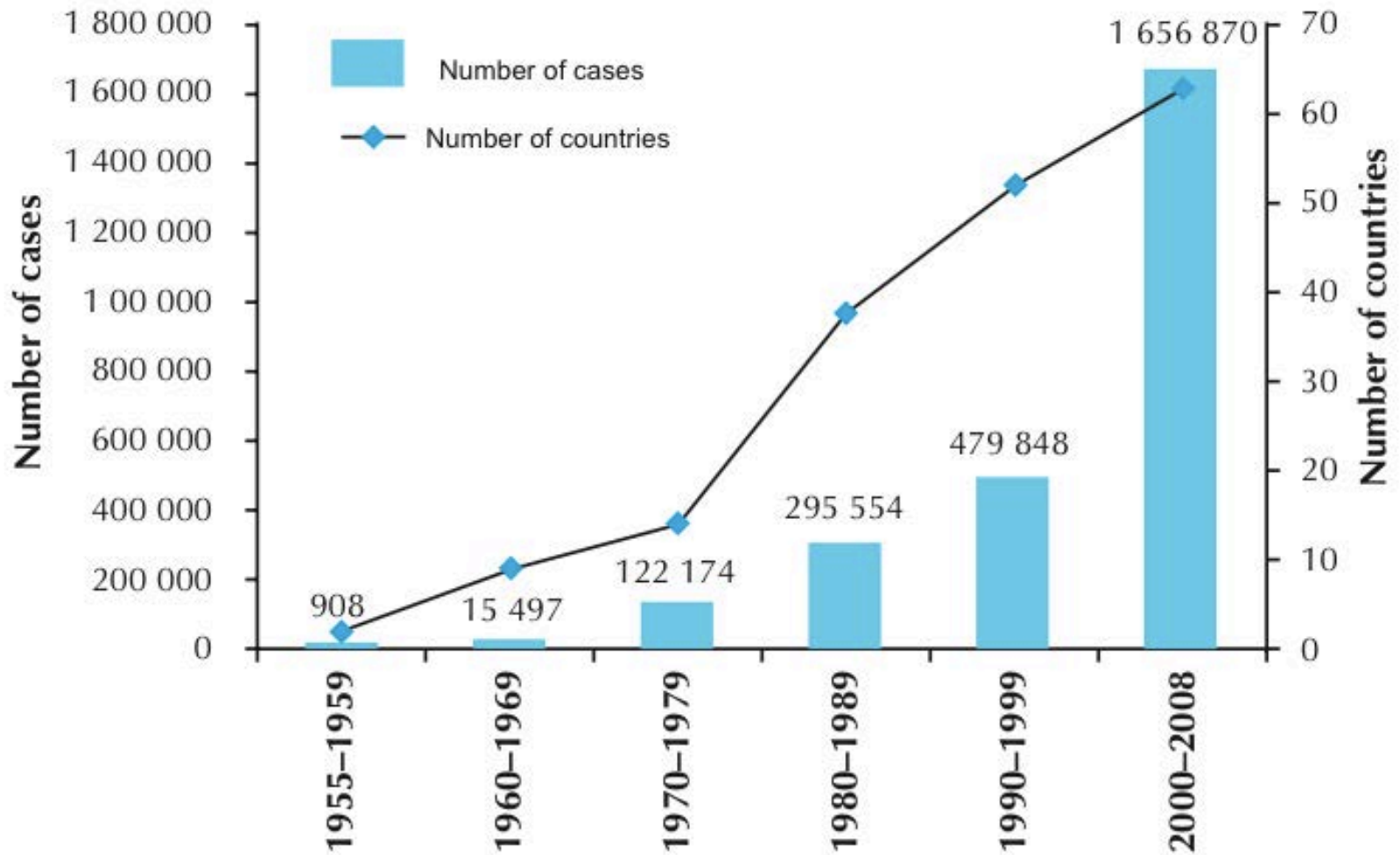


Dengue fever

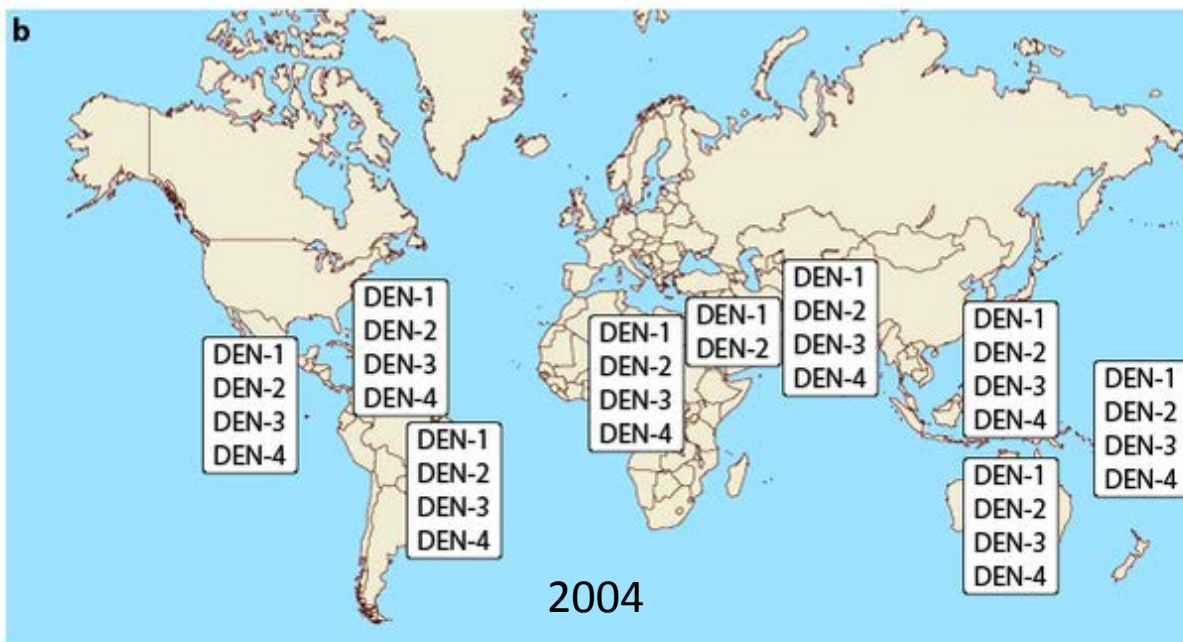
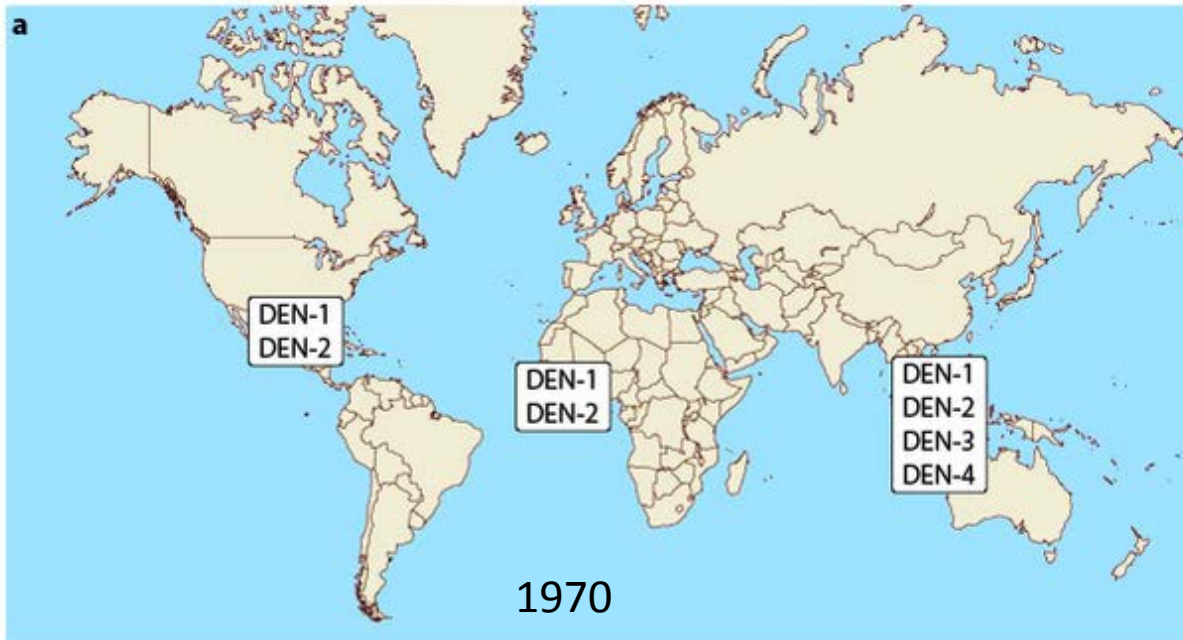


Dr Owen Tsang
Princess Margaret Hospital
31 August 2018
ID forum

World figures







Epidemiology

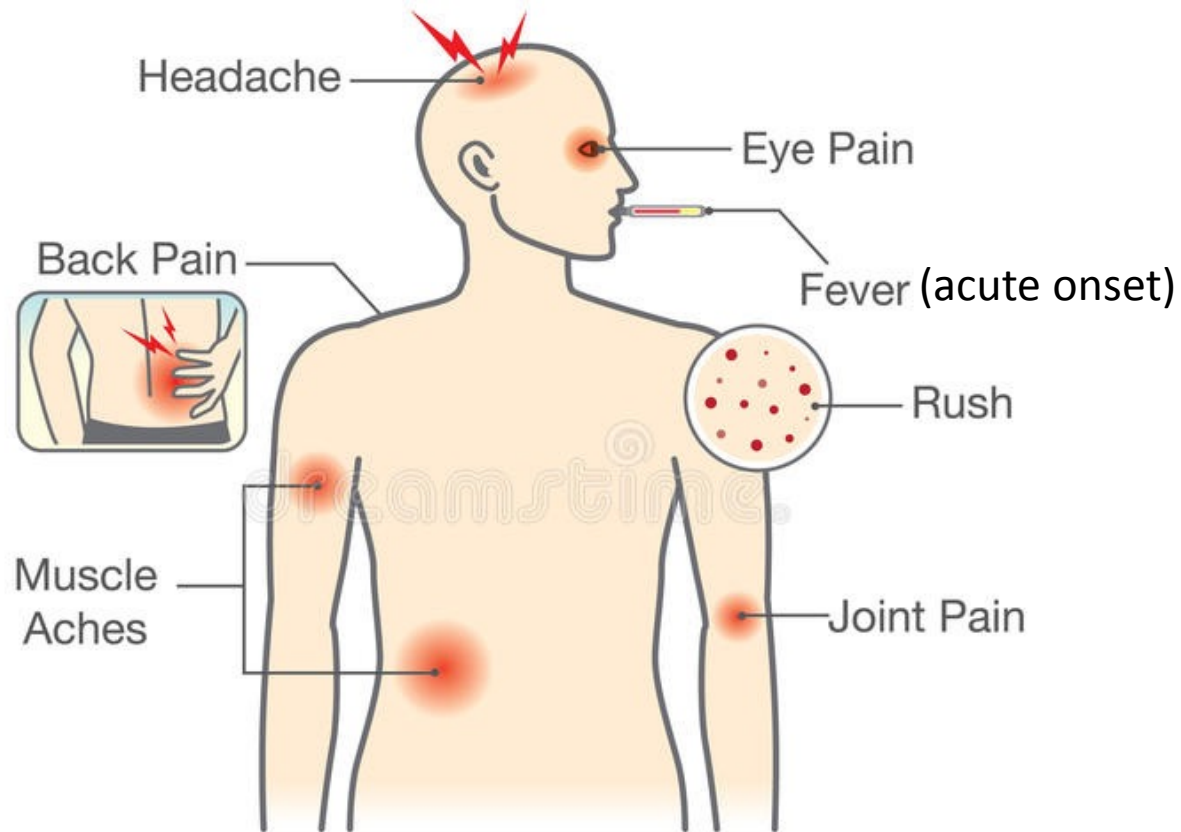
- WHO reports **30x increase** in cases since 1960
- No. of countries reporting epidemic dengue has **increase > 4x** since 1970
- **Half** the world population are at risk
- ~ **50-100 millions** new infections per year
- **Case fatality 1-5% (overall)**, lower in Developed countries
- ~ **75%** global population exposed to dengue are in **Asia-pacific** region

Clinical features of *Arbovirus* related disease

From IEC
Reference: WHO, CDC, CHP, HA Factsheet

	Zika virus	Dengue fever	Chikungunya fever	West Nile virus	Yellow fever	Japanese encephalitis
Mosquito 1° vector	<i>Aedes aegypti</i>	<i>Aedes aegypti</i>	<i>Aedes</i> mosquitos	<i>Culex</i> mosquitoes	<i>Aedes aegypti</i>	<i>Culex tritaeniorhynchus</i>
Incubation period	3 - 12 days	3 - 14 days	1 to 12 days	2-14 days	3 to 6 days	5-15 days
Asymptomatic %	80%	50%	3-28%	Estimated 70-80%	Majority	99%
CF	<ul style="list-style-type: none"> Fever Rash (maculopapular) Muscle and joint pain Conjunctivitis (non-purulent) 	<ul style="list-style-type: none"> Fever Headache Rash Muscle and joint pain Retro-orbital pain Nausea, vomiting Minor Bleeding (Petechiae/ Bruises) 	<ul style="list-style-type: none"> Fever Headache Rash (maculopapular) affecting the trunk and limbs Muscle and joint pain of the wrist, knee, ankle, and small joint, can be severe and debilitating Conjunctivitis Nausea, vomiting 	<ul style="list-style-type: none"> Fever Headache Rash (maculopapular) on the trunk of the body Muscle pain Enlarged lymph node Retro-orbital pain Nausea / vomiting 	<ul style="list-style-type: none"> Fever Headache Muscle pain with prominent backache Shivers Loss of appetite Nausea / vomiting 	<ul style="list-style-type: none"> Fever Headache vomiting
Severe form	<ul style="list-style-type: none"> Rare 	<ul style="list-style-type: none"> Severe abdominal pain persistent vomiting bleeding gums blood in vomit 		<u>Severe form</u> <ul style="list-style-type: none"> Headache High fever Neck stiffness Stupor Disorientation Coma Tremors Convulsions Muscle weakness Paralysis 	<ul style="list-style-type: none"> (15% of cases) Jaundice Abdominal pain Vomiting Bleeding CFR (20-50%) 	<ul style="list-style-type: none"> High fever Headache Neck stiffness Disorientation Coma Seizures Spastic paralysis
Vaccine available	No	Yes a live attenuated (recombinant) tetravalent vaccine, (CYD-TDV, or Dengvaxia®) has been registered in several countries	No	No	Yes (>9m old, visit to affected areas, effective after 10 days)	Yes (inactivated Vero cell culture-derived vaccine (JE-VC) & cell culture-derived live attenuated vaccine)

Symptoms of Dengue fever



ORIGINAL
ARTICLE

Review of dengue fever cases in Hong Kong during 1998 to 2005

Vivien WM Chuang 莊慧敏
TY Wong 黃天佑
YH Leung 梁耀康
Edmond SK Ma 馬紹強
YL Law 羅育龍
Owen TY Tsang 曾德賢
KM Chan 陳啟明
Iris HL Tsang 曾愷玲
TL Que 郭德麟
Raymond WH Yung 翁維雄
SH Liu 劉少懷

Objective To describe the epidemiology, clinical and laboratory findings, and outcomes of patients presenting locally with dengue.

Design Retrospective review of case records.

Setting Public hospitals, Hong Kong.

Patients Medical records of all laboratory-confirmed dengue patients admitted to public hospitals during 1998 to 2005 were reviewed retrospectively.

Results A total of 126 cases were identified, 123 (98%) being dengue fever and three (2%) dengue haemorrhagic fever. One patient who had blood transfusion-acquired dengue fever was highlighted. A total of 116 (92%) cases were 'imported', while 10 (8%) were local. Among the 56 serotypes confirmed by reverse transcription-polymerase chain reaction, dengue virus type 1 was the most

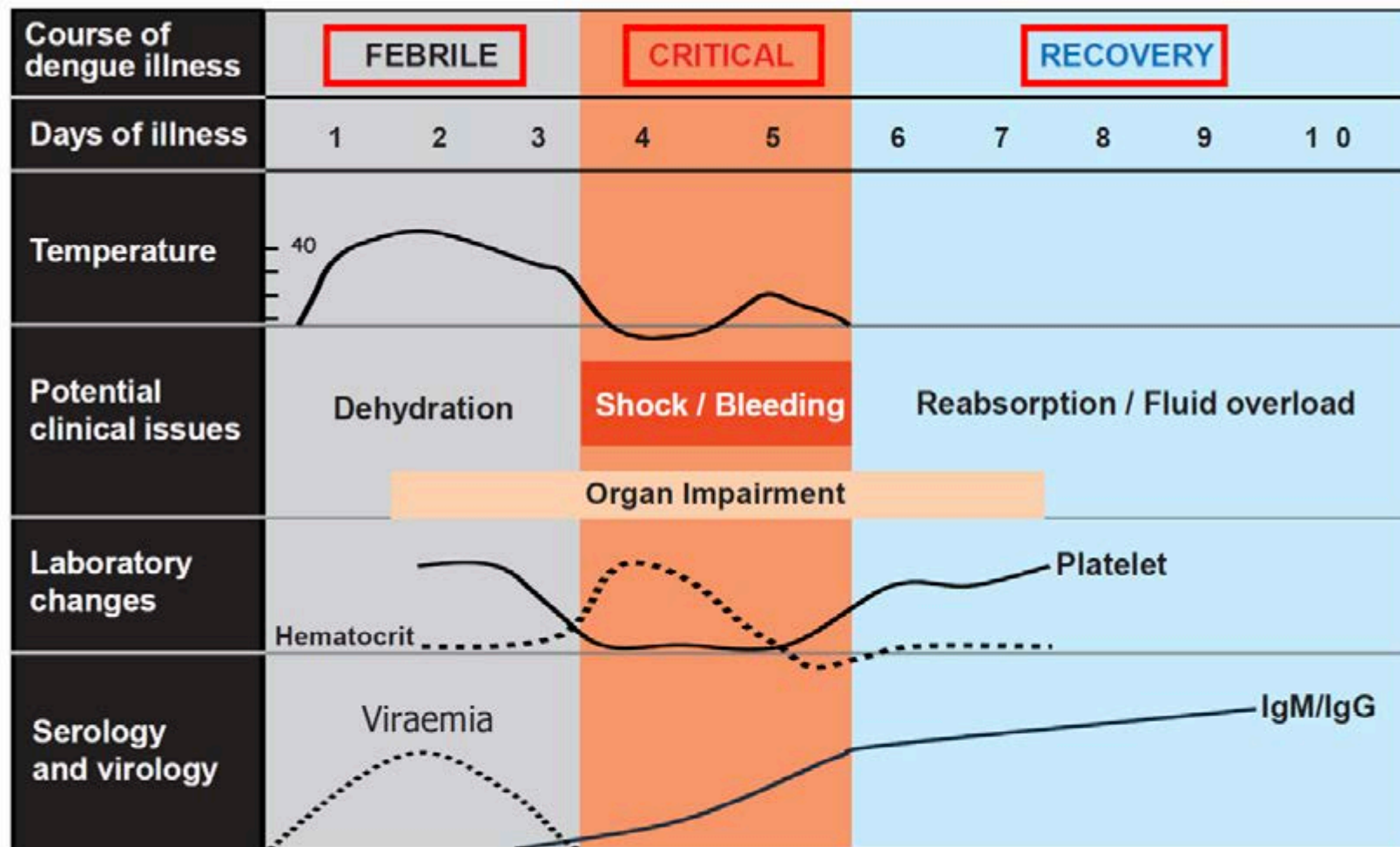
Clinical features of cases in HK

Symptoms	Percentage (N= 124)
Fever	98%
Myalgia	83%
Headache	65%
Skin rash	60%
Fatigue	59%
Dizziness	45%
Retrobulbar pain	34%
GI (nausea, vomiting, diarrhoea)	35%
URT (Dry cough, sore throat)	29%
Epistaxis	10%
Gum bleeding	12%
Hematemesis	2%
Tarry stool	1%
Petechiae	45%
Lymphadenopathy	16%

Laboratory findings

Laboratory findings	Percentage
Thrombocytopenia	86%
Lymphopenia	69%
Neutropenia	78%
Atypical lymphocytes	75%
Prolonged APTT	51%
Elevated AST	91%
Elevated ALT	80%
Hypoalbuminaemia	28%

Clinical course



Dengue case classification by severity

Dengue ± warning signs

Severe dengue



Criteria for dengue ± warning signs

Probable dengue

Live in/travel to dengue endemic area. Fever and 2 of the following criteria:

- Nausea, vomiting
- Rash
- Aches and pains
- Tourniquet test positive
- Leucopenia
- Any warning sign

Laboratory confirmed dengue

(important when no sign of plasma leakage)

Warning signs*

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy; restlessness
- Liver enlargement >2cm
- *Laboratory*: Increase in HCT concurrent with rapid decrease in platelet count

* Requiring strict observation and medical intervention

Criteria for severe dengue

1. Severe plasma leakage

leading to:

- Shock (DSS)
- Fluid accumulation with respiratory distress

2. Severe bleeding

as evaluated by clinician

3. Severe organ involvement

- Liver: AST or ALT ≥ 1000
- CNS: Impaired consciousness
- Heart and other organs

Dengue Case Management

Assessment

Presumptive Diagnosis:

Live in / travel to endemic area plus

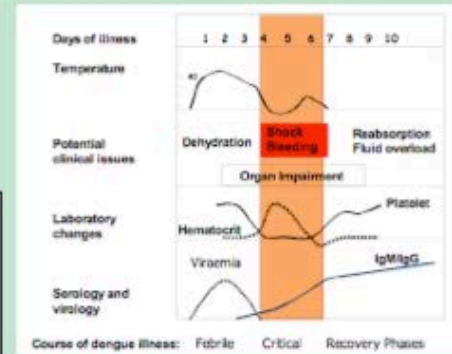
Fever and two of the following:

- Anorexia and nausea
- Rash
- Aches and pains
- Warning signs
- Leucopenia
- Tourniquet test positive

Lab.confirmed dengue
(important when no sign of plasma leakage)

Warning signs:

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy; restlessness
- Liver enlargement >2cm
- Laboratory: Increase in HCT concurrent with rapid decrease of platelet count



Classification

negative

Co-existing conditions
Social circumstances

negative

Dengue without warning signs

Group A
May be sent home

positive

Dengue with warning signs

Group B
Referred for in-hospital care

positive

Severe Dengue

Group C
Require emergency treatment

PMH case



PMH cases



PMH case



PMH case



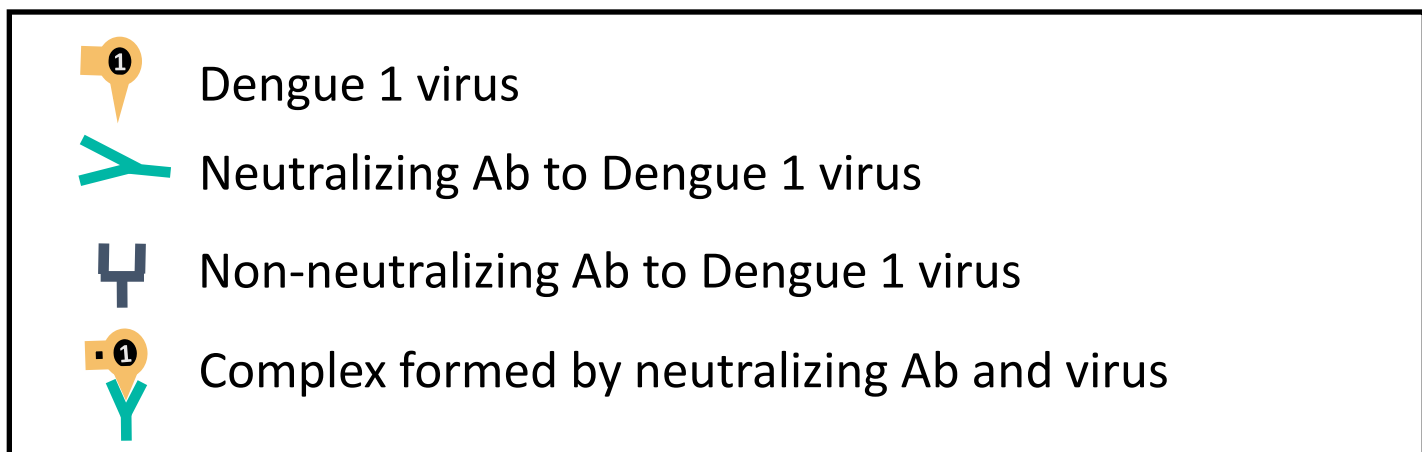
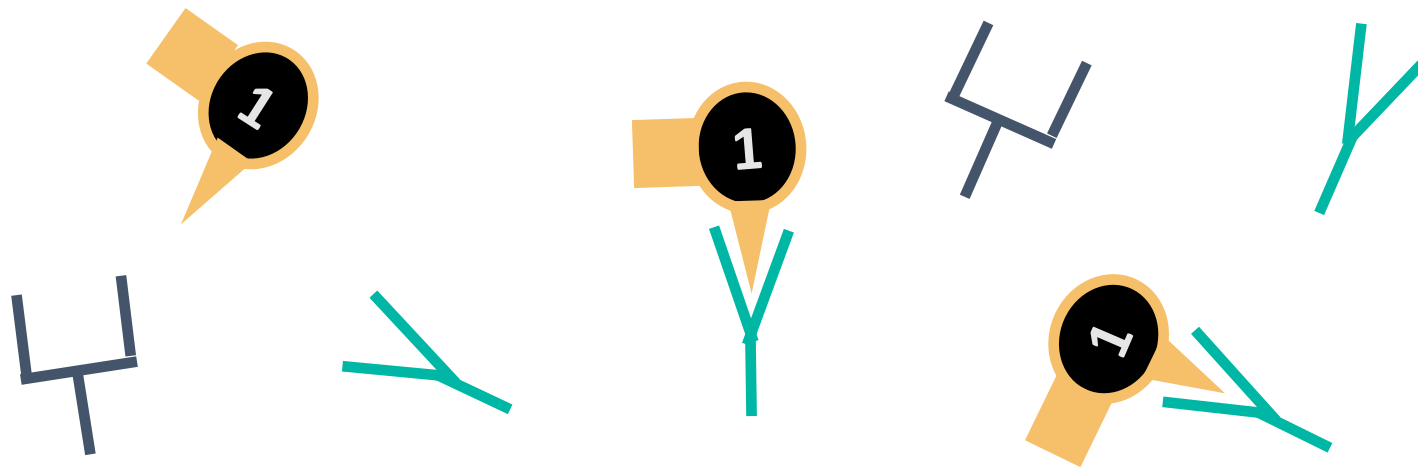
Clinical pearls

- **Leucopenia** followed by progressive **thrombocytopenia**
- **Atypical lymphocyte** is common
- A rising **HCT** accompanying **progressive thrombocytopenia** is critical phase.
- In the absence of a baseline HCT, a HCT > **40%** in **female** & > **46%** in **male** should raise the suspicion of **plasma leakage**.
- Evidence of **increased vascular permeability**: pleural effusions, ascites

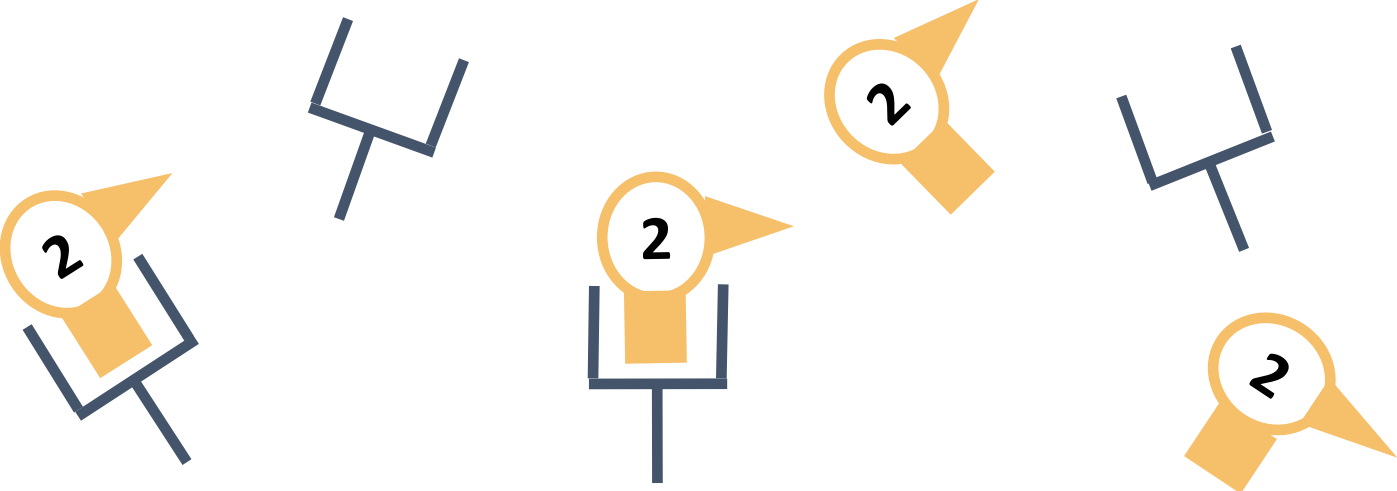
Why 2nd Dengue infection with a different serotype has a higher chance of having complications

Antibody dependent enhancement

STEP 1- Homologous Ab Form Non-infectious Complexes

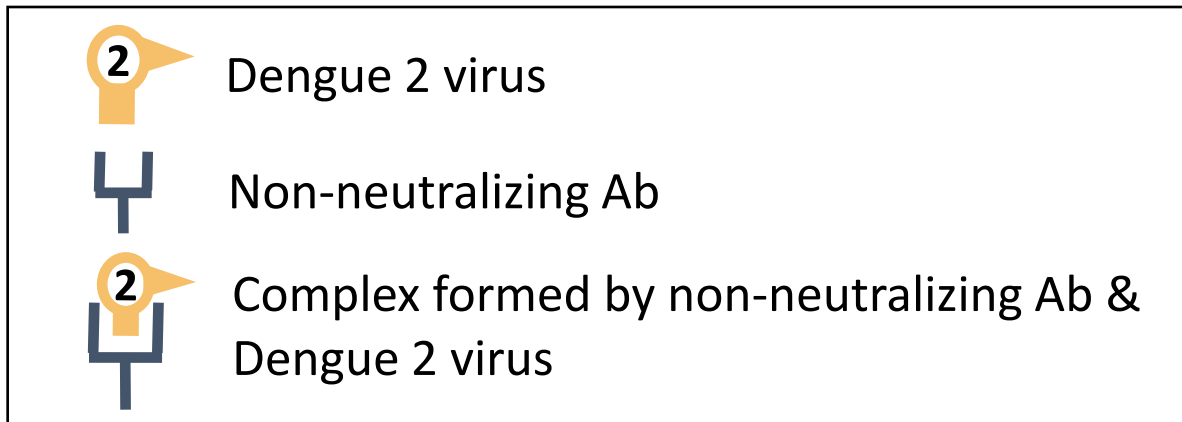
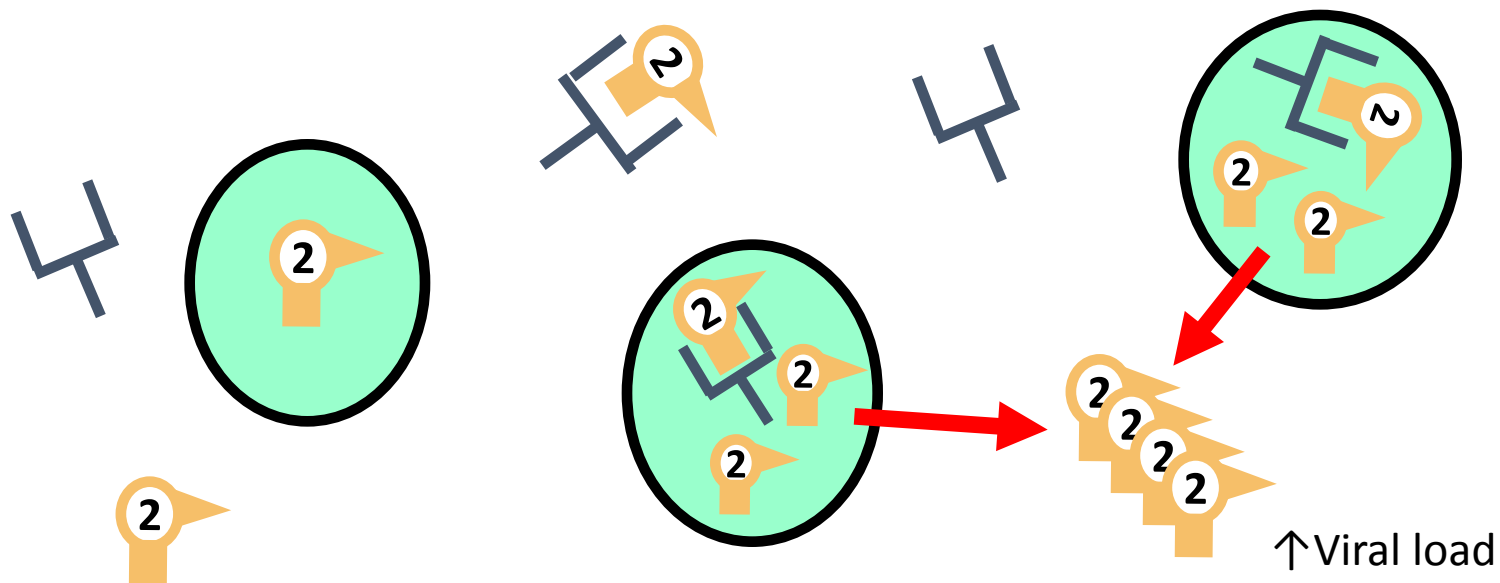


STEP2- Heterologous Ab of first serotype infection form Infectious Complexes with second serotype

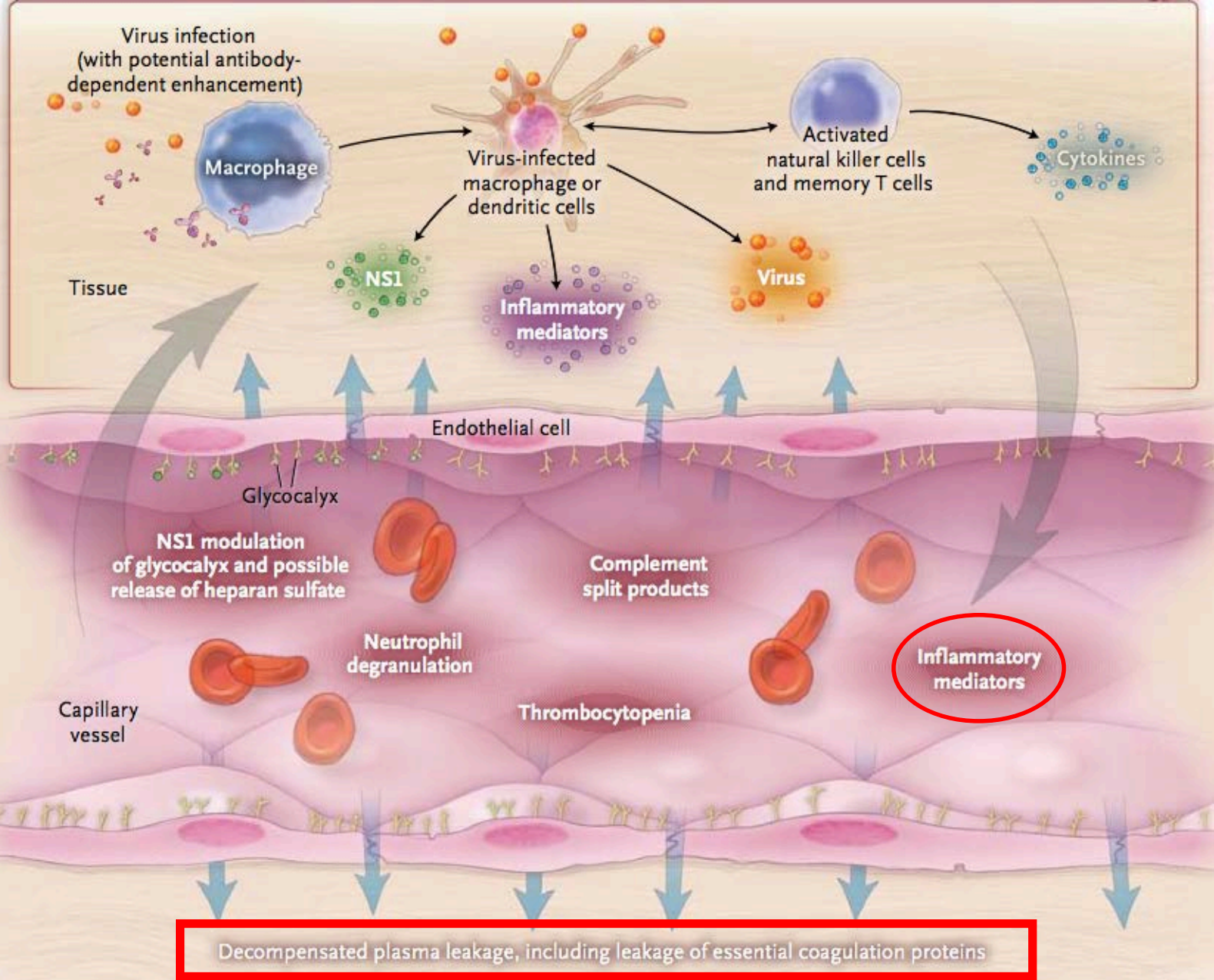


	Dengue 2 virus
	Non-neutralizing Ab to Dengue 1 virus
	Complex formed by non-neutralizing Ab and virus

STEP3 - Heterologous Complexes Enter More Monocytes, Where Virus Replicates



STEP4 – pathogenesis



Treatment for dengue

TREATMENT OF DENGUE



Drink plenty of water
to avoid dehydration



Take bed rest



Acetaminophen
can relieve pain & reduce pain

Group A: Sent home

- Criteria:
 - Tolerate oral fluid
 - No warning signs
 - Passing urine regularly
- Treatment:
 - Adequate bed rest
 - Adequate fluid intake
 - PRN paracetamol
- Monitoring:
 - Daily review for progression: decrease WBC, fever resolve, warning signs
 - Advice to return to hospital if warning signs

Group B: with warning sign or coexisting conditions

- Coexisting conditions: pregnancy, infancy, elderly, DM, CRF
- Social conditions: far from hospital, live alone
- Encourage oral fluid, IV fluid (isotonic solution) if not tolerated
- Adjust fluid requirement based on clinical status & HCT, avoid over-hydration
- Monitoring:
 - Vital signs
 - Temperature: esp defervescence
 - Warning signs
 - CBP, HCT
 - Urine output
 - Organ functions

Group C: Require emergency treatment

- Criteria:
 - **Severe plasma leakage** with shock and/or fluid accumulation with respiratory distress
 - **Severe bleeding:** GIB
 - **Severe organ impairment**
- Management of shock
- Support the organs
- If HCT low (<40% in male, < 45% in female): look for bleeding
- If HCT high (> 50%): continue IV fluid replacement
- Give PC or whole blood for hemorrhagic complication

Criteria for hospital discharge

- Absence of fever for 48 hours
- Improve in clinical status:
 - general well-being, appetite,
 - hemodynamic status,
 - urine output,
 - no respiratory distress
- Increasing trend of platelet count
- Stable HCT without IVF

Effect of pregnancy on clinical manifestation of Dengue infection

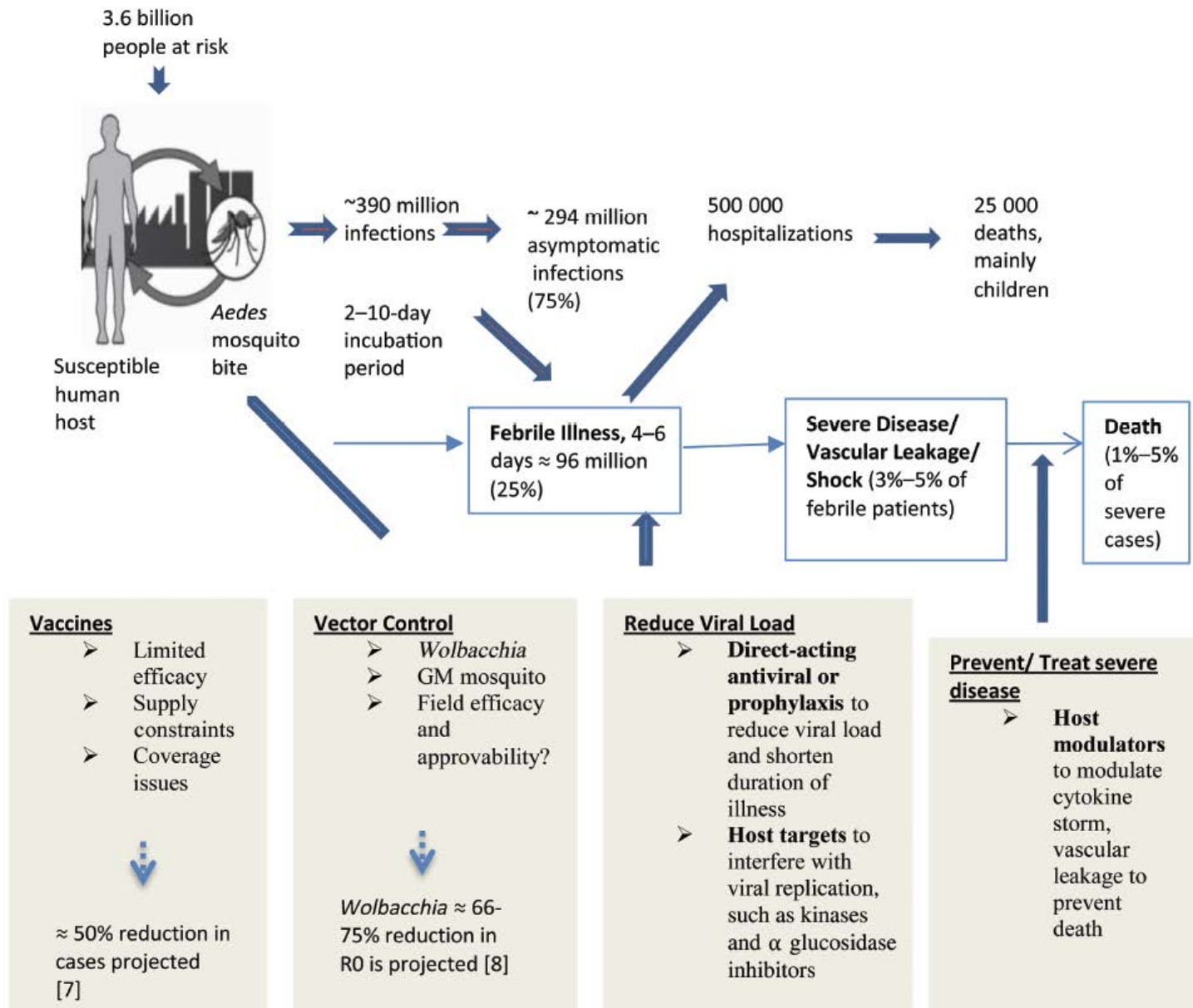
- Physiology of pregnancy
 - Coagulation
 - Hemodilution: Hb lower
 - Cardiovascular system: heart rate ↑, BP lower, pulse pressure wider
- Confuse with others pregnancy complications
 - HELLP syndrome: Hemolysis, Elevated Liver enzyme, Low Platelet
 - Variant of pre-eclampsia pregnancy complication
 - Thrombocytopenia
 - Impaired liver function
 - Capillary leakage

Effect of dengue infection on pregnancy

- On Mother:
 - Maternal death
 - Severe bleeding at time of delivery
 - Abortion
- On Babies:
 - Fetal death: Plasma leakage may compromise placental circulation
 - Premature birth: 13%-55%
 - Neural tube defect
 - Low birth weight
- Vertical transmission:
 - Maternal infection close to delivery: neonate dengue infection
 - Maternal infection early in pregnancy: less fetal damage due to protective maternal Ab

Management in pregnancy

- Considered as “**co-existing condition**” requiring hospital admission
- Clinical **plasma leakage** may be difficult to confirm: ultrasound of the abdomen and chest
- Monitor **change** in CBP, HCT, L/RFT (compare with baseline or previous results)
- Adequate **fluid** replacement
- Monitor **fetal** parameters
- Dengue infection is **not** an indication for termination of pregnancy



Specific anti-virals in clinical trials

Drug	Developer	Phase	Trial site	Current status (end date)
Ivermectin	Mahidol University (RNA helicase inhibitors)	II/III	Thailand	Yet to initiate
UV-4B	Unither Virology	I	?	Yet to initiate
Ribavirin	Guangzhou 8th People's Hospital	II	China	Ongoing (December 2015)
Low statin	Oxford University Clinical Research Unit & Wellcome Trust	I	Vietnam	Ongoing [90] (January 2015)
Chloro quine	University of Sao Paulo	I/II	Brazil	? (June 2009)
Chloro quine	Oxford University Clinical Research Unit & Wellcome Trust	I	Vietnam	Completed [91] (July 2008)
Predn isolone	Oxford University Clinical Research Unit & Wellcome Trust	I	Vietnam	Completed [92] (January 2011)
Carica folia extract	Fr. Muller Homeopathic Medical College	I	India	Completed ^{NR} (December 2013)
Balapiravir	Hoffmann-La Roche	I	Vietnam	Completed [93] (April 2011)
Celg osivir	Singapore Gen Hospital & Duke-NUS Graduate Med School	I/II	Singapore	Completed [94] (July 2013)

Vaccines for Dengue virus

Dengue

Acambis and Sanofi Pasteur

Live, attenuated chimeric dengue–yellow fever

WRAIR and GlaxoSmithKline

Live, attenuated

NIH, Biologicals E (India), Panacea (India)

Live, attenuated chimeric dengue–dengue

Mahidol University (Bangkok)

Live, attenuated

CDC, Inviragen, Shantha (India)

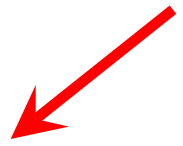
Live, attenuated chimeric dengue–dengue

Hawaii Biotech

Recombinant, subunit

U.S. Navy

DNA



Approved in Mexico, the Philippines, Brazil, El Salvador, Paraguay and Costa Rica.

Efficacy of Recombinant live-attenuated tetravalent Dengue vaccines

Year	Phase	Setting	Cases	Schedule	FU	Efficacy
2012	2b	Thailand	4002 cases, 4-11 yo	Injection at 0, 6 & 12m	25m	Overall: 30.2% DEN-1: 55.6% DEN-2: 9.2% DEN-3: 75.3% DEN-4: 100%
2014	3	5 Asian countries	10275 cases, 2-14 yo	Injection at 0, 6 & 12m	25m	Overall: 56.3% DEN-1: 54.5% DEN-2: 34.7% DEN-3: 65.2% DEN-4: 72.4% Vs DHF: 80% Vs severe disease : 70%
2014	3	5 Latin American countries	20869 cases, 9-16 yo	Injection at 0, 6 & 12m	25m	Overall: 64.7% DEN-1: 50.3% DEN-2: 42.3% DEN-3: 74% DEN-4: 77.7% Vs severe disease : 95.5% Vs admission: 80.3%

Subsequent studies on Dengue vaccine

- Children > 9 YO is more efficacious in preventing dengue, hospitalization and severe dengue
- Children < 9 YO, especially among 2-5 YO, the vaccine causes more hospitalization and severe dengue
- Dengue vaccine is effective in those who are **seropositive**

WHO position statement on Dengue vaccine

- The 1st Dengue vaccine: Dengvaxia[®] (CYD-TDV) has been licensed
- Use in individuals 9-45 years of age living in endemic areas, > 50% seroprevalence rate.
- live recombinant tetravalent dengue vaccine, given as a 3-dose series on a 0/6/12 month schedule
- No recommendation in pregnant and lactating women due to lack of sufficient data in this population. However, the limited data collected during the clinical trials on inadvertent immunization of pregnant women have yielded no evidence of harm to the fetus or pregnant woman
- No recommendation in HIV or immunocompromised individuals.
- No recommendation for vaccination of travellers or health-care workers

RESEARCH ARTICLE

In a randomized trial, the live attenuated tetravalent dengue vaccine TV003 is well-tolerated and highly immunogenic in subjects with flavivirus exposure prior to vaccination

Stephen S. Whitehead^{1†}, Anna P. Durbin^{2†}, Kristen K. Pierce³, Dan Elwood², Benjamin D. McElvany³, Ellen A. Fraser³, Marya P. Carmolli³, Cecilia M. Tibery², Noreen A. Hynes², Matthew Jo², Janece M. Lovchik², Catherine J. Larsson³, Elena A. Doty³, Dorothy M. Dickson³, Catherine J. Luke¹, Kanta Subbarao¹, Sean A. Diehl^{3*}, Beth D. Kirkpatrick^{3*}

- Phase 1 study
- 58 flavivirus exposed volunteers
- Given 2 doses of TV003 with 6 m apart

Table 5. Frequency of seropositivity to each DENV serotype after one or two doses of TV003 in subjects who were flavivirus-experienced or -naïve^a prior to vaccination.

Seropositivity		DENV-1	DENV-2	DENV-3	DENV-4
Dose 1	FV-experienced (n = 38)	89%	95% ¹	97%	100%
	FV-naïve (n = 58) ^a	95%	67%	98%	100%
Dose 2	FV-experienced (n = 33)	82%	97% ²	94%	100%
	FV-naïve (n = 44) ^a	75%	70%	91%	98%

Comparison of cumulative seropositivity for each DENV serotype post-TV003 between subjects who were flavivirus-exposed versus flavivirus-naïve at Day 0.

¹ Dose 1 unadjusted *P*-value = 0.0019.

² Dose 2 unadjusted *P*-value = 0.0057.

Significant values in **BOLD** (At *P* < 0.03 level after adjusting for multiple comparisons) by Chi-square exact test of proportions.

^aTV003 vaccine response data in flavivirus-naïve subjects are from ref. [19], and include both cohorts (CIR279 and CIR268) from that study.

<https://doi.org/10.1371/journal.pntd.0005584.t005>

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 Anna P. Durbin^{3†}

- Phase II study, RCT
- Given either TV003 (N=21) or placebo (N=20)
- Challenge with DEN 2 virus 6 months later
- 100% protection vs DEN 2 viremia, rash & neutropenia after Den 2 virus challenge

Summary

- > ½ of the world population is at risk for Dengue infection
- No. of dengue infections & dengue endemic countries is increasing
- Clinical features of dengue is non-specific
- **Leucopenia** followed by **thrombocytopenia** with presence of **atypical lymphocytes** are suggestive
- Supportive management & organs support are important
- Special precaution for pregnant lady because of clinical & laboratory challenge
- Live-attenuated tetravalent vaccines provide good efficacy for children in endemic areas

Thanks

