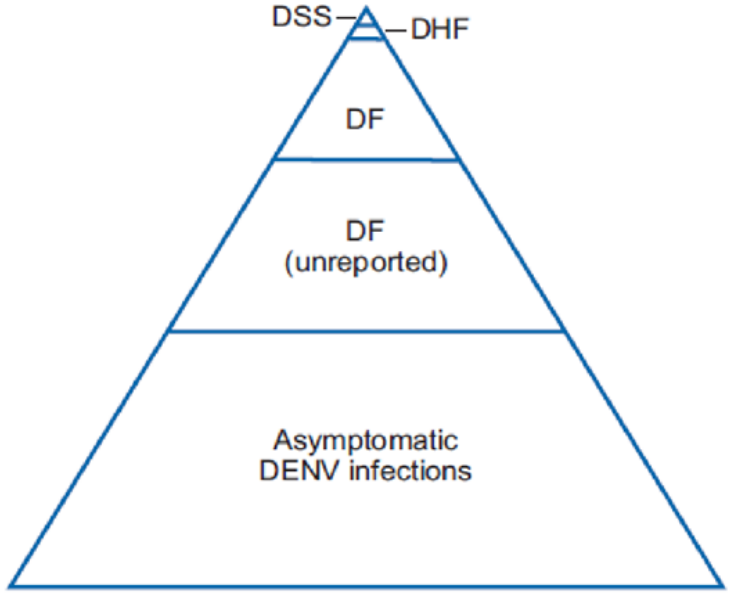
Pathogenesis of dengue and asymptomatic vs symptomatic dengue



G.N. Malavige, G.S. Ogg / Journal of Clinical Virology 58 (2013) 605–611

Those who do not develop endothelial dysfunction directly progress to the recovery phase

Are we seeing a higher number of dengue cases due to increase in symptomatic infection as more adults are infected?



1 in 4 (25%) of dengue infections have shown to be symptomatic.

The likelihood of symptomatic infection increases with age. <7% in children <10 years, 8% to 11% by 20 years. (Thai et al, PLOS Neg, 2011)

DNDi
Drugs for Neglected Diseases *initiative*

Risk factors for severe dengue

Diabetes, cardiac disorders and asthma as risk factors for severe organ involvement among adult dengue patients: A matched case-control study

Junxiong Pang[1,2], Jung Pu Hsu[1], Tsin Wen Yeo[1,3], Yee Sin Leo[1,2,4] & David C. Lye[1,3,4]

SCIENTIFIC REPORTS | 7:39872 | DOI: 10.1038/srep39872

The association between diabetes and obesity with Dengue infections

S. D. Sekaran[1*], Z. M. Liew[2], H. C. Yam[2] and C. S. Raju[3]

Sekaran *et al.*
Diabetology & Metabolic Syndrome (2022) 14:101

Is Diabetes a Risk Factor for a Severe Clinical Presentation of Dengue? - Review and Meta-analysis

Nan Shwe Nwe Htun[1,2], Peter Odermatt[1,2], Ikenna C. Eze[1,2], Noémie Boillat-Blanco[1,2,3], Valérie D'Acremont[1,2,4], Nicole Probst-Hensch[1,2]*

Original Article

Diabetic patients suffering dengue are at risk for development of dengue shock syndrome/ severe dengue: Emphasizing the impacts of co-existing comorbidity(ies) and glycemic control on dengue severity

Ing-Kit Lee [a,b], Ching-Jung Hsieh [c,§], Chien-Te Lee [b,d], Jien-Wei Liu [a,b,*]

Journal of Microbiology, Immunology and Infection (2020) 53, 69–78

Diabetes with Hypertension as Risk Factors for Adult Dengue Hemorrhagic Fever in a Predominantly Dengue Serotype 2 Epidemic: A Case Control Study

Junxiong Pang[1,2]*, Agus Salim[2], Vernon J. Lee[2,3], Martin L. Hibberd[1,2], Kee Seng Chia[2], Yee Sin Leo[4,5], David C. Lye[4,5]

www.plosntds.org

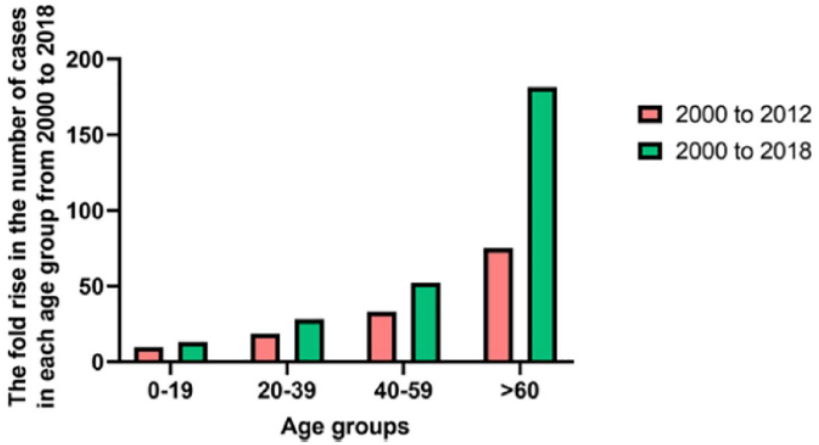
May 2012 | Volume 6 | Issue 5 | e1641

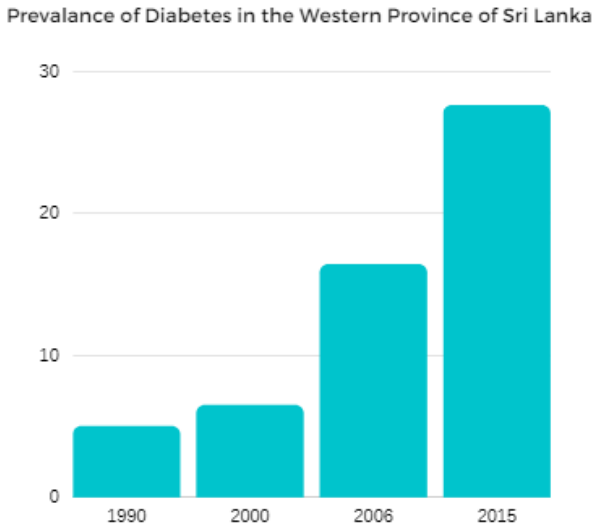
DNDi
Drugs for Neglected Diseases *initiative*

REVIEW

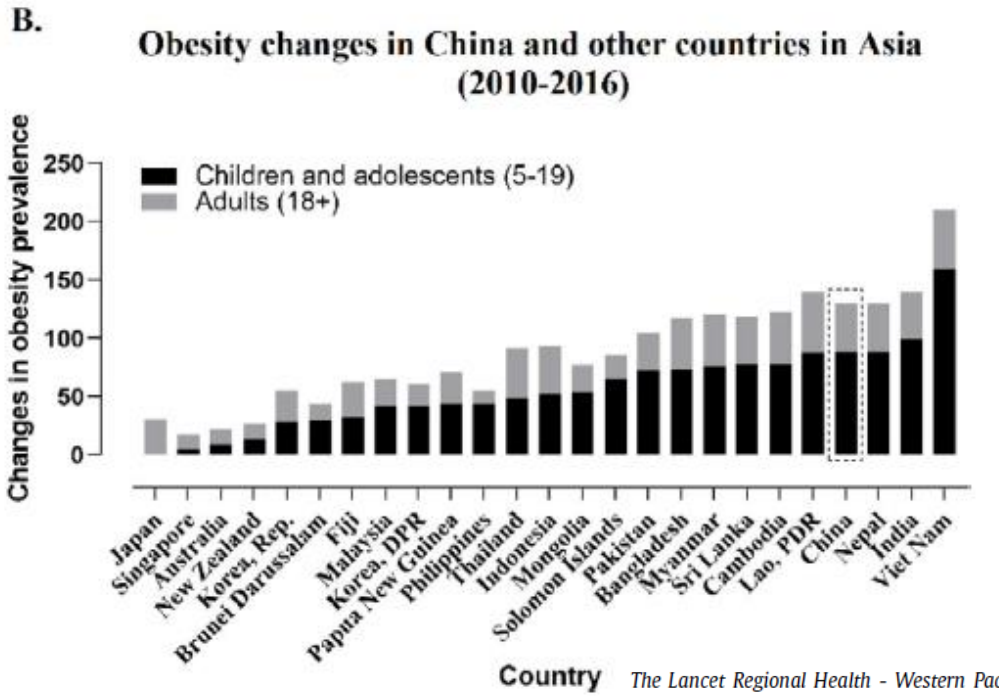
Changing epidemiology of dengue in Sri Lanka —Challenges for the future

Gathsaurie Neelika Malavige[1,2]*, Chandima Jeewandara[1,2], Azhar Ghouse[3], Gayasha Somathilake[2], Hasitha Tissera[3]





Obesity and hypertension in Asia: Current status and challenges



The Lancet Regional Health - Western Pacific 15 (2021) 100243

There is a marked rise in diabetes, obesity and hypertension in Asia.

Do these epidemiological risk factors lead to overall increase in symptomatic dengue or severe dengue?

DNDi
Drugs for Neglected Diseases *initiative*

Dengue in pregnancy and maternal mortality: a cohort analysis using routine data

Enny S. Paixao[1,2,3], Katie Harron[1], Oona Campbell[1], Maria Glória Teixeira[2,3], Maria da Conceição N. Costa[2], Mauricio L. Barreto[2,3] & Laura C. Rodrigues[1,3]

Dengue is a mosquito-borne disease with major public health importance due to its growing incidence and geographical spread. There is a lack of knowledge on its contribution to maternal death. We conducted a population-based cohort study to investigate the association between symptomatic dengue during pregnancy and deaths in Brazil from 2007 to 2012. We did this by linking routine records of confirmed dengue cases to records of deaths of women who had a live birth. Using the Firth method, we estimated odds ratios for maternal deaths associated with dengue during pregnancy. Dengue increased the risk of maternal death by 3 times (95%CI,1.5–5.8) and dengue haemorrhagic fever increased the risk of maternal death by 450 times (95%CI,186.9–1088.4) when compared to mortality of pregnant women without dengue. The increase in risk occurred mostly during acute dengue 71.5 (95%CI,32.8–155.8), compared with no dengue cases. This study showed an increased risk of adverse outcomes in pregnant women with dengue. Therefore in areas where dengue is circulating, the health of pregnant women should be not only a public health priority, but health professionals attending pregnant women with dengue should more closely observe these patients to be able to intervene in a timely way and avoid deaths.

SCIENTIFIC REPORTS | (2018) 8:9938 | DOI:10.1038/s41598-018-28387-w

Dengue in pregnancy is associated with adverse maternal and fetal outcomes and high risk of severe dengue and death, especially around the time of delivery.

Clinical Characteristics and Obstetric Outcome of Symptomatic Dengue Infection in Pregnancy from a Tertiary Care Center in South India

Sutharsika Thiyagalingam[1], Sasirekha Rengaraj[2] and Saranya Rajamanickkam[3]*

Abstract

Dengue, the most prevalent mosquito-borne viral infection has a wide range of clinical presentation and the incidence is on the rise in the recent past. There is a concern that dengue infection in pregnancy might be associated with adverse maternal and perinatal outcome however there is paucity in the literature available. The aim of the present study was to analyze the outcome of dengue infection which required hospitalizations and were managed in a tertiary care center. A total of 52 pregnant women of confirmed dengue infection were studied for the severity of dengue, the clinical course and obstetric outcome. Out of 52 women, 34 (65.3%) had either severe dengue or some warning sign and there were 4 maternal deaths (7.7%). Thrombocytopenia was seen in 69.2% (n = 36) of women and 21.2% required platelet transfusions. Oligohydramnios was seen in 21.3% (n = 12) and 26.9% (n = 14) of women had PROM. The caesarean section rate was 44.2% (n = 22) and there were 2 stillbirths (3.8%). Adverse maternal and perinatal outcome was more in women with severe forms of dengue especially when they present near term gestation. Prompt diagnosis and appropriate supportive management are extremely important and avoiding interventions during the critical phase equally prevents maternal morbidity and mortality.

Thiyagalingam et al. J Infect Dis Epidemiol 2020, 6:133

DNDi
Drugs for Neglected Diseases *initiative*

Risk factors for severe dengue

Dengue	Dengue and COVID-19	COVID-19
Age All ages	**Age** Older age	**Gender** Male sex
Immune status Secondary infection	**Physiological status** Pregnancy	**Comorbidities** Cardiovascular disease Chronic lung disease
Viral factors All four dengue viruses cause severe dengue DENV4 infection milder?	**Comorbidities** Diabetes Obesity Hypertension Asthma Chronic kidney disease	Immunosuppression Cancers **Viral factors** Wide differences in hospitalizations and mortality due to different variants in different countries.

Fig. 1 Risk factors for severe dengue and COVID-19. The common changes are highlighted in the middle box, while those specific to dengue (green box) and COVID-19 (blue box) are shown separately

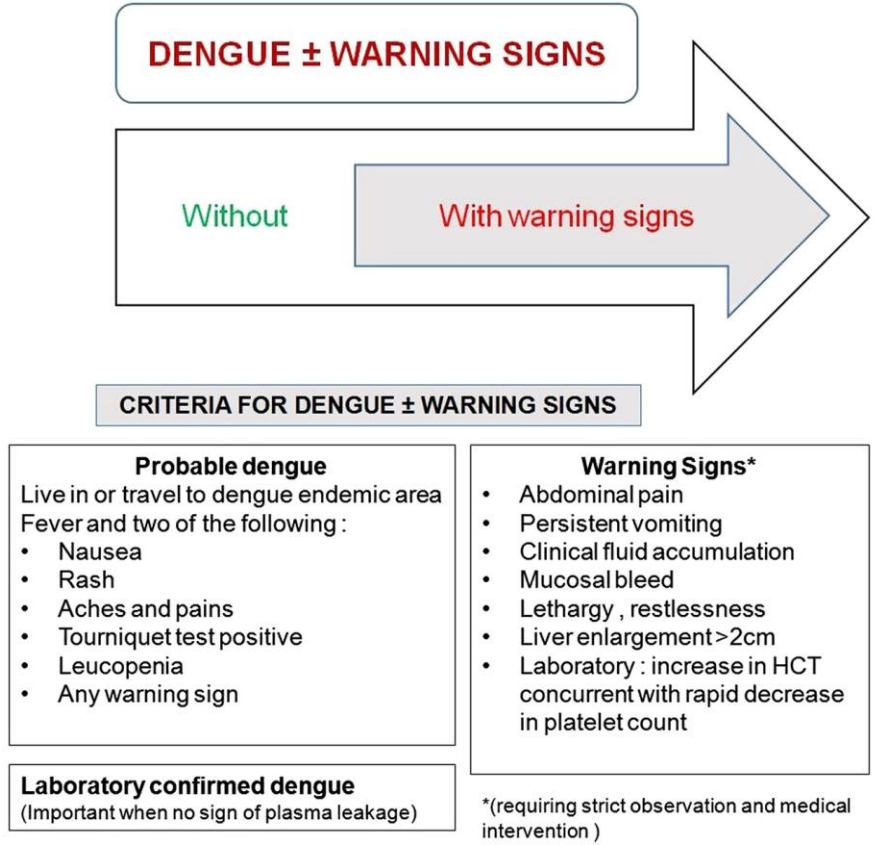
Malavige *et al. Journal of Biomedical Science* (2022) 29:48

DNDi
Drugs for Neglected Diseases *initiative*

How do you diagnose severe dengue/ dengue haemorrhagic fever?

DF/DHF	Grade	Signs and Symptoms	Laboratory
DF		Fever with two of the following: • Headache • Retro-orbital pain • Myalgia • Arthralgia/ bone pain • Rash • Hemorrhagic manifestations • No evidence of plasma leakage	• Leucopenia (WBC ≤5000 cells/mm3). • Thrombocytopenia (Platelet count <150 000 cells/mm3) • Rising hematocrit (5% – 10%) • No evidence of plasma loss
DHF	I	Fever and hemorrhagic manifestation (positive tourniquet test) and evidence of plasma leakage	Thrombocytopenia <100 000 cells/ mm3; HCT rise ≥20%
DHF	II	As in Grade I plus spontaneous bleeding	Thrombocytopenia <100 000 cells/mm3; HCT rise ≥20%.
DHF	III	As in Grade I or II plus circulatory failure [weak pulse, narrow pulse pressure (≤20 mmHg), hypotension, restlessness]	Thrombocytopenia <100 000 cells/mm3; HCT rise ≥20%.

WHO dengue classification 1997



WHO dengue classification 2009

warning signs. Hence, clinical warning signs at presentation had 77.3% (95% CI 58.3–94.1) sensitivity and 39.7% (95% CI 34.7–44.9) specificity for predicting progression to SD (Fig. 3C), corresponding to positive and negative likelihood ratios of 1.3 (95% CI 0.9–1.6) and 0.6 (95% CI 0.2–1.1), respectively (Table 3). In adults, warning signs were an especially poor predictor of SD, with sensitivity and specificity of 66.7% and 45.2%, respectively

Liu *et al. Genome Medicine* (2022) 14:33
https://doi.org/10.1186/s13073-022-01034-w

DNDi
Drugs for Neglected Diseases *initiative*

Clinical presentation of dengue

Symptoms

Fever

Lethargy

Muscle pains and joint pains

Headache

Sore throat (25% of children)

GIT symptoms: abdominal pain, vomiting, diarrhoea

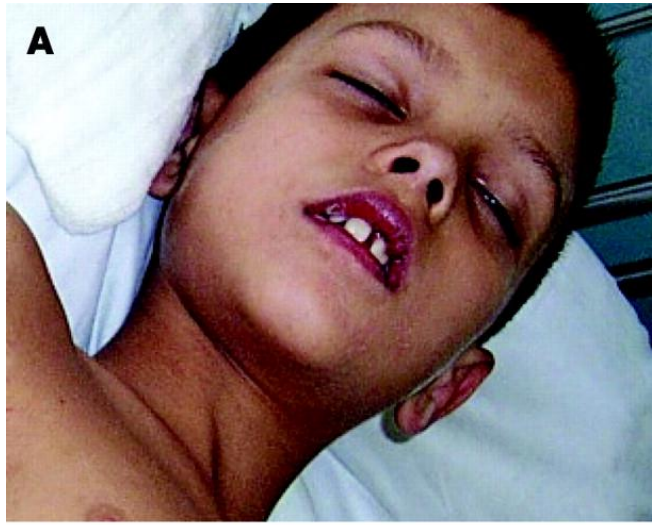
Laboratory features

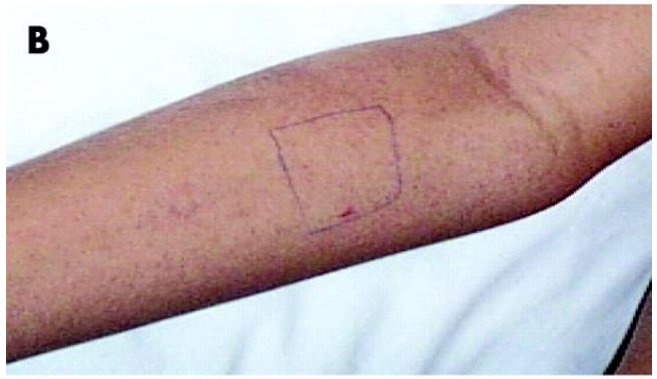
Lymphopenia

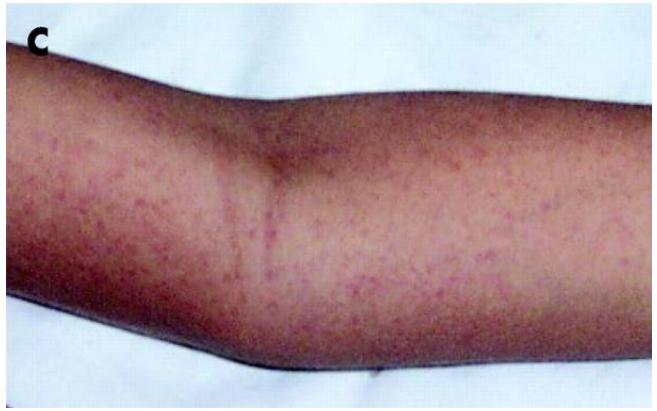
Thrombocytopenia

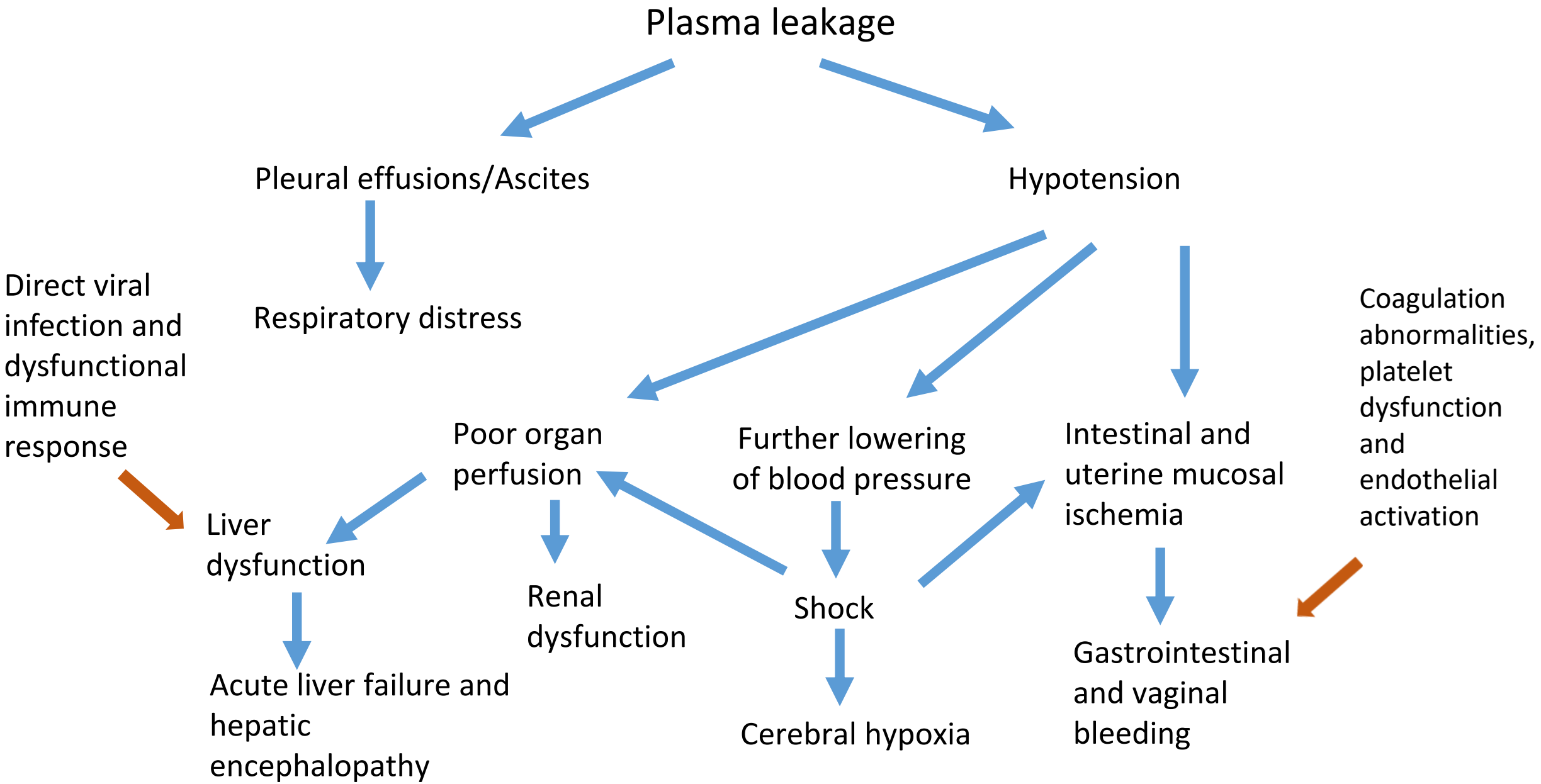
Elevated liver enzymes

Elevated CRP (usually not more than 50)








Plasma leakage
Pleural effusions/Ascites
Respiratory distress
Hypotension
Direct viral infection and dysfunctional immune response
Poor organ perfusion
Further lowering of blood pressure
Intestinal and uterine mucosal ischemia
Coagulation abnormalities, platelet dysfunction and endothelial activation
Liver dysfunction
Renal dysfunction
Shock
Acute liver failure and hepatic encephalopathy
Cerebral hypoxia
Gastrointestinal and vaginal bleeding

What causes plasma leakage?

Viral factors

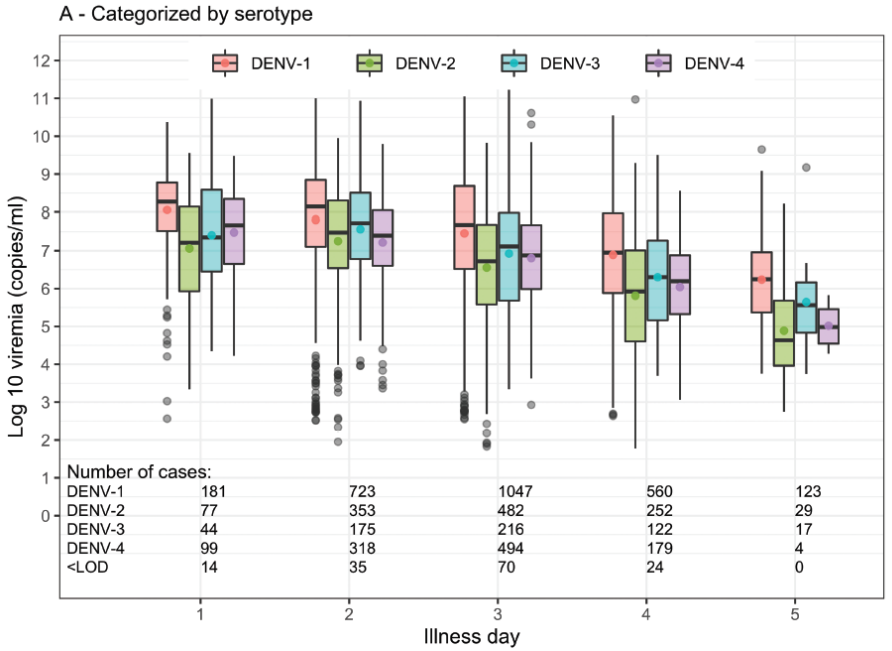
- NS1
- Virus genotypes, certain mutations

Host factors

- Immune status: primary vs secondary dengue
- Comorbidities: dysfunctional/aberrant immune response in those with metabolic disease

Higher Plasma Viremia in the Febrile Phase Is Associated With Adverse Dengue Outcomes Irrespective of Infecting Serotype or Host Immune Status: An Analysis of 5642 Vietnamese Cases

Nguyen Lam Vuong,[1,2] Nguyen Than Ha Quyen,[1] Nguyen Thi Hanh Tien,[1] Nguyen Minh Tuan,[3] Duong Thi Hue Kien,[1] Phung Khanh Lam,[1] Dong Thi Hoai Tam,[1] Tran Van Ngoc,[4] Sophie Yacoub,[1,5] Thomas Jaenisch,[6] Ronald B. Geskus,[1,5] Cameron P. Simmons,[1,5,7] and Bridget A. Wills[1,5]



Viral loads were highest for DENV1.

Risk of hospitalization and severe disease was highest with DENV2.

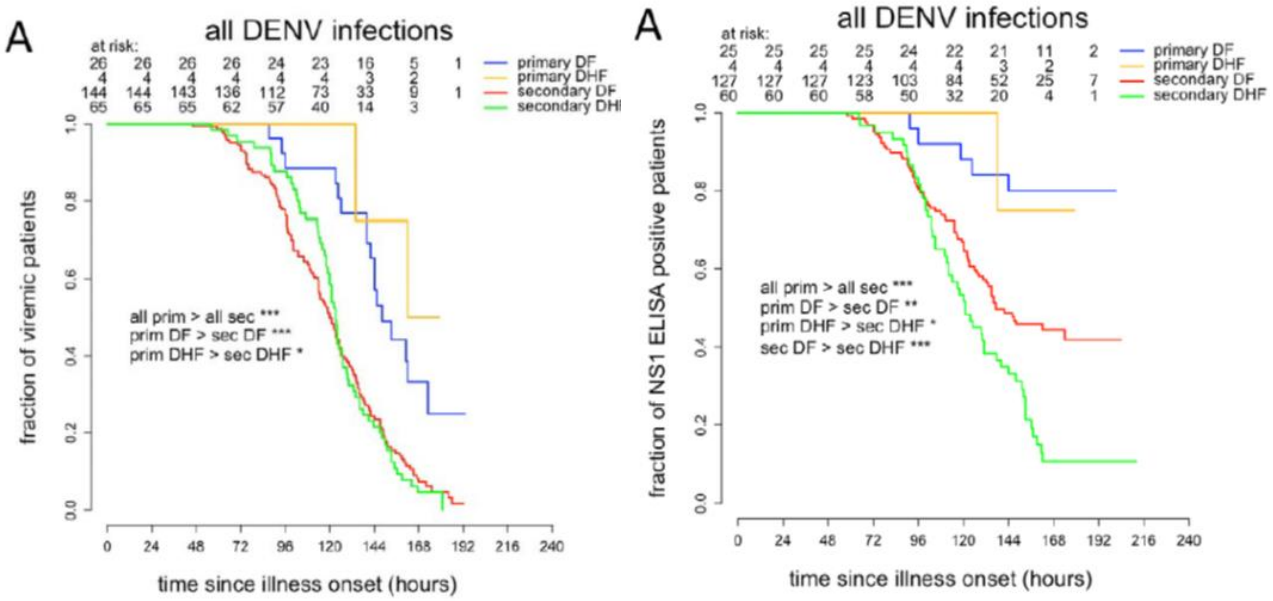
Consistent with previous research, the study also confirms that DENV-2 carries the greatest risk of adverse outcomes despite manifesting the lowest daily viremia levels and that viremia is typically highest for DENV-1 [14, 32, 33]. However,

DNDi Drugs for Neglected Diseases *initiative*

Kinetics of Viremia and NS1 Antigenemia Are Shaped by Immune Status and Virus Serotype in Adults with Dengue

Vianney Tricou[1*], Nguyet Nguyen Minh[1,2], Jeremy Farrar[1,3], Hien Tinh Tran[1], Cameron P. Simmons[1,3]

Conclusions: Collectively, our findings suggest that the early magnitude of viremia is positively associated with disease severity. The clearance of DENV is associated with immune status, and there are serotype dependent differences in infection kinetics. These findings are relevant for the rational design of randomized controlled trials of therapeutic interventions, especially antivirals.

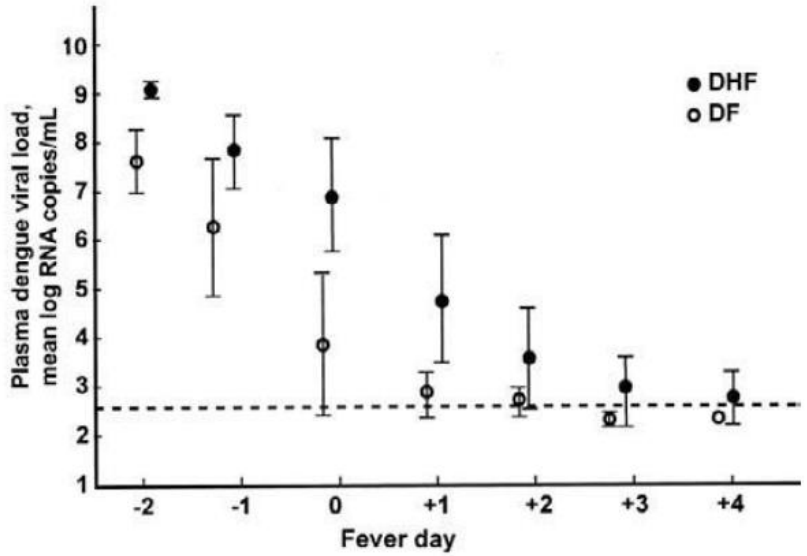


September 2011 | Volume 5 | Issue 9 | e1309

Patients with primary dengue had higher viral loads and NS1 antigen levels persisting than secondary dengue.

Severe dengue is more frequent in secondary dengue.

Slower Rates of Clearance of Viral Load and Virus-Containing Immune Complexes in Patients with Dengue Hemorrhagic Fever



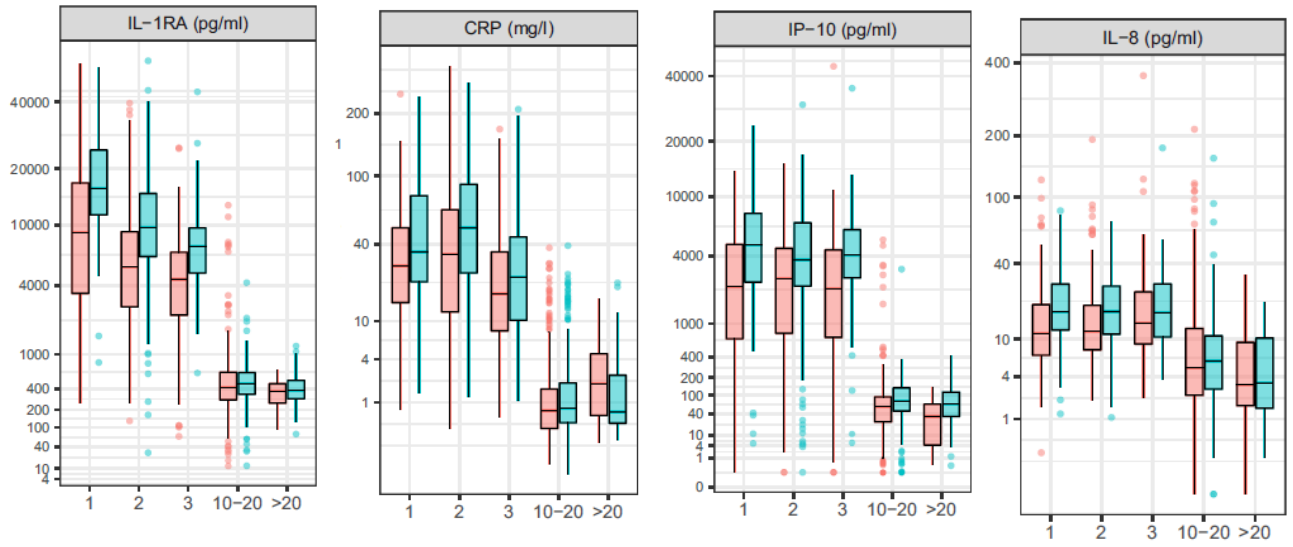
CID 2006:43 (15 October) • 1023

Patients who progress to develop severe dengue are unable to effectively clear the virus.

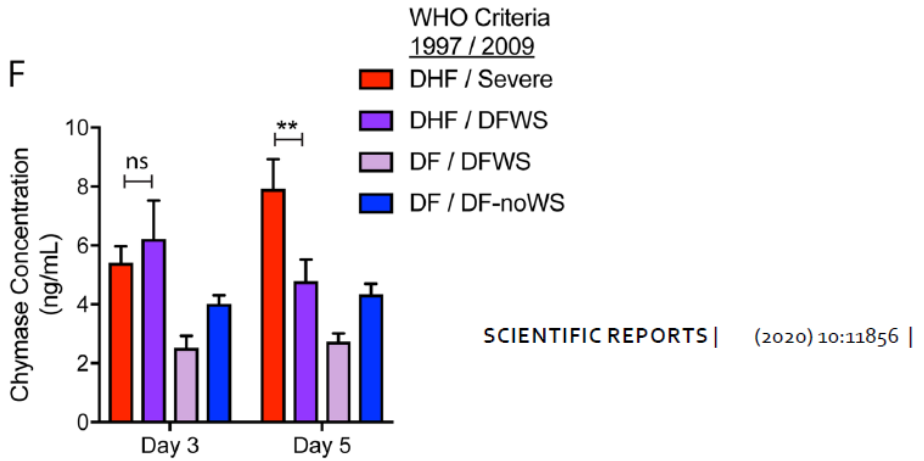
DNDi
Drugs for Neglected Diseases *initiative*

Combination of inflammatory and vascular markers in the febrile phase of dengue is associated with more severe outcomes

Vuong *et al.* eLife 2021;10:e67460.



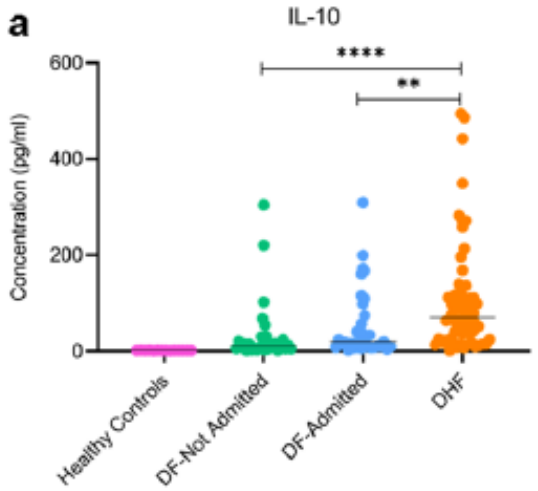
Serum chymase levels correlate with severe dengue warning signs and clinical fluid accumulation in hospitalized pediatric patients



SCIENTIFIC REPORTS | (2020) 10:11856 |

Similarities and differences between the 'cytokine storms' in acute dengue and COVID-19

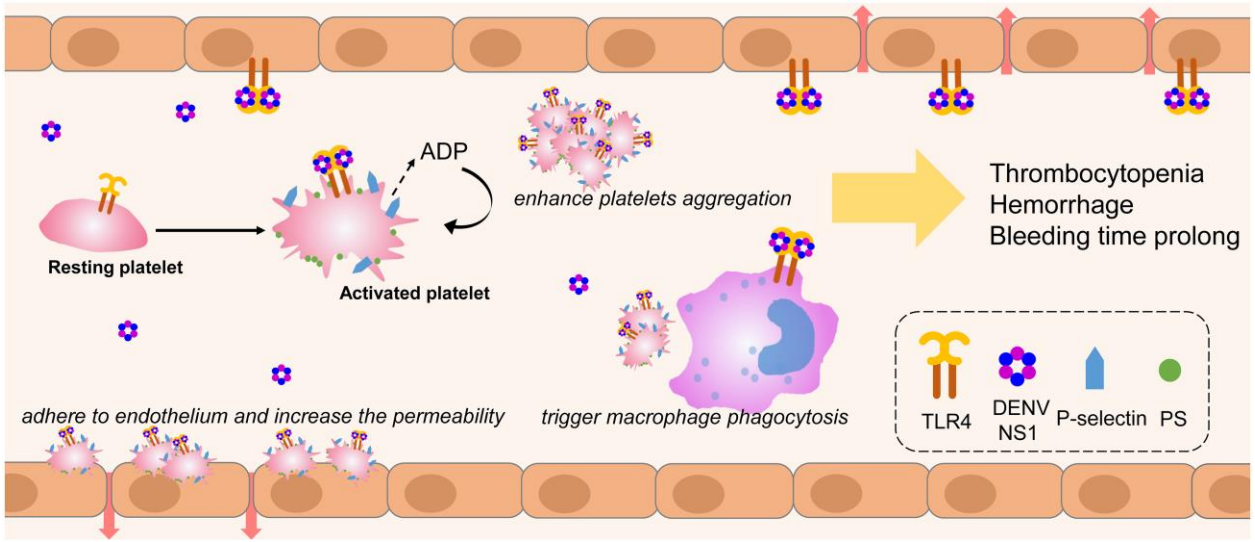
Scientific Reports | (2020) 10:19839 |



Those who progressed to develop DHF/severe dengue had a dysfunctional immune response during early illness leading to immunopathology and delayed clearance of the virus.

DNDi
Drugs for Neglected Diseases *initiative*

Pathogenesis of vascular leak: NS1



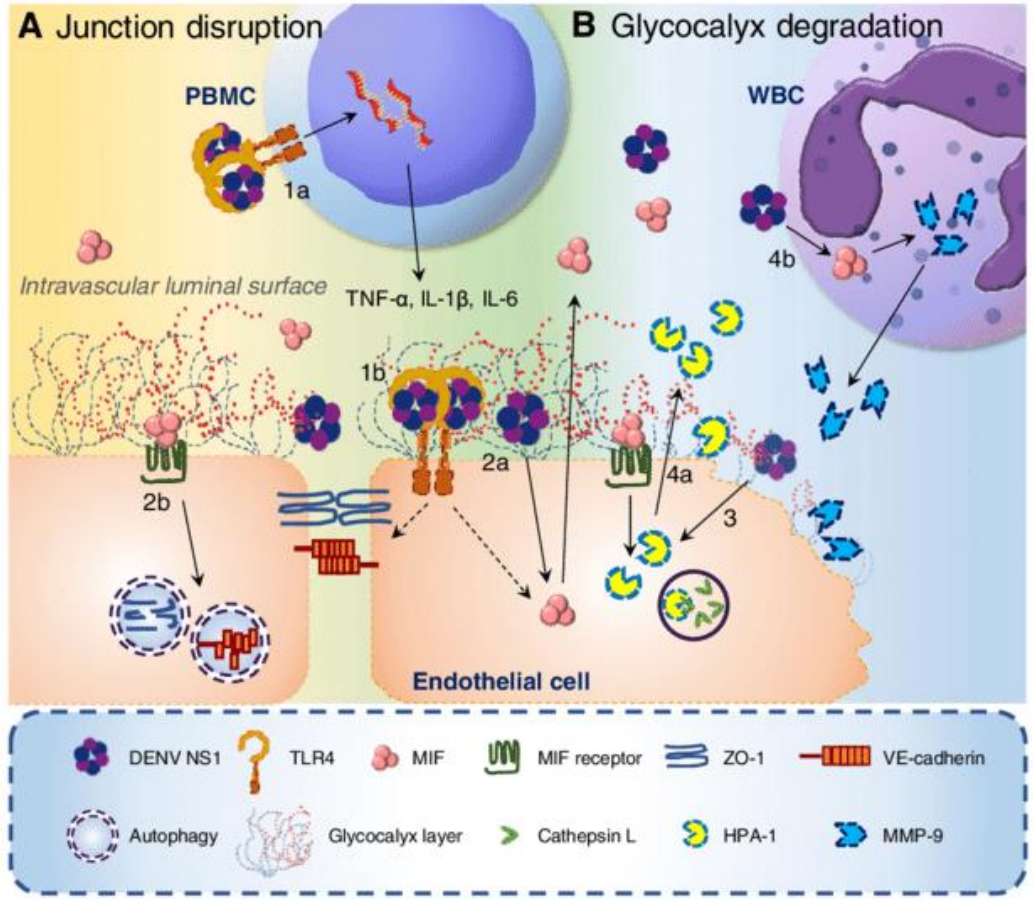
(Chao et al, PLOS Pathogens, 2019)

NS1 causes vascular leak by:

1. Disruption of the glycocalyx of the endothelium
2. Inducing cytokines and inflammatory mediators that cause disruption of tight junctions and gap junctions
3. MMP-9 secretion of PBMCS

NS1 contributes to thrombocytopenia and bleeding by

1. Platelet activation
2. Enhancing aggregation



(Chen et al, J Bio Sci, 2018)

DNDi
Drugs for Neglected Diseases *initiative*

Is secondary dengue a risk factor for severe disease and if so why?

Risk predictors of progression to severe disease during the febrile phase of dengue: a systematic review and meta-analysis

Sorawat Sangkaew, Damien Ming, Adhiratha Boonyasiri, Kate Honeyford, Siripen Kalayanarooj, Sophie Yacoub, Ilaria Dorigatti, Alison Holmes**

Findings Of 6643 studies identified, 150 articles were included in the systematic review, and 122 articles comprising 25 potential predictors were included in the meta-analyses. Female patients had a higher risk of severe dengue than male patients in the main analysis (2674 [16·2%] of 16 481 *vs* 3052 [10·5%] of 29 142; odds ratio [OR] 1·13 [95% CI 1·01–1·26) but not in the subgroup analysis of studies with children. Pre-existing comorbidities associated with severe disease were diabetes (135 [31·3%] of 431 with *vs* 868 [16·0%] of 5421 without; crude OR 4·38 [2·58–7·43]), hypertension (240 [35·0%] of 685 *vs* 763 [20·6%] of 3695; 2·19 [1·36–3·53]), renal disease (44 [45·8%] of 96 *vs* 271 [16·0%] of 1690; 4·67 [2·21–9·88]), and cardiovascular disease (nine [23·1%] of 39 *vs* 155 [8·6%] of 1793; 2·79 [1·04–7·50]). Clinical features during the febrile phase associated with progression to severe disease were vomiting (329 [13·5%] of 2432 with *vs* 258 [6·8%] of 3797 without; 2·25 [1·87–2·71]), abdominal pain and tenderness (321 [17·7%] of 1814 *vs* 435 [8·1%] of 5357; 1·92 [1·35–2·74]), spontaneous or mucosal bleeding (147 [17·9%] of 822 *vs* 676 [10·8%] of 6235; 1·57 [1·13–2·19]), and the presence of clinical fluid accumulation (40 [42·1%] of 95 *vs* 212 [14·9%] of 1425; 4·61 [2·29–9·26]). During the first 4 days of illness, platelet count was lower (standardised mean difference –0·34 [95% CI –0·54 to –0·15]), serum albumin was lower (–0·5 [–0·86 to –0·15]), and aminotransferase concentrations were higher (aspartate aminotransferase [AST] 1·06 [0·54 to 1·57] and alanine aminotransferase [ALT] 0·73 [0·36 to 1·09]) among individuals who progressed to severe disease. Dengue virus serotype 2 was associated with severe disease in children. Secondary infections (*vs* primary infections) were also associated with severe disease (1682 [11·8%] of 14 252 with *vs* 507 [5·2%] of 9660 without; OR 2·26 [95% CI 1·65–3·09]). Although the included studies had a moderate to high risk of bias in terms of study confounding, the risk of bias was low to moderate in other domains. Heterogeneity of the pooled results varied from low to high on different factors.

www.thelancet.com/infection Vol 21 July 2021

There are four dengue viruses. While infection with one serotype is generally believed to induce lifelong immunity, subsequent infection with other serotype may enhance disease.

Clinical predictors of severe dengue: a systematic review and meta-analysis

Results: We included 143 articles in the meta-analysis from a total of 13 090 articles retrieved from the literature search. The risk factors of severe dengue were: being a child [*OR* = 1.96; 95% confidence interval (*CI*): 1.22–3.13], secondary infection (*OR* = 3.23; 95% *CI*: 2.28–4.57), and patients with pre-existing diabetes (*OR* = 2.88; 95% *CI*: 1.72–4.81) and renal disease (*OR* = 4.54; 95% *CI*: 1.55–13.31). Warning signs strongly associated with severe disease were increased haematocrit with a concurrent decrease in platelet count (*OR* = 5.13; 95% *CI*: 1.61–16.34), abdominal pain (*OR* = 2.00; 95% *CI*: 1.49–2.68), lethargy (*OR* = 2.73; 95% *CI*: 1.05–7.10), vomiting (*OR* = 1.80; 95% *CI*: 1.43–2.26), hepatomegaly (*OR* = 5.92; 95% *CI*: 3.29–10.66), ascites (*OR* = 6.30; 95% *CI*: 3.75–10.60), pleural effusion (*OR* = 5.72; 95% *CI*: 3.24–10.10) and melena (*OR* = 4.05; 95% *CI*: 1.64–10.00).

Tsheten *et al. Infect Dis Poverty* (2021) 10:123

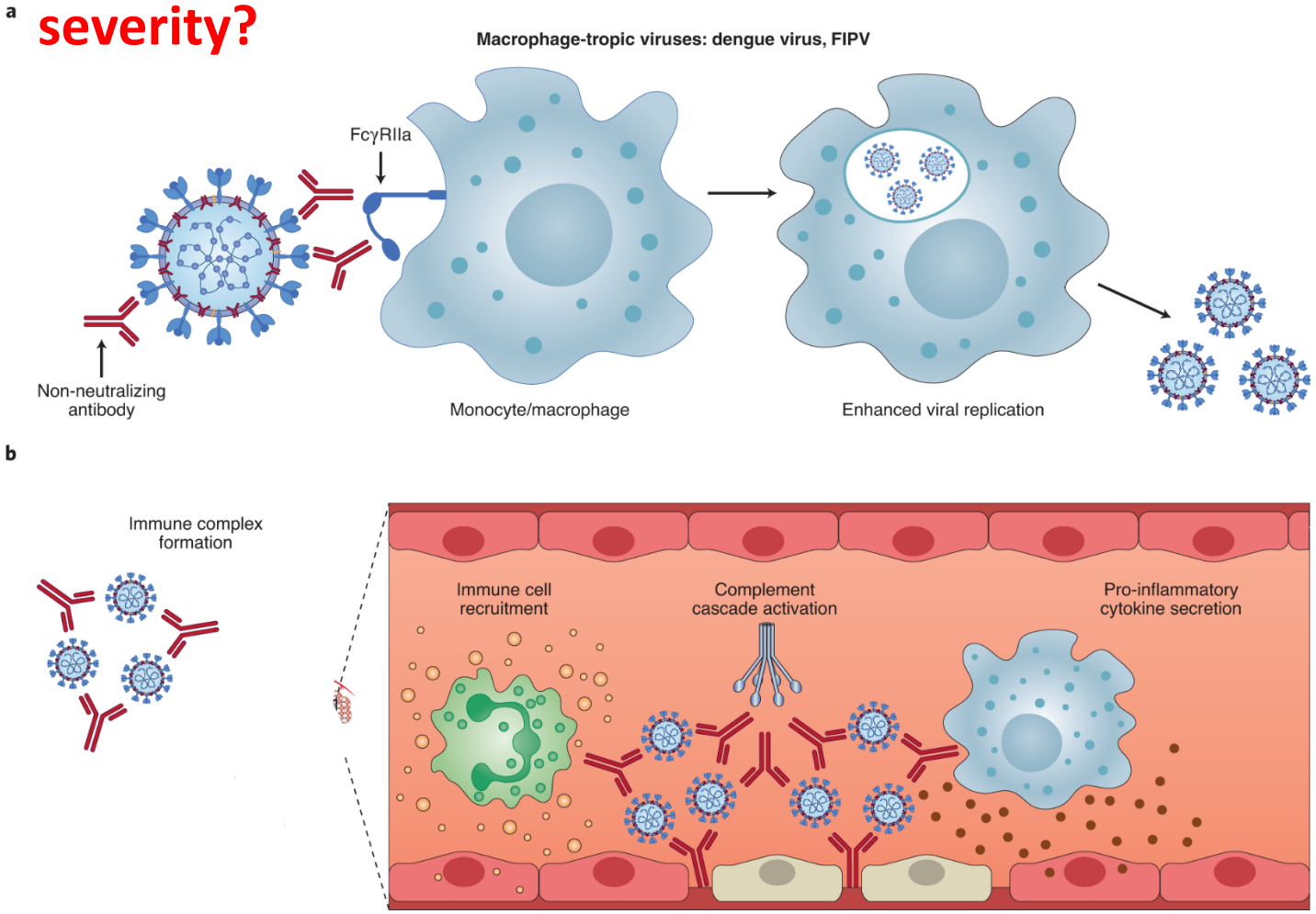
Benefits and risks of the Sanofi-Pasteur dengue vaccine: Modeling optimal deployment

NEIL M. FERGUSON , ISABEL RODRÍGUEZ-BARRAQUER, ILARIA DORIGATTI, LUIS MIER-Y-TERAN-ROMERO, [...], AND DEREK A. T. CUMMINGS +1 authors Authors Info & Affiliations

The first approved dengue vaccine has now been licensed in six countries. We propose that this live attenuated vaccine acts like a silent natural infection in priming or boosting host immunity. A transmission dynamic model incorporating this hypothesis fits recent clinical trial data well and predicts that vaccine effectiveness depends strongly on the age group vaccinated and local transmission intensity. Vaccination in low-transmission settings may increase the incidence of more severe "secondary-like" infection and, thus, the numbers hospitalized for dengue. In moderate transmission settings, we predict positive impacts overall but increased risks of hospitalization with dengue disease for individuals who are vaccinated when seronegative. However, in high-transmission settings, vaccination benefits both the whole population and seronegative recipients. Our analysis can help inform policy-makers evaluating this and other candidate dengue vaccines.

DNDi
Drugs for Neglected Diseases *initiative*

How do pre-existing antibodies to the previous dengue virus lead to increased disease severity?



Epidemiological risk factors associated with high global frequency of inapparent dengue virus infections

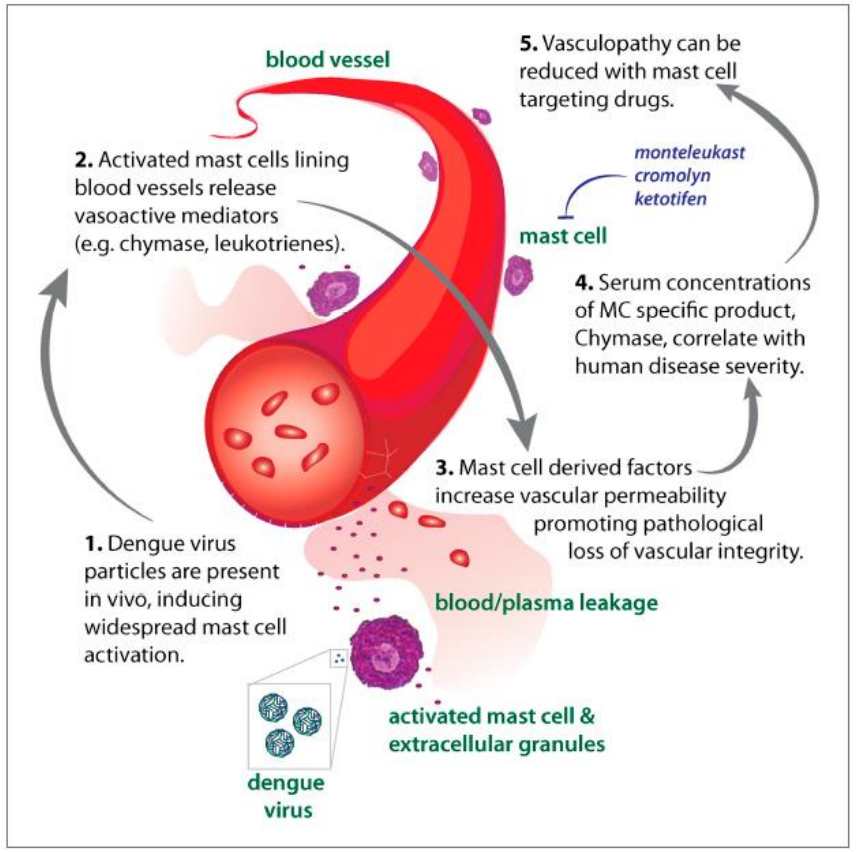
Laura Grange[1,2], Etienne Simon-Loriere[1,2], Anavaj Sakuntabhai[1,2], Lionel Gresh[3], Richard Paul[1,2] and Eva Harris[4]**

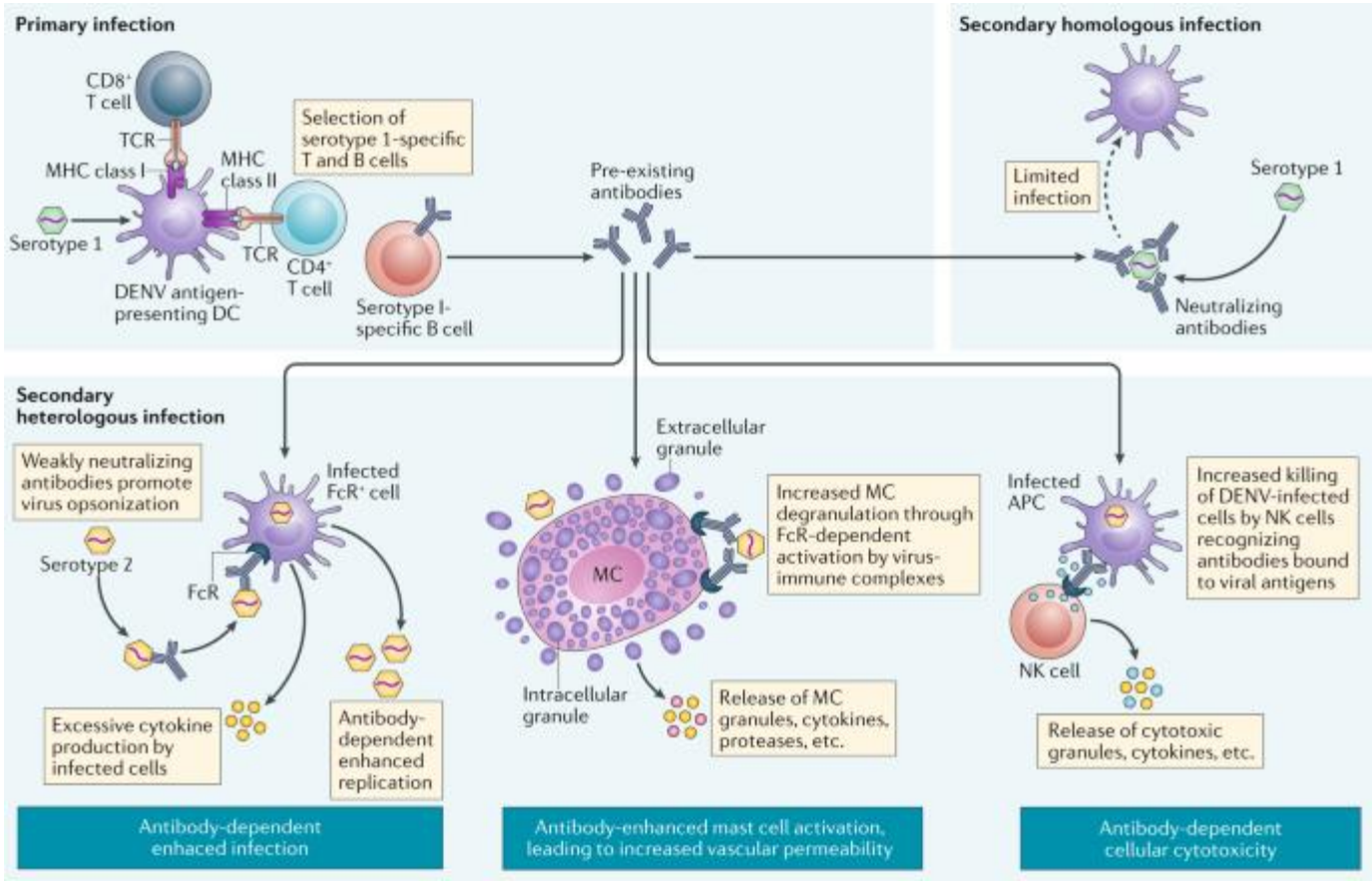
Dengue is a major international public health concern, and the number of outbreaks has escalated greatly. Human migration and international trade and travel are constantly introducing new vectors and pathogens into novel geographic areas. Of particular interest is the extent to which dengue virus (DENV) infections are subclinical or inapparent. Not only may such infections contribute to the global spread of DENV by human migration, but also seroprevalence rates in naïve populations may be initially high despite minimal numbers of detectable clinical cases. As the probability of severe disease is increased in secondary infections, populations may thus be primed, with serious public health consequences following introduction of a new serotype. In addition, pre-existing immunity from inapparent infections may affect vaccine uptake, and the ratio of clinically apparent to inapparent infection could affect the interpretation of vaccine trials. We performed a literature search for inapparent DENV infections and provide an analytical review of their frequency and associated risk factors. Inapparent rates were highly variable, but "inapparent" was the major outcome of infection in all prospective studies. Differences in the epidemiological context and type of surveillance account for much of the variability in inapparent infection rates. However, one particular epidemiological pattern was shared by four longitudinal cohort studies: the rate of inapparent DENV infections was positively correlated with the incidence of disease the previous year, strongly supporting an important role for short-term heterotypic immunity in determining the outcome of infection. Primary and secondary infections were equally likely to be inapparent. Knowledge of the extent to which viruses from inapparent infections are transmissible to mosquitoes is urgently needed. Inapparent infections need to be considered for their impact on disease severity, transmission dynamics, and vaccine efficacy and uptake.

Its not just the antibody concentrations that matter. Quality of the antibodies matter too:

1. Their specificity: recognition of common areas of a
2. Their ability to activate complement, induce phagocytosis (by opsonization), ability to activate NK cells

Mast cells, inflammatory mediators and immune complexes in vascular leak





(St John et al, eLIFE, 2013 and St John, Nature Reviews Immunology, 2019)

DNDi
Drugs for Neglected Diseases *initiative*

How do we find safe and effective drugs for dengue?

A hospital ward in the dengue outbreak in Sri Lanka 2017
Photo: courtesy DR. Lakkumar Fernando

We need drugs that prevent progression to severe dengue

Drugs for treatment for dengue

Drugs that have undergone clinical trials

Antivirals

- Celgosivir
- Balapiravir

Host directed therapies

- Chroloquine
- Lovastatin
- Prednisolone
- Dexamethasone
- Rupatadine
- Montelukast

Ongoing clinical trials with repurposed and new drugs

NITD-688, a pan-serotype inhibitor of the dengue virus NS4B protein, shows favorable pharmacokinetics and efficacy in preclinical animal models

STEPHANIE A. MOQUIN, OLIVER SIMON, RATNA KARUNA, SURESH B. LAKSHMINARAYANA, [...], AND FENG GU +34 authors Authors Info & Affiliations

Article | Published: 06 October 2021

A pan-serotype dengue virus inhibitor targeting the NS3–NS4B interaction

Ketotifen as a Treatment for Vascular Leakage During Dengue Fever

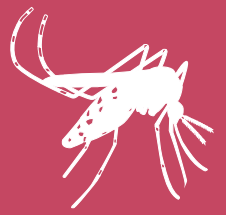
Ketotifen as a Treatment for Vascular Leakage During Dengue Fever (KETODEN)

Sponsors

Lead Sponsor: National University Hospital, Singapore

Collaborator: Duke-NUS Graduate Medical School
Singapore General Hospital

Metformin as adjunctive therapy for dengue in overweight and obese patients: a protocol for an open-label clinical trial (MeDO)



DENGUE

TACKLING A RAPIDLY SPREADING CLIMATE-SENSITIVE DISEASE THROUGH SOUTH-SOUTH COLLABORATION

FACTS

3.9 billion
people at risk

390 million
people infected annually

85%
increase in number of cases from 1990 to 2019

CHALLENGES

- **Most prevalent** mosquito-borne viral disease
- **Climate sensitive:** rising burden of disease
- **No existing treatments for uncomplicated dengue fever** to prevent progression to severe disease and complications

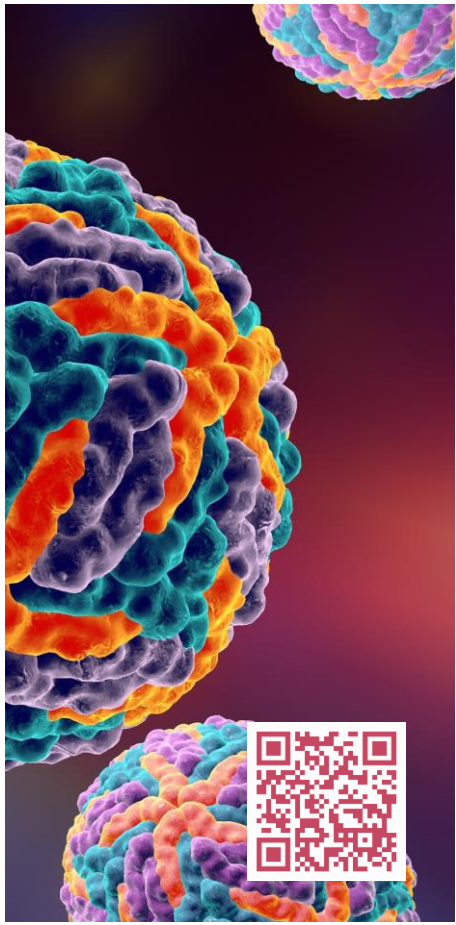
OPPORTUNITIES

- **Window of opportunity** to meet growing medical need
- **Well-defined populations** for clinical trials and endpoints to define success
- **Opportunities in small-molecule drugs and/or biologicals**
- **COVID-19 learnings** and opportunities for cross-fertilization

OUR GOALS

2021- 2028: Advance treatment solutions that can prevent progression to severe disease and reduce burden on public health systems

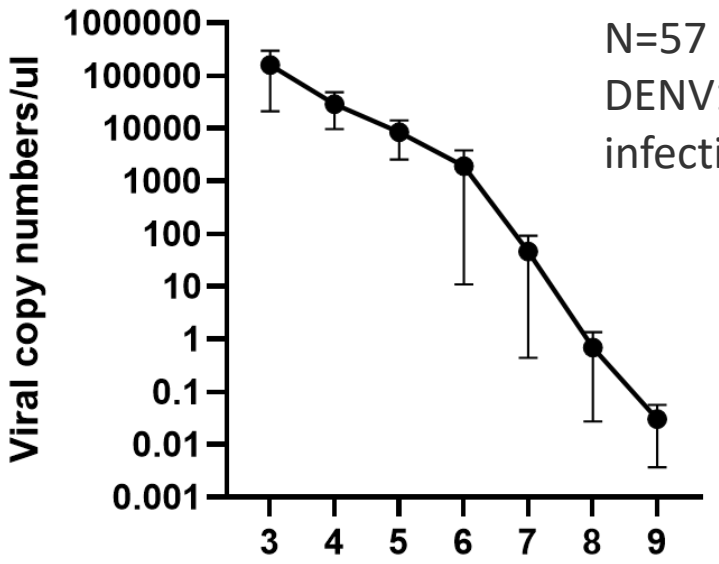
- Together with leaders in endemic countries, coordinate **public-private partnerships for dengue R&D**
- Accelerate evaluation of **candidate repurposing agents** as well as **novel treatments,** in monotherapy and in combination
- **Antiviral + host-directed therapy combination**, to be deployed with rapid diagnostic tests at point of care
- **Affordable, sustainable, and adapted** for use in resource-limited settings, suitable for children/adults/elderly



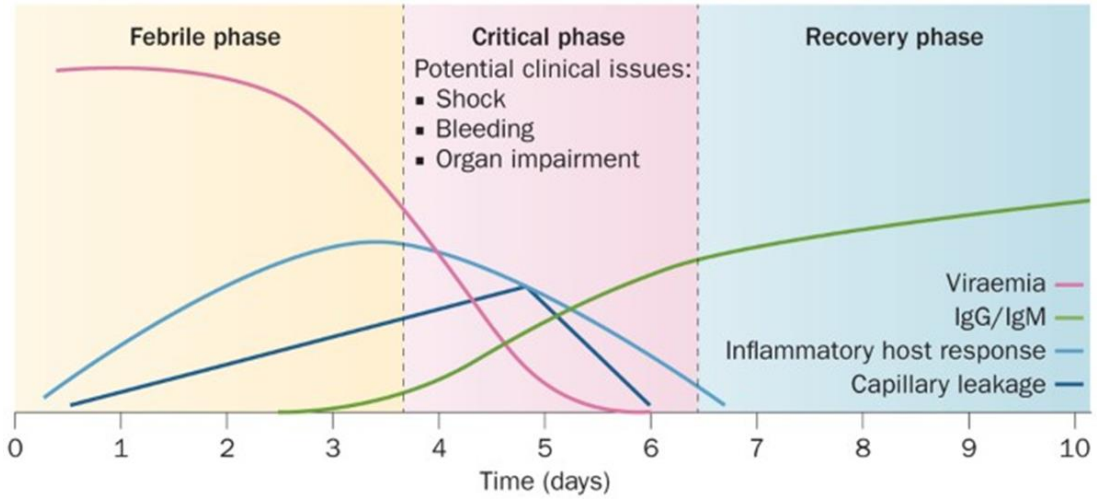
MAIN PARTNERS: *Ministry of Health Malaysia, Siriraj Hospital Faculty of Medicine - Mahidol University - Thailand, Oswaldo Cruz Foundation (Fiocruz) - Brazil, Translational Health Science and Technology Institute - India*

DNDi
Drugs for Neglected Diseases *initiative*

DENGUE STRATEGY



N=57
DENV1 and DENV2 infection



Both DAAs and HDTs will have to be given fairly early in illness.

Direct acting antivirals: repurposing

- Reduce/inhibit viral replication and reduction of NS1
- Fast delivery of a safe and effective treatment

Host directed therapies: repurposing

- Mast cell products: proteases, platelet activating factor, leukotrienes, serotonin, other lipid mediators
- Platelet products: Inflammatory cytokines
- Macrophage products: inflammatory cytokines and lipid mediators

DNDi
Drugs for Neglected Diseases *initiative*

Dengue alliance: to develop a treatment which is co-created, co-owned and co-funded by partners

Preclinical testing

- In vitro testing for antivirals: antiviral assays with different cell lines for different DENV serotypes
- Host directed therapies

In vivo testing: mouse models

Clinical trials

- Establishing a clinical network
- POC trials
- Phase II and III trials

Mahidol University - Siriraj Hospital, Bangkok, Thailand
Dr. Panisadee Avirutnan,
Prof. Prasert Auewarakul

Translational Health Science and Technology Institute (THSTI), Faridabad, India
Dr. Guruprasad Medigeshi,
Dr. Sweety Samal

Institute for Medical Research National Institutes of Health, Selangor, Malaysia
Datuk Dr Muhammad Radzi Abu Hassan
Dr Ami Fazlin Mohamed
Head of Herbal Medicine Research, IMR

FIOCRUZ
Rio de Janeiro, Brazil
Dr. Thiago Moreno,
Dr. Ernesto Marques

UFMG, Brazil
Prof. Mauro Teixeeira
Prof. Vivian Vasconcelos Costa

DNDi
Drugs for Neglected Diseases *initiative*

facebook.com/dndi.org
youtube.com/dndiconnect
twitter.com/dndi
instagram.com/drugsforneglecteddiseasesinitiative
linkedin.com/company/dndi

DNDi
Drugs for Neglected Diseases *initiative*