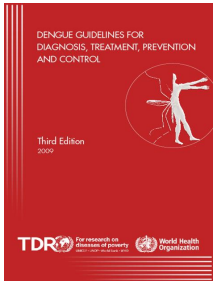
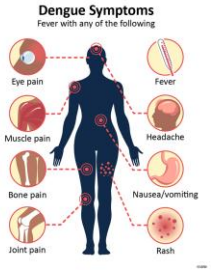
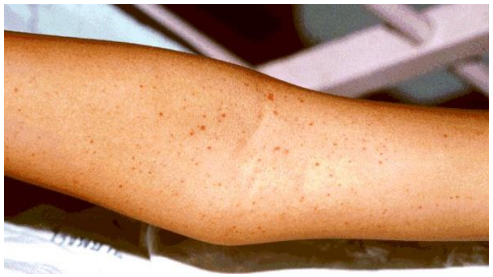
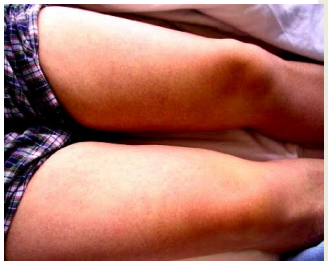
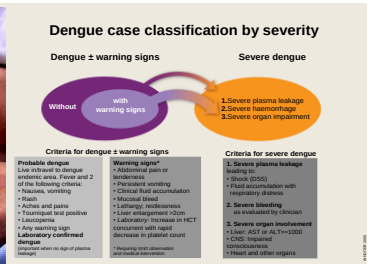








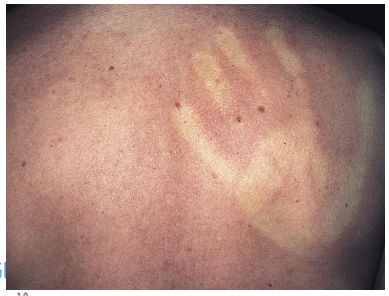


Dengue

Emanuele Nicastri

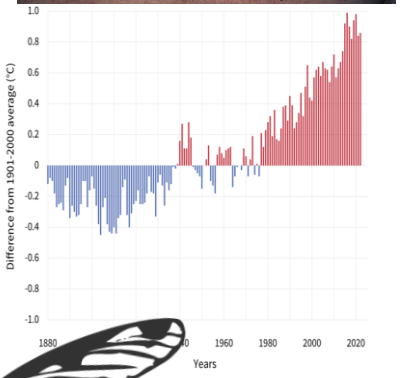
Istituto Nazionale per le Malattie Infettive L. Spallanzani IRCCS

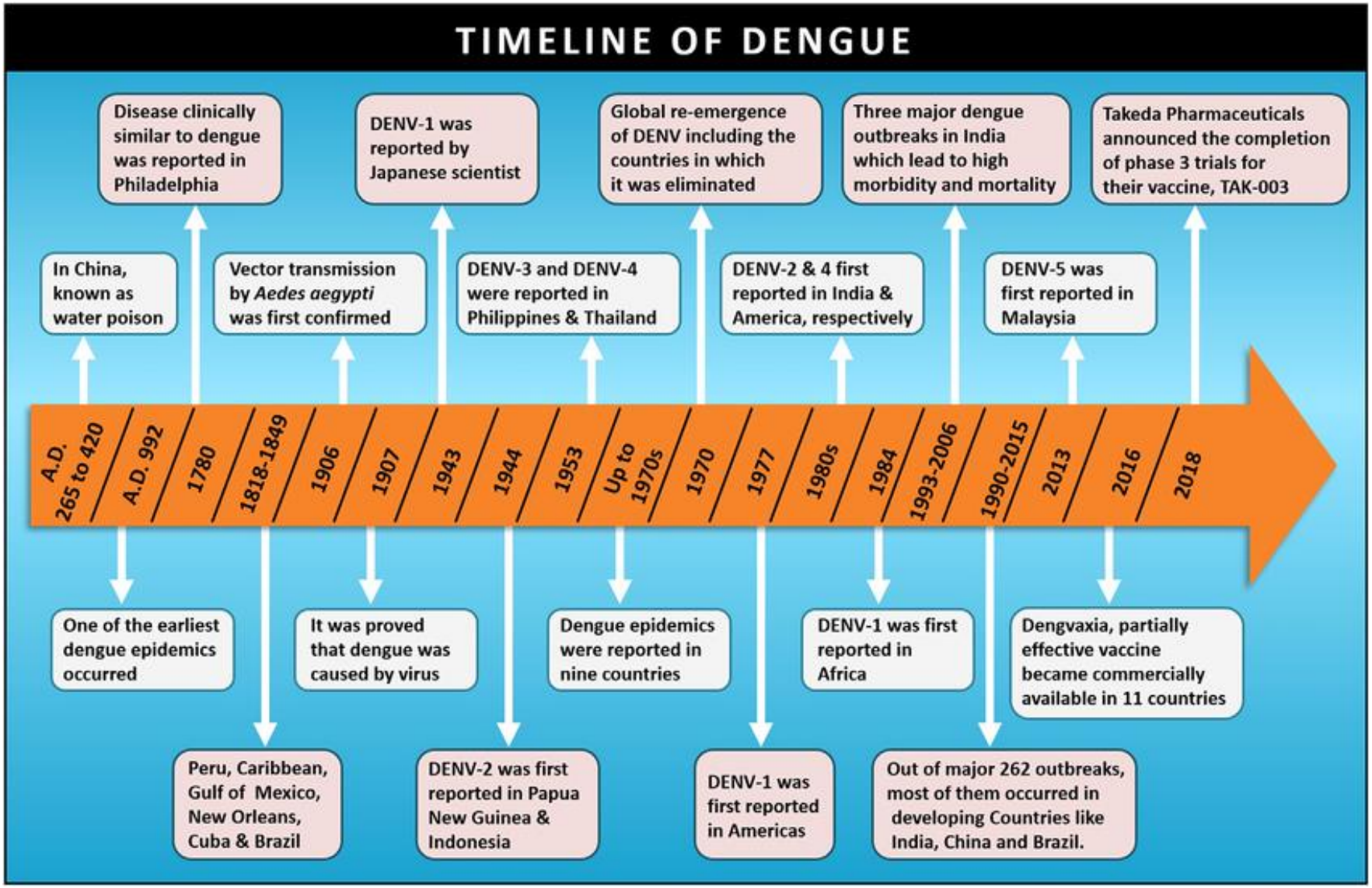
emanuele.nicastri@inmi.it



GIORNATE INFETTIVOLOGICHE "LUIGI SACCO" 2024

Milano, 29 e 30 ottobre 2024





Sharma, Infez Med, 2023

Epidemiological data

January to September 2024

Total cases
12 735 934

Severe cases
41 921

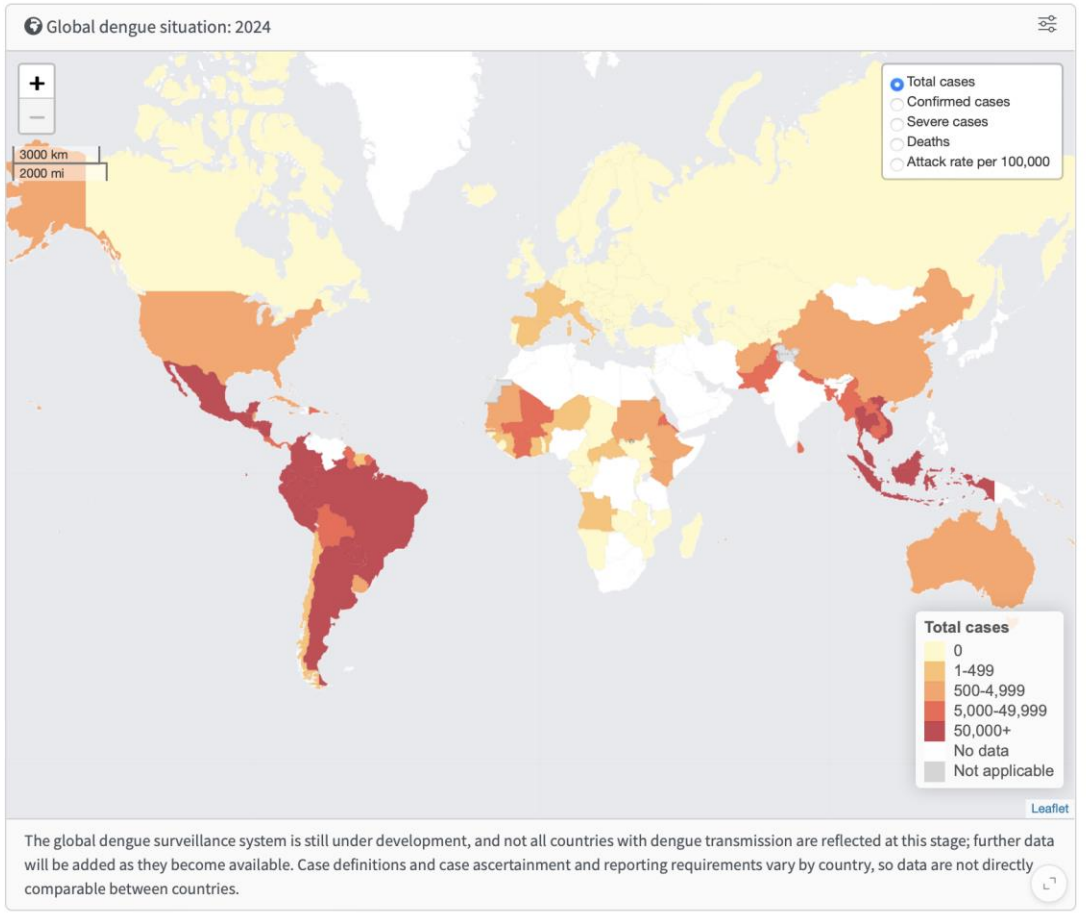
Lab confirmed cases
6 807 349

Total deaths
8 791

Trend | Table by region | Table by country/area/territory

Epidemic curve

Figure 7. Geographic distribution of serotypes in the Region of the Americas, 2024 EW 39



World Health Organization Global dengue surveillance

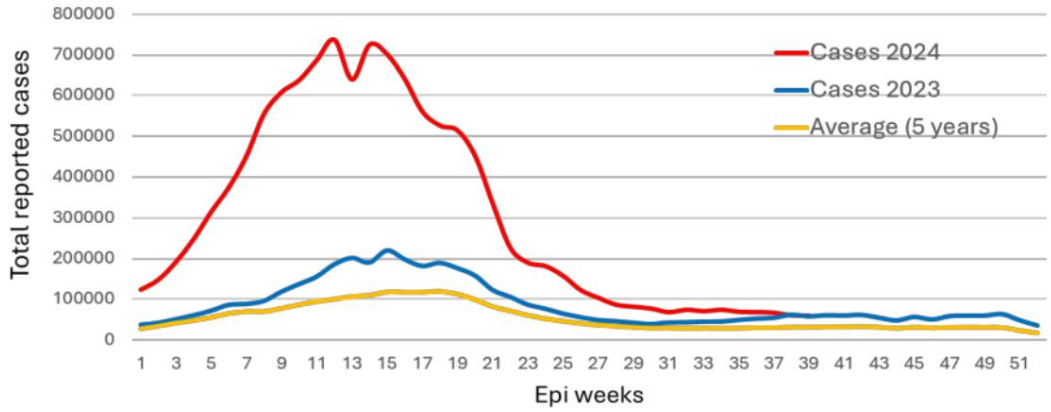
Epidemiological data

Report on the epidemiological situation of dengue in the Americas

As of epidemiological week 39, 2024. Update: October 17, 2024, 14:00 PM (GMT-5)

Between epidemiological weeks (EW) 1 and 39 of 2024, a total of 12,027,427 suspected cases of dengue were reported, resulting in a cumulative incidence of 1,259 per 100,000 population. This represents an increase of 215% compared to the same period in 2023 and 394% compared to the average of the last 5 years. Figure 1 shows the trend of suspected dengue cases as of EW 39.

Figure 1. Suspected dengue cases as of EW 39 in 2024 and 2023, and average of the last 5 years. Region of the Americas



Selected indicators
Corresponding to EW 39
14 countries reported cases
59,161 suspected cases
13,051 lab confirmed (22%)
230 severe dengue cases (0.4%)
34 deaths
0.057% case fatality rate (CFR)

Cumulative dengue cases as of EW 1 –39
12,027,427 suspected cases
6,467,168 lab confirmed (54%)
18,895 severe dengue cases (0.16%)
7,152 deaths
0.059% case fatality rate (CFR)

Brazil epidemiological data

Epidemiological situation

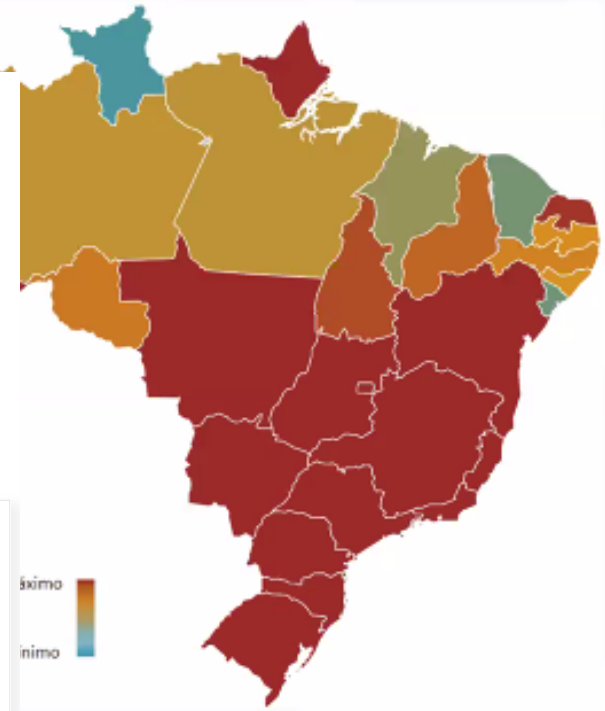
GOV.BR/SAUDE

minsaude

PROVÁVEIS CASES OF DENGUE IN BRAZIL (2024)

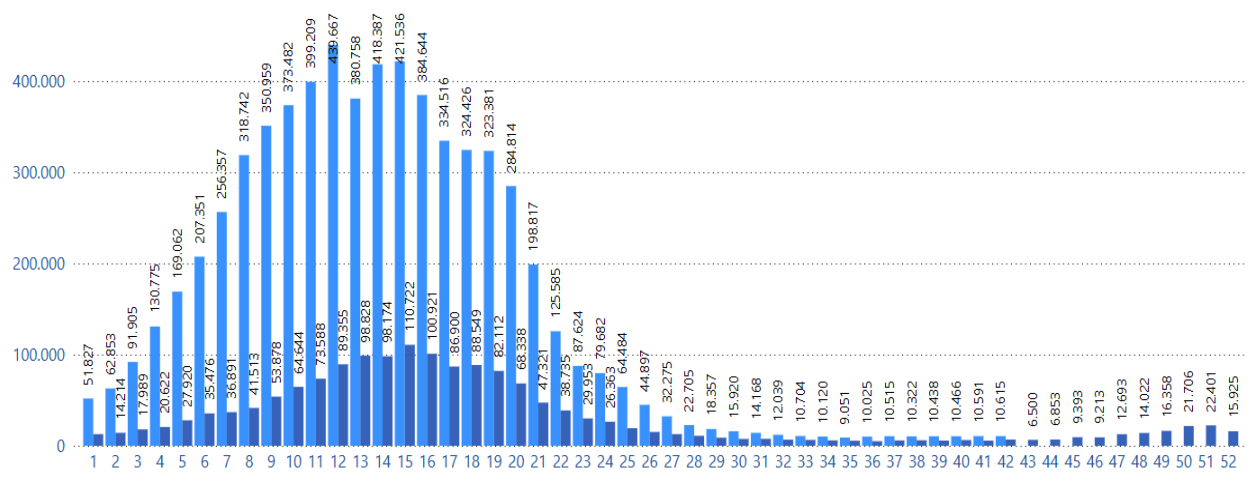
Casos prováveis	Óbitos em investigação	Óbitos por Dengue
6.544.051	1.372	5.682

Coeficiente de incidência	Letalidade em casos prováveis	Letalidade em casos graves
3222,7	0,09	5,61



Casos prováveis de dengue por ano e semana epidemiológica, 2023 e 2024

Exibir por ano/mês



SUS

MINISTÉRIO DA SAÚDE

GOVERNO FEDERAL

BRASIL

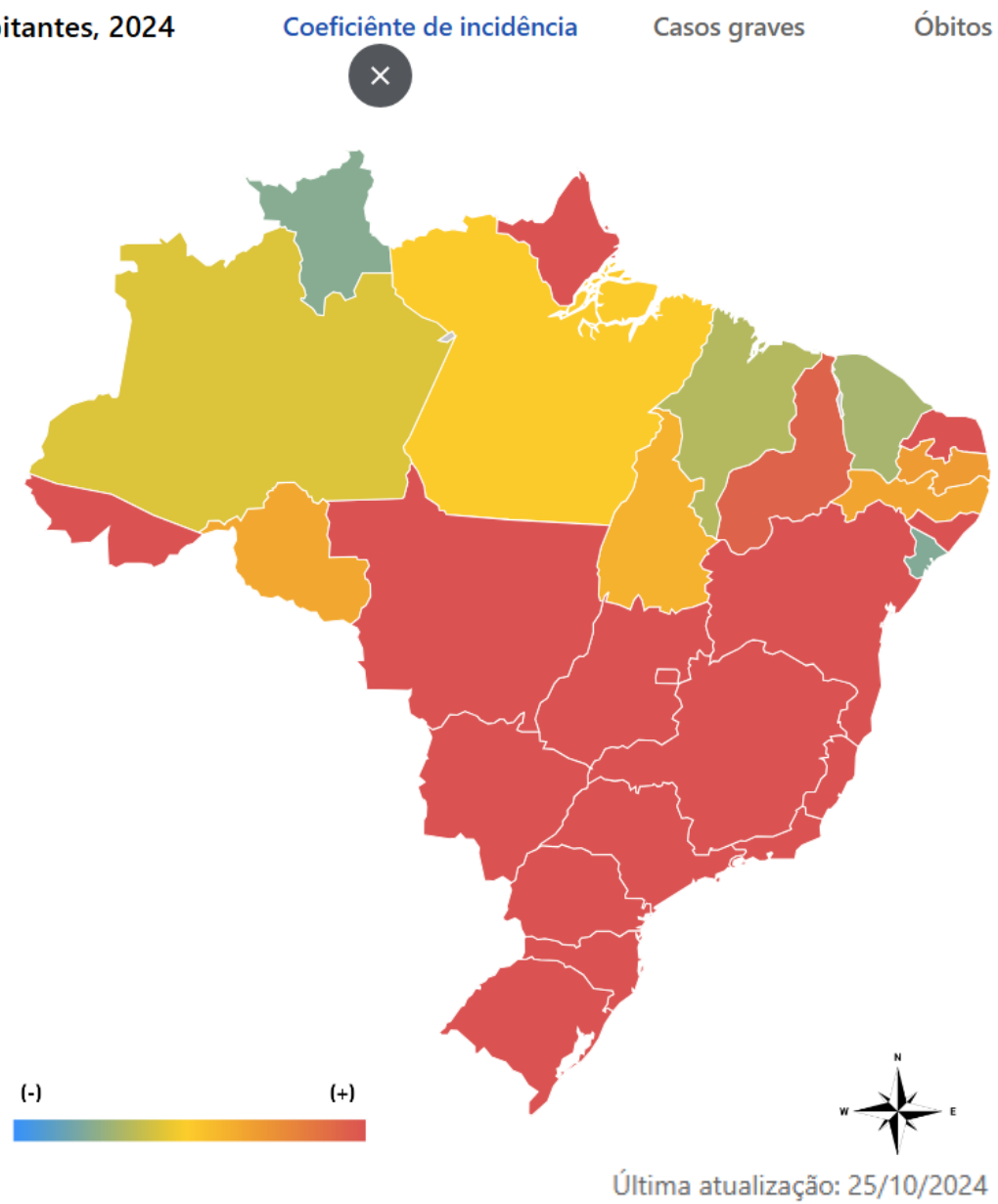
UNIÃO E RECONSTRUÇÃO

Última atualização: 25/10/2024

Brazil epidemiological data

Coeficiente de incidência dos casos prováveis, por 100 mil habitantes, 2024

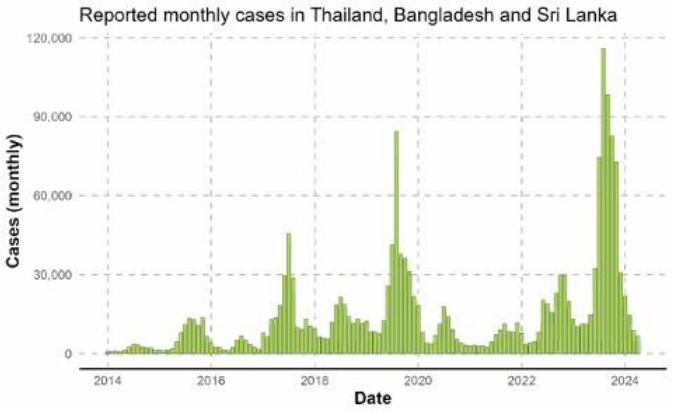
Unidade Federada	Coeficiente de incidência	Casos prováveis
Distrito Federal	9821,2	276.671
Minas Gerais	8224,3	1.689.163
Paraná	5690,8	651.204
São Paulo	4800,8	2.132.553
Santa Catarina	4638,0	352.932
Goiás	4590,2	323.849
Espírito Santo	3868,0	148.280
Rio de Janeiro	1871,6	300.482
Rio Grande do Sul	1863,2	202.720
Bahia	1636,6	231.350
Amapá	1317,9	9.667
Mato Grosso	1138,1	41.640
Mato Grosso do Sul	692,9	19.101
Acre	553,2	4.592
Alagoas	550,6	17.221
Rio Grande do Norte	519,1	17.141
Piauí	467,2	15.272
Paraíba	352,0	13.992
Pernambuco	331,0	29.980
Rondônia	325,6	5.147
Tocantins	305,5	4.618
Pará	255,1	20.706
Amazonas	212,3	8.367
Maranhão	165,7	11.226
Ceará	149,6	13.150
Roraima	111,1	707
Sergipe	104,7	2.313

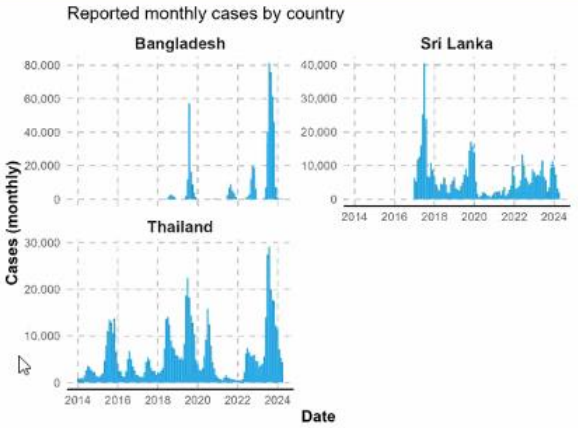


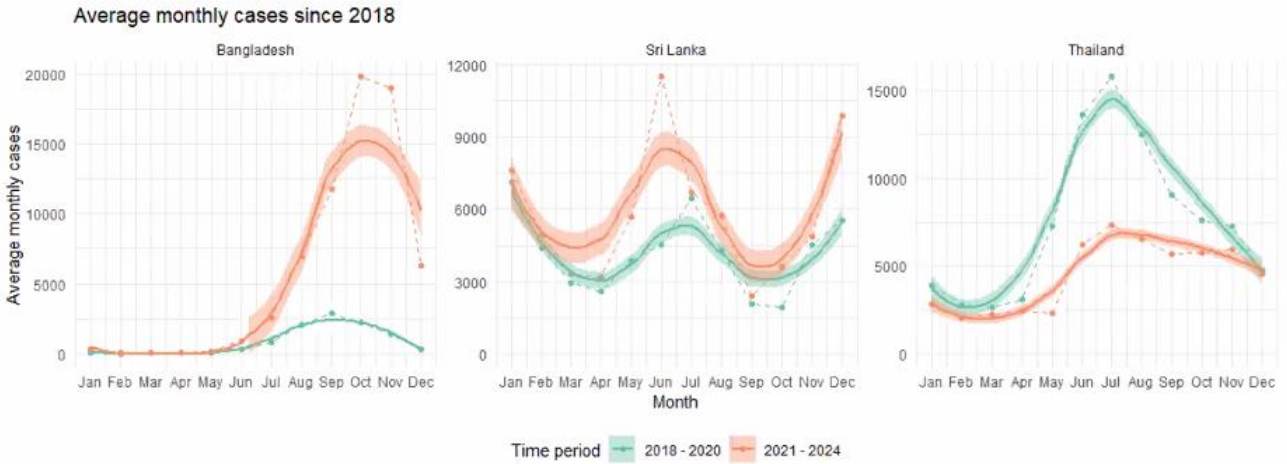
Epidemiological data

South-East Asia:
Focus on Bangladesh, Thailand, Sri Lanka

- The 2023 season in the region was the largest recorded, driven primarily by surges in cases in Bangladesh and Thailand
- Peak transmission season across Bangladesh and Thailand typically occurs in the latter half of the year; two peak seasons in Sri Lanka
- Substantial variation in trends in season incidence, duration and timing at a country level

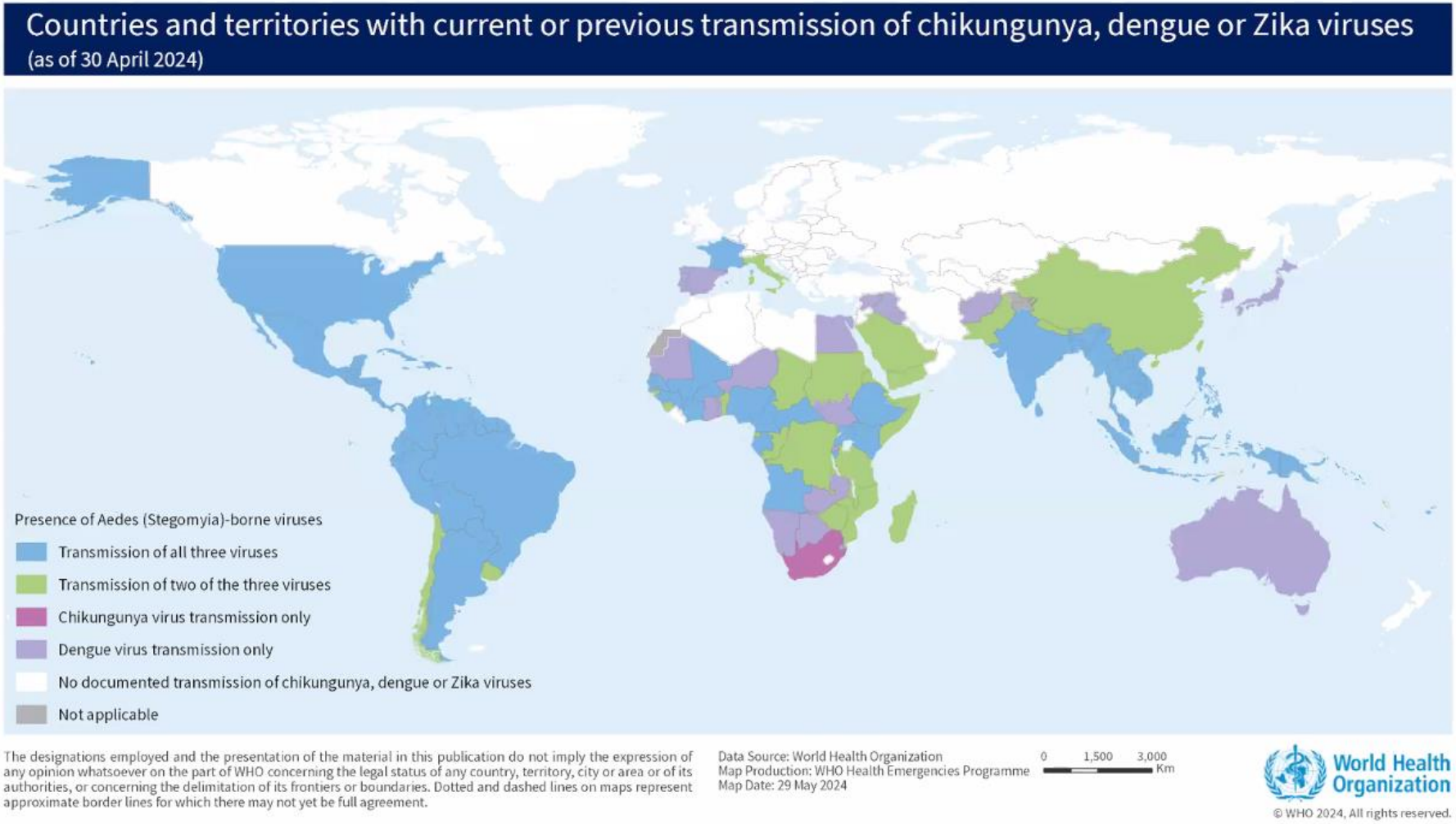






Note: Case definitions, case ascertainment and reporting requirements vary by country, so data are not directly comparable between countries

Epidemiological data



362	51.93% | 48.07%	37 anni	1	82 casi | 280 casi
Casi*	Maschi | Femmine*	Età mediana*	Decessi*	Autoctoni | Importati*

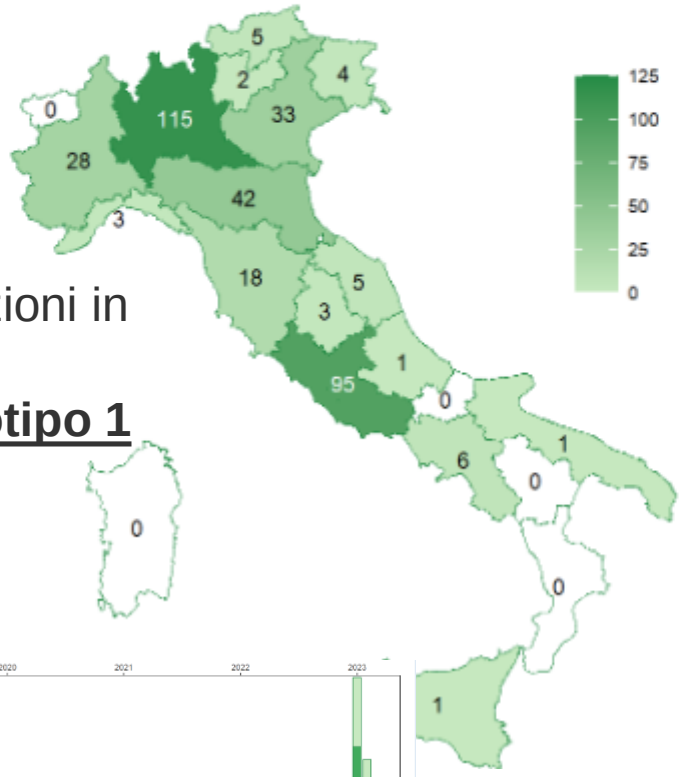
*Dati dell'anno 2023 in fase di consolidamento

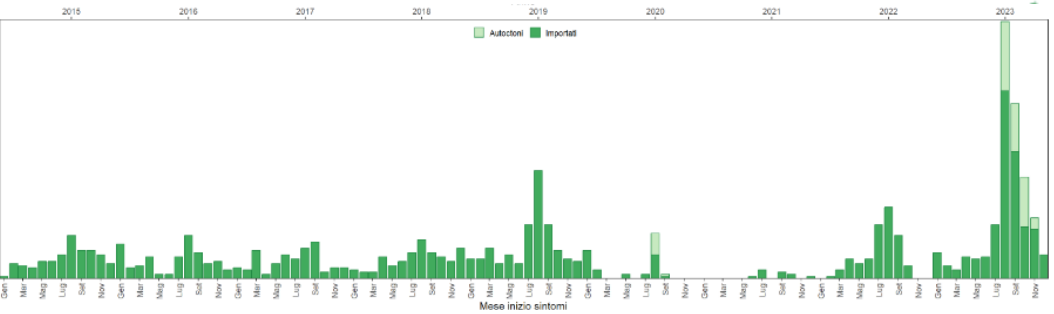
Casi per Regione*

Casi autoctoni

Lodi 36 casi **genotipo 1**

Latina 2 casi **genotipo 3**
Roma 43 casi con esposizioni in diverse parti della città metropolitana di Roma **genotipo 1**
Anzio 1 caso **genotipo 2**





firenze.repubblica.it

la Repubblica

Muore per la dengue dopo un viaggio in Thailandia, disinfestazione contro le zanzare a Fucecchio e San Miniato

Chiarastella Foschini

▲ 2016 Getty Images

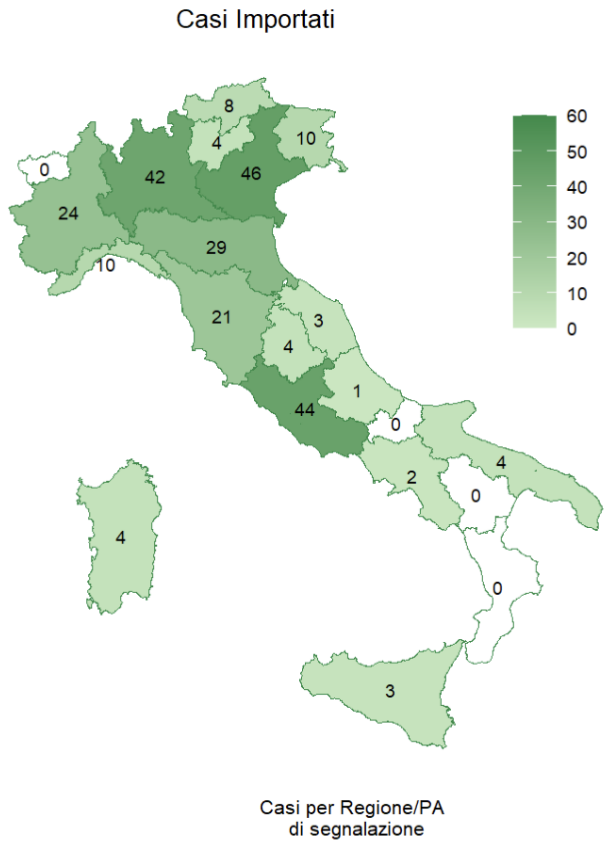
In Toscana nel 2023 sono stati registrati 14 casi

https://www.epicentro.iss.it/arbovirosi/dashboard acces Jan 27, 24

259	50% | 50%	43 anni	0	0 casi | 259 casi
Casi*	Maschi | Femmine*	Età mediana*	Decessi*	Autoctoni | Importati*

*Dati in fase di consolidamento

Casi per Regione*



Del Manso, ISS 22 giugno, 2024

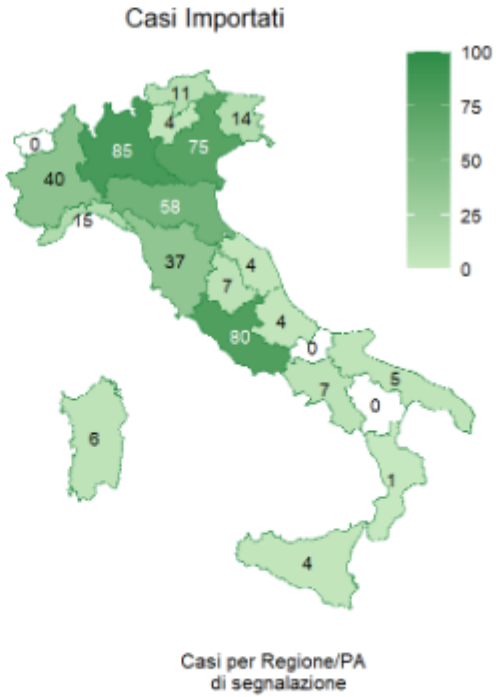
657	51% | 49%	45 anni	0	200 casi | 457 casi
Casi*	Maschi | Femmine*	Età mediana*	Decessi*	Autoctoni | Importati*

*Dati in fase di consolidamento

Casi per Regione/PA*

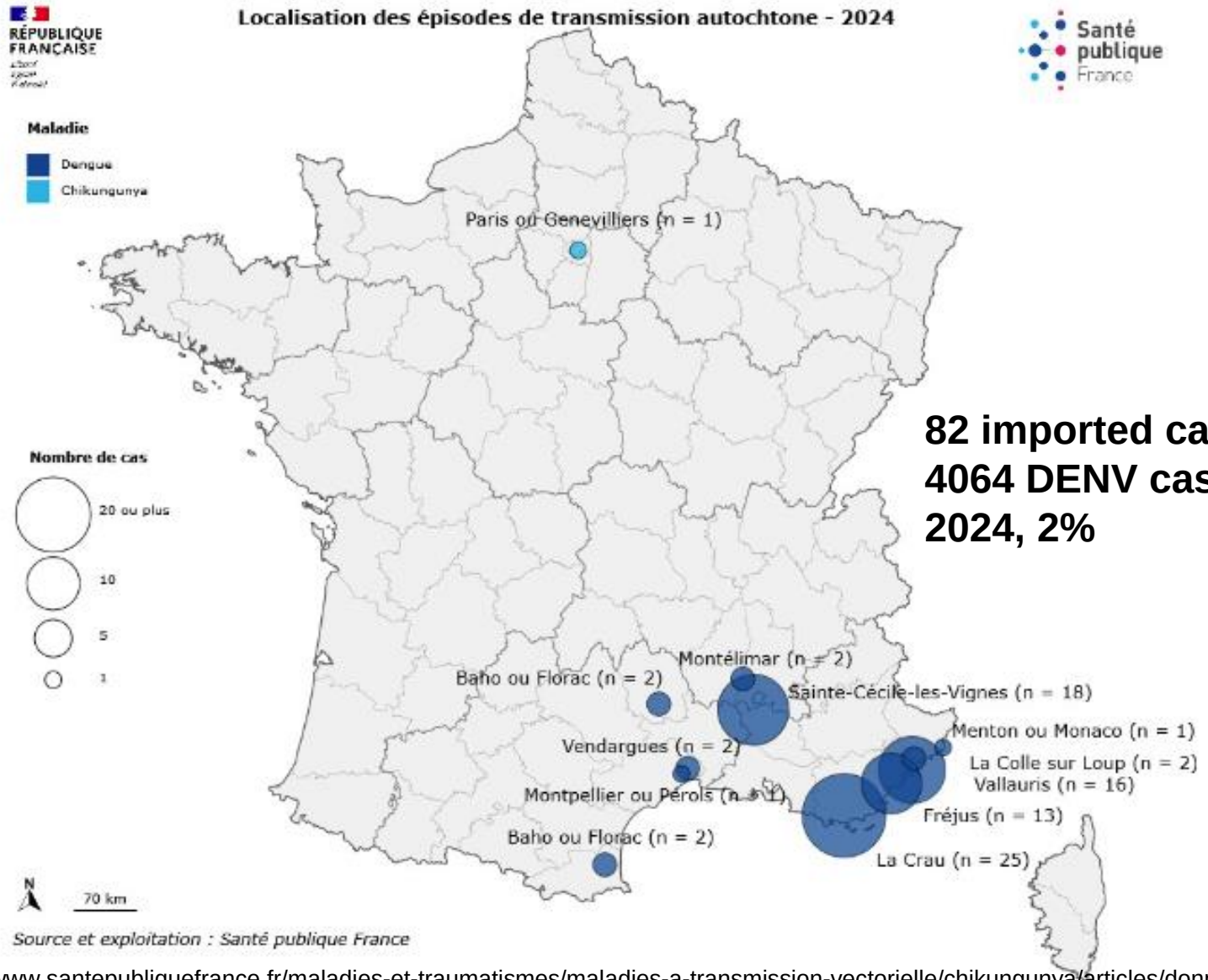
200 imported cases on 657 DENV cases in 2024, 30.5% nei comuni di **Albinea** (RE), **Ospitaletto** e **Cazzago San Martino** (BR), **Pesaro, Fano** e **San Costanzo** (PU), **Rapolano Terme** (SI), **Cavezzo** (MD), **Malo** (VI), **Ortona** (CH), **Sesto Fiorentino** (FI), **Castelfidardo** (AN)

Un caso segnalato dall'Abruzzo non è riportato nella mappa essendo ancora in corso indagini sull'attribuzione geografica.



Del Manso, ISS 22 ottobre 2024

Carte des épisodes de transmission autochtone de dengue et de chikungunya en France hexagonale, saison 2024, à la date du 22/10/2024

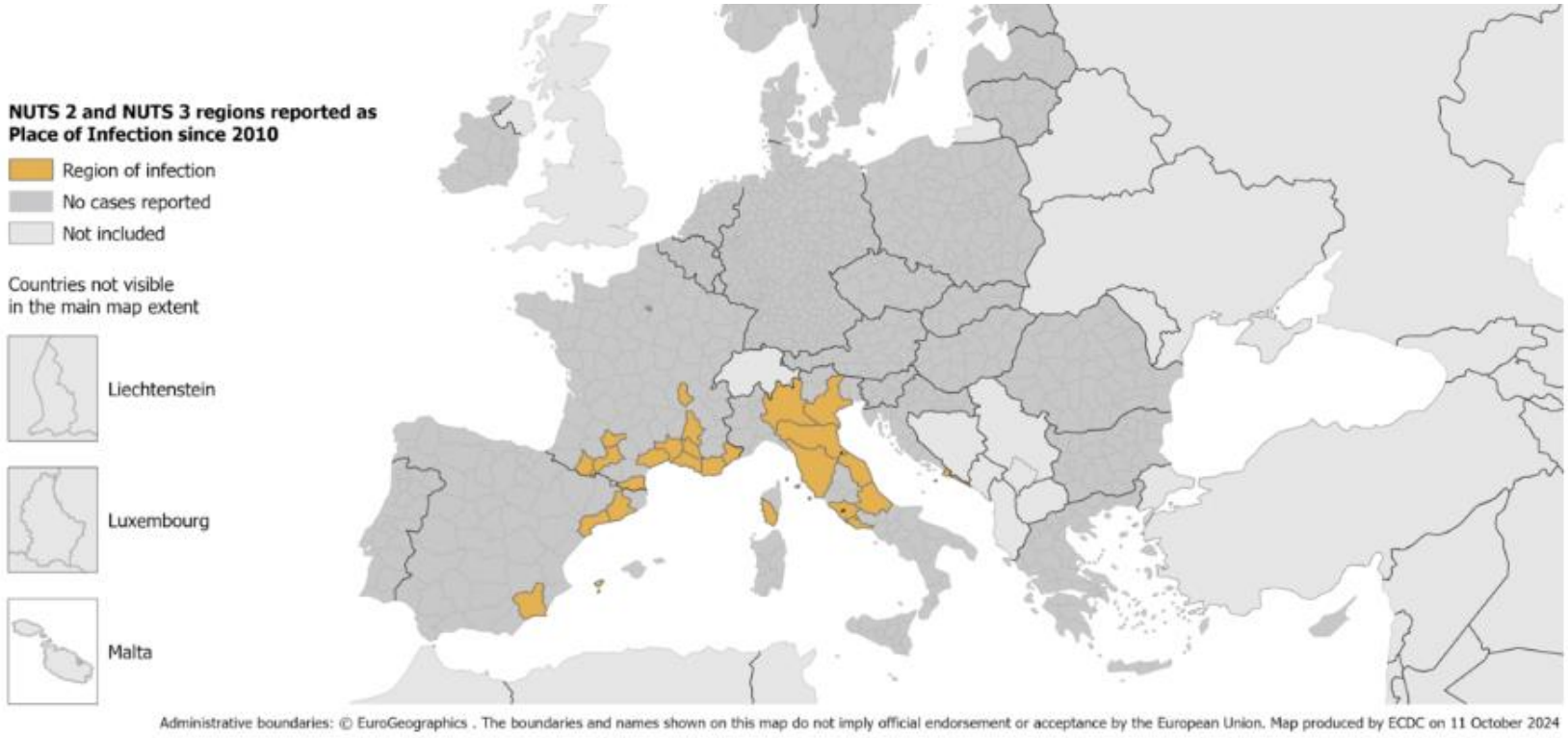


82 imported cases on 4064 DENV cases in 2024, 2%

https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-a-transmission-vectorielle/chikungunya/articles/donnees-en-france-metropolitaine/chikungunya-dengue-et-zika-donnees-de-la-surveillance-renforcee-en-france-hexagonale-2024

Local transmission of dengue virus in mainland EU/EEA, 2010-present

2024	France	Alpes-Maritimes (19 cases in 3 clusters), Drôme (2 cases), Hérault (3 cases in 2 clusters), Pyrénées-Orientales or Lozère (2 cases), Vaucluse (18 cases), Var (38 cases in 2 clusters) departments	82	Mid-June - September	[35-37]
2024	Italy	Abruzzo (9 cases), Emilia-Romagna (36 cases), Lombardy (12 cases), the Marches (139 cases), Tuscany (2 cases), Veneto (1 case) regions*	199	August-September	[43]
2024	Spain	Catalonia region (Tarragona province)	8	August-September	[43,44]



https://www.ecdc.europa.eu/en/all-topics-z/dengue/surveillance-and-disease-data/autochthonous-transmission-dengue-virus-eueea

Dengue scenarios

Scenario 1 No autochtonous cases

2025 < 2024 <20023: non focolai autoctoni ma necessità di mantenere alta preparedness & response

- INFORMAZIONE: corretta, continua e ossessiva comunicazione per la prevenzione delle punture di insetto. Uso di larvicidi biologici
- FORMAZIONE: operatori sanitari di MMG, PlS, PSDEA
- IDENTIFICAZIONE precoce dei casi umani importati (link epidemiologico viaggio), disponibilità di test diagnostico rapido in strutture centralizzate, immediata notifica ed isolamento per ridurre rischio di puntura da zanzare sino a 7 gg da esordio
- DISINFESTAZIONE con adultici e larvicidi con possibilità di ingresso nelle aree private.

The current and future global distribution and population at risk of dengue

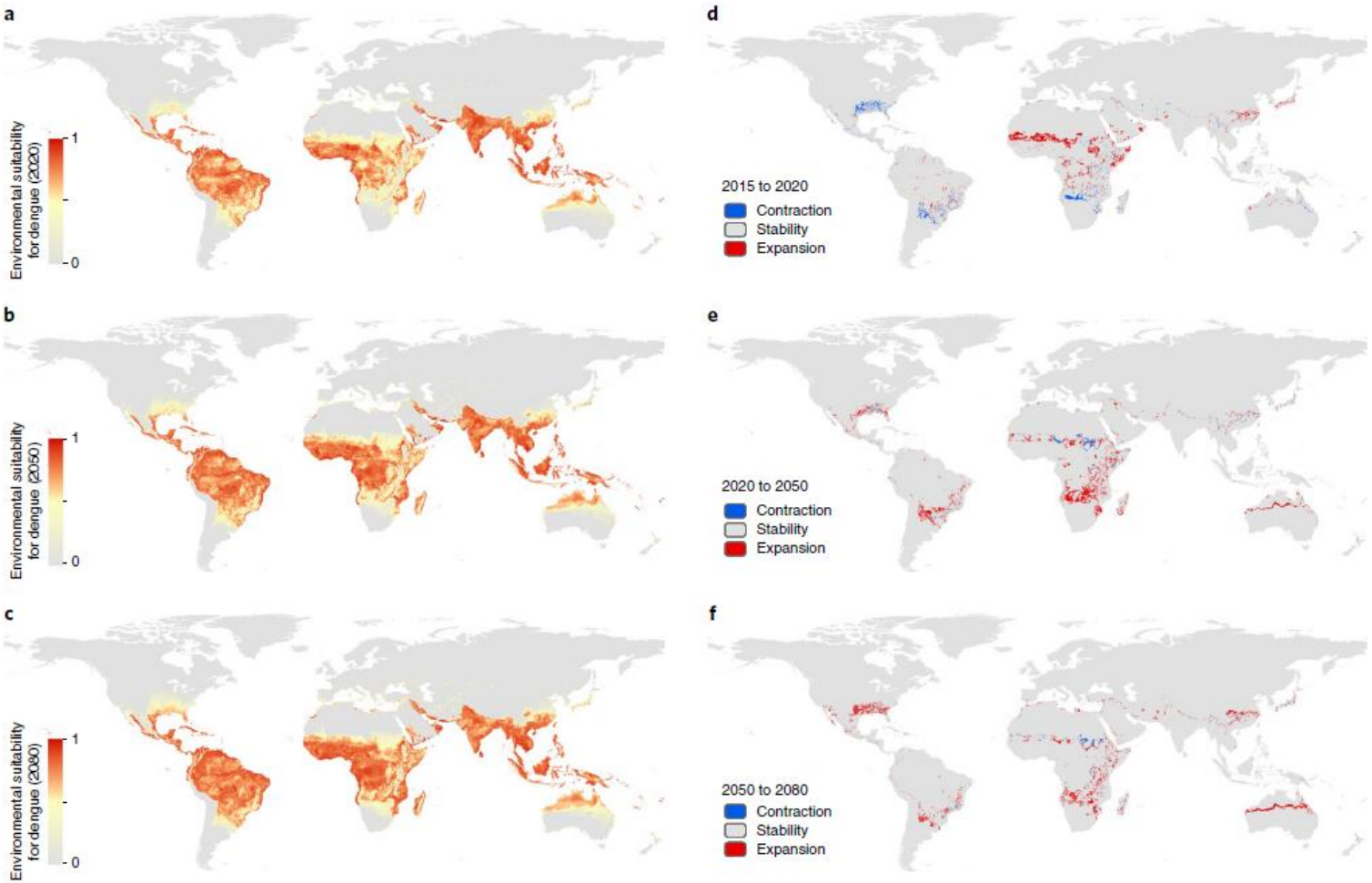


Fig. 2 | Environmental suitability for dengue occurrence according to RCP6.0 and SSP2. a–c, Projected data shown for 2020 (**a**), 2050 (**b**) and 2080 (**c**). **d–f**, Changes in areas classified as at-risk (using the suitability threshold of 0.467).

Messina Nat Micob 2019

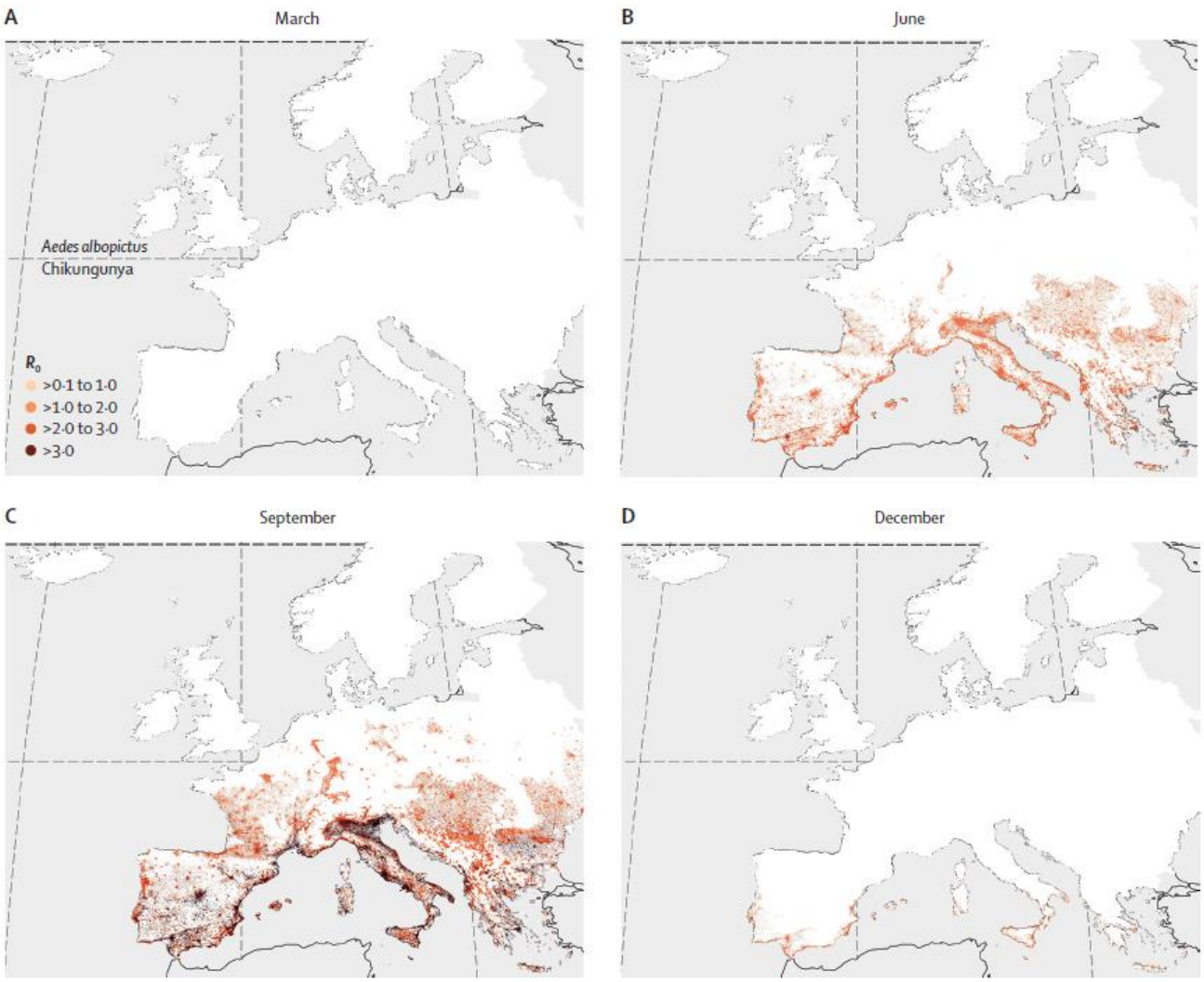
Dengue scenarios

Scenario 2 sporadic outbreak autochtonous cases

2025 simile al 2024>20323

- INFORMAZIONE: corretta, continua e ossessiva comunicazione per la prevenzione della MALATTIA da DENGUE e non più solo delle punture di insetto, uso di larvicidi biologici
- FORMAZIONE: operatori sanitari di MMG, PlS, PSDEA
- Identificazione precoce dei casi umani importati e autoctoni (estremamente difficile va immediata notificata agli operatori sanitari la **geolocalizzazione** dei casi), disponibilità di test diagnostico rapido in strutture centralizzate e laddove sia presente focolaio, immediata notifica ed isolamento per ridurre rischio di puntura da sino a 7 gg da esordio, notifica centro regionale sangue
- 4. DISINFESTAZIONE con adultici e larvicidi con possibilità di ingresso nelle aree private.

Estimating the potential risk of transmission of arboviruses in the Americas and Europe: a modelling study

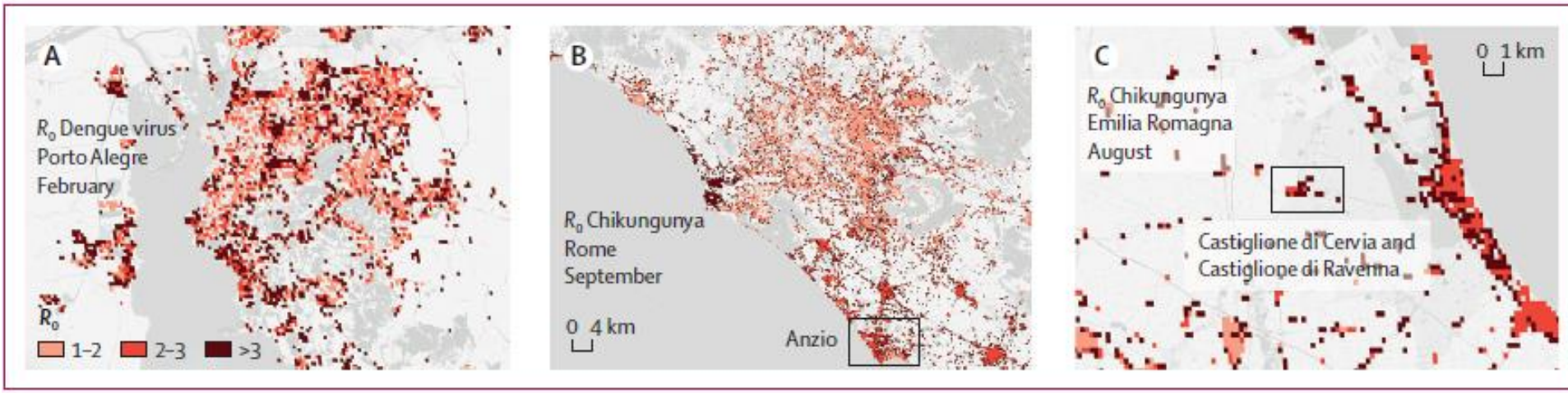


Estimated temporal dynamics of the chikungunya reproduction number in Europe

Estimated temporal dynamics of the reproduction number, *R0*, for chikungunya in Europe, as obtained by assuming *Aedes albopictus* to be the main vector species. Estimates are shown only for areas with at least ten inhabitants per hectare and an estimated *R0* greater than 0·1. Estimates are provided at a spatial scale of 250 m × 250 m; displayed values represent average estimates obtained with

Zardini A Lancet Plan Health 2024

Estimating the potential risk of transmission of arboviruses in the Americas and Europe: a modelling study



Average model estimates of *R*0 for dengue virus and chikungunya in Brazil and Italy

(A) Average model estimates of the dengue virus *R*0 in Porto Alegre, Brazil, as obtained by considering *Aedes aegypti* to be the dominant competent vector for the transmission. *R*0 estimates reported in the literature for this area peak at 1·4–1·9 between 2013 and 2016.22 Average model estimates of the chikungunya *R*0 as obtained by considering *Aedes albopictus* as the dominant vector in Rome, Italy (B), and in two villages of Emilia Romagna (Castiglione di Cervia and Castiglione di Ravenna), Italy (C). Published estimates of *R*0 associated with the outbreaks that occurred in these locations were 1·8–6·0 in the 2007 outbreak9 and 1·5–2·6 in the

Zardini A Lancet Plan Health 2024

Dengue scenarios

Scenario 3 sustained outbreak autochtonous cases

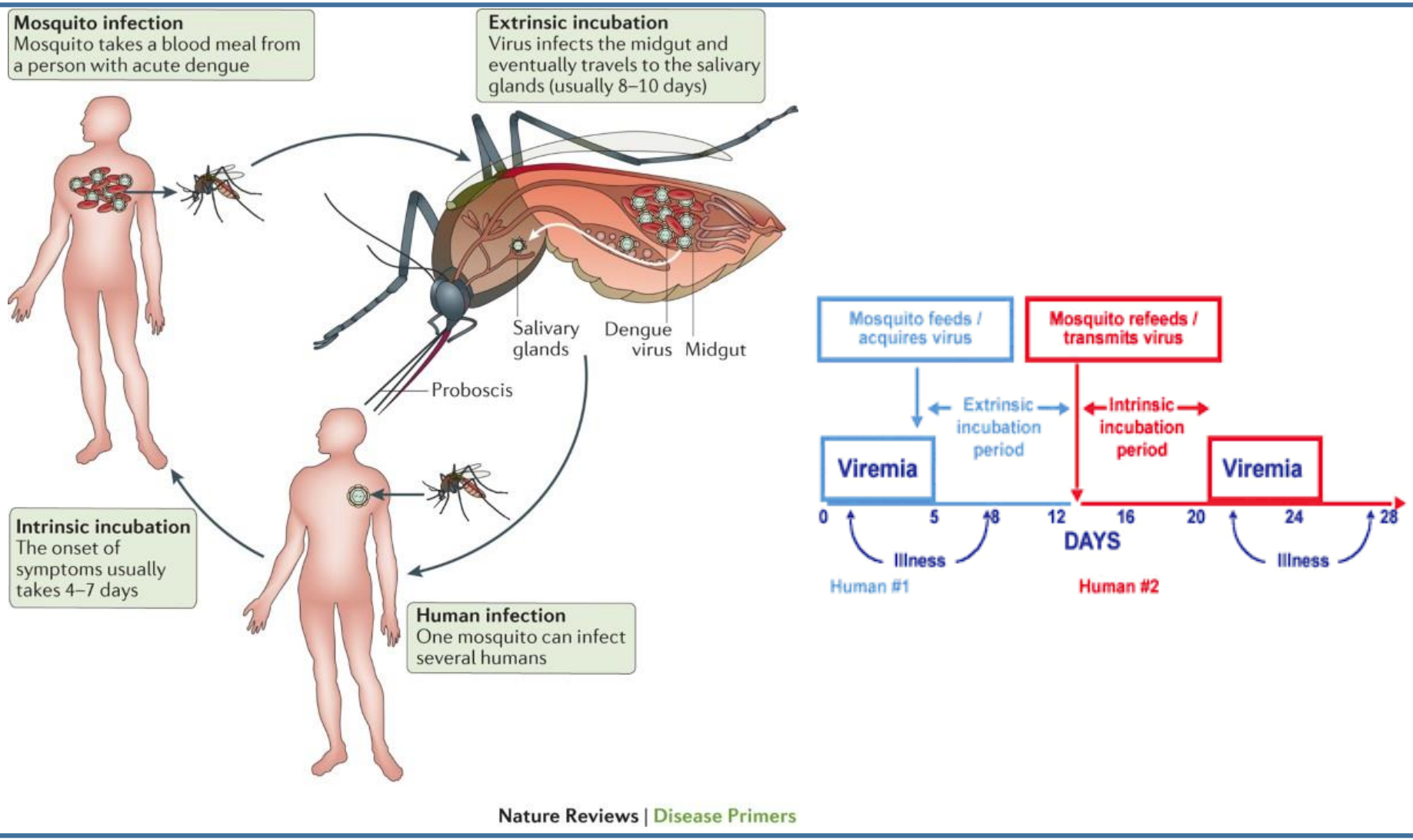
2025 peggiore del 2024 >2023: > focolai > casi

- INFORMAZIONE: corretta, continua e ossessiva comunicazione per la prevenzione della MALATTIA da DENGUE e non solo delle punture di insetto, uso di larvicidi bioogici
- FORMAZIONE: operatori sanitari di MMG, PlS, PSDEA
- Identificazione precoce dei casi umani importati e autoctoni (estremamente difficile va immediata notificata agli operatori sanitari la **geolocalizzazione** dei casi), disponibilità di test diagnostico rapido in strutture centralizzate e laddove sia presente focolaio (MMG/farmacie?), immediata notifica ed isolamento per ridurre rischio di puntura da sino a 7 gg da esordio, notifica centro regionale sangue
- DISINFESTAZIONE con adultici e larvicidi con possibilità di ingresso nelle aree private.
- INTERVENTI STRAORDINARI: rilascio intenzionale di zanzare meno suscettibili alla infezione virale (ad esempio infettate da Wolbachia)

Dengue transmission

- ***Aedes aegypti* breeds in clean water in and around houses:** efficient transmission in urban areas and is the principal vector throughout the tropical world,
- ***Aedes albopictus*** transmits inefficiently in more rural areas of the tropics but is quite **efficient in urban areas**
- **Daytime biting** with 2 peaks early in the morning and late in the evening
- It usually in-house and **maximun 200 mt** distance length
- **Human transmission** requires the same female mosquito to bite a viremic human and then a susceptible human **after 10-12 days.**

Dengue intrinsic and extrinsic incubation period



Guzman, Nature Rev 2016

Four Dengue viruses 1-4

- **RNA single strand** virus **-** ***flavivirus***
- **Life time immunity follows infection to one type.**
- **Second, third and possibly four infections are possible.**
- **CHILDREN – first infections are mild, largely unapparent.**
- **ADULTS - first infections may produce DF, some viruses more overt than others, attention to comorbities and coinfection for severity**

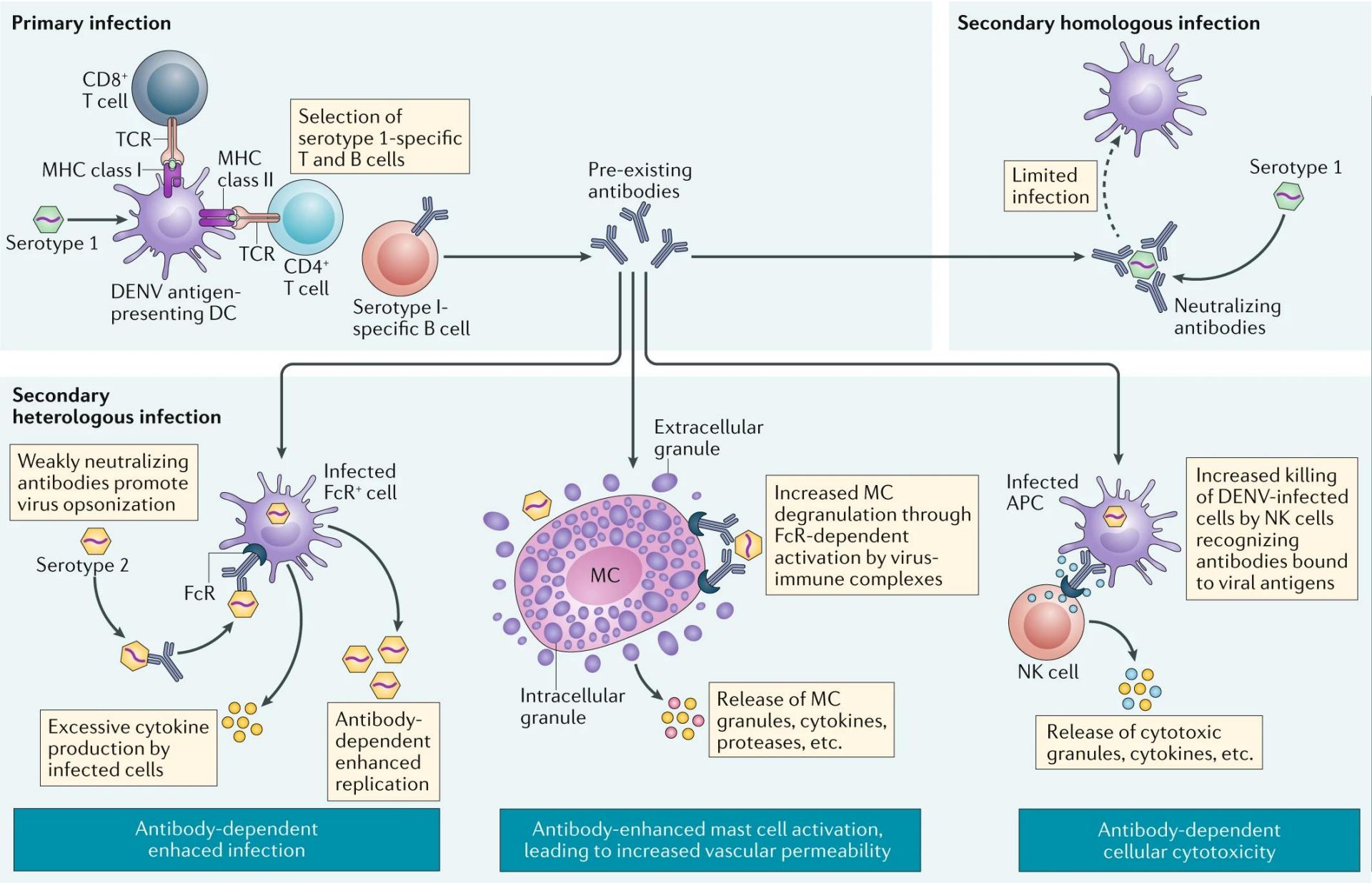
Dengue Clinical Spectrum: a unique infection with different disease progression

1 - Asymptomatic Dengue 80% cases

2 - Dengue with no alert signs, most primary infections apart from elderly, <1yo, comorbidity

3 - Dengue with alert signs, most secondary cases

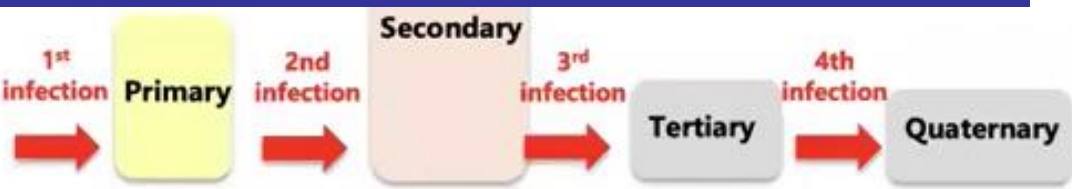
4 - Dengue with major organs failure: severe dengue or DHF/DSS, <1 x 1000, relevant iatrogenic etiology



Cross reactivity sub neutralizing Ab

John, 2019, Nat Rev Imm

Dengue Clinical Spectrum: a unique infection with different disease progression

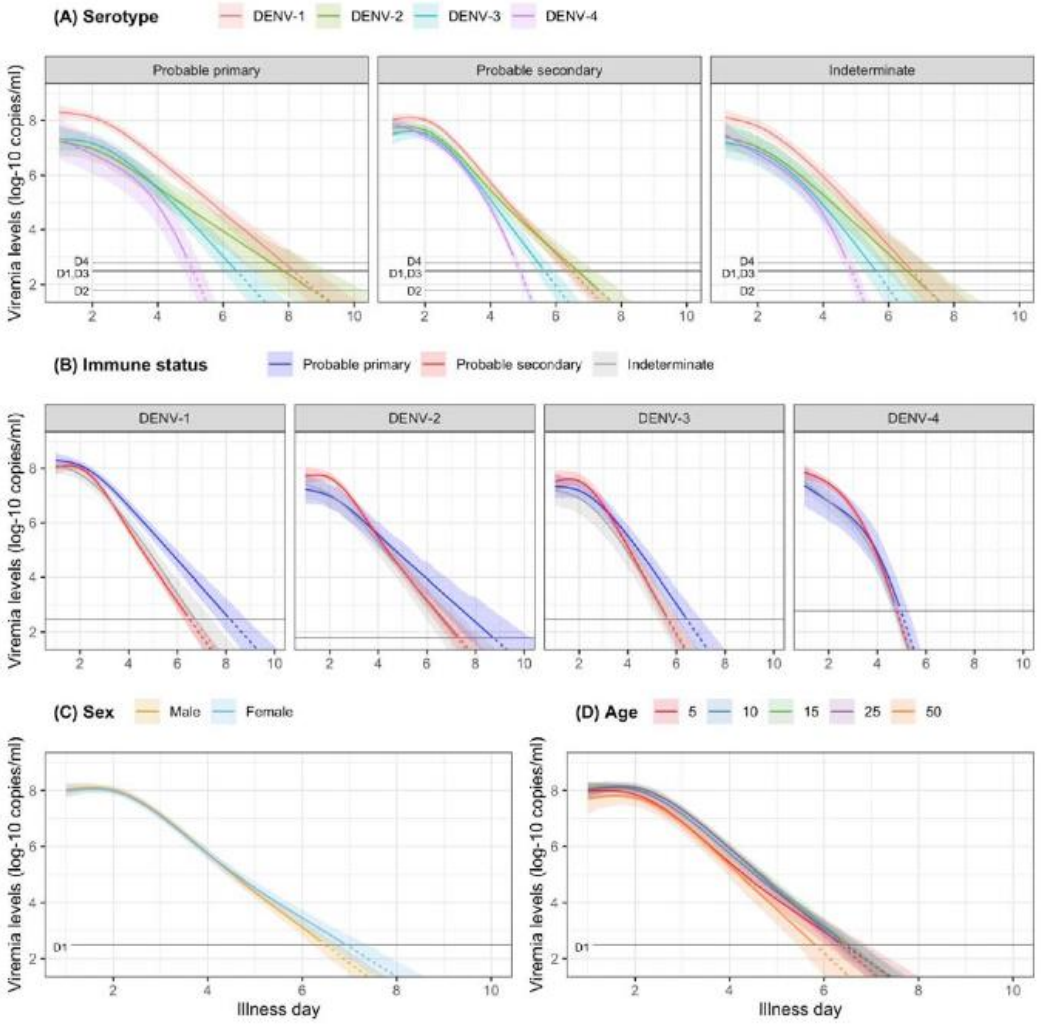


- Four antigenically distinct serotypes (DENV1-4)

- Clinical spectrum:
  - 80% asymptomatic
  - Self-limiting febrile illness
  - Secondary infections have a **RR 2-3** to develop severe dengue compared to primary infection
  - **Not every secondary infection leads to severe dengue: 2-4%**
  - CFR < 0.4% (during epidemic situations 10x higher)

Flasche et al, PLoS Med.2016

Dengue Viremia Kinetics and Effects on Platelet and Clinical Outcomes: An Analysis of 2340 Patients from Vietnam



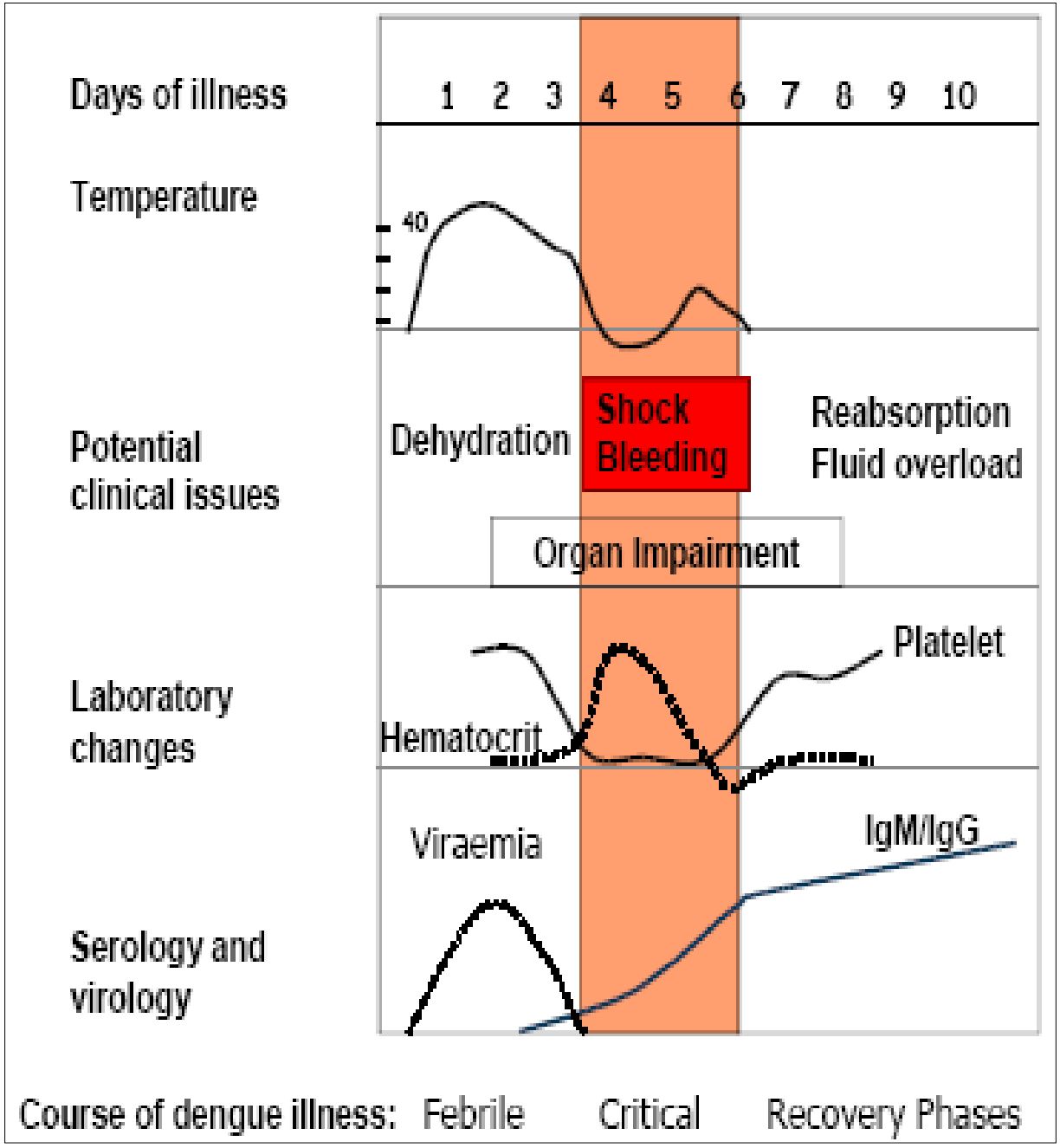
1. **Dengue viremia rapidly decreases** following the onset of symptoms,

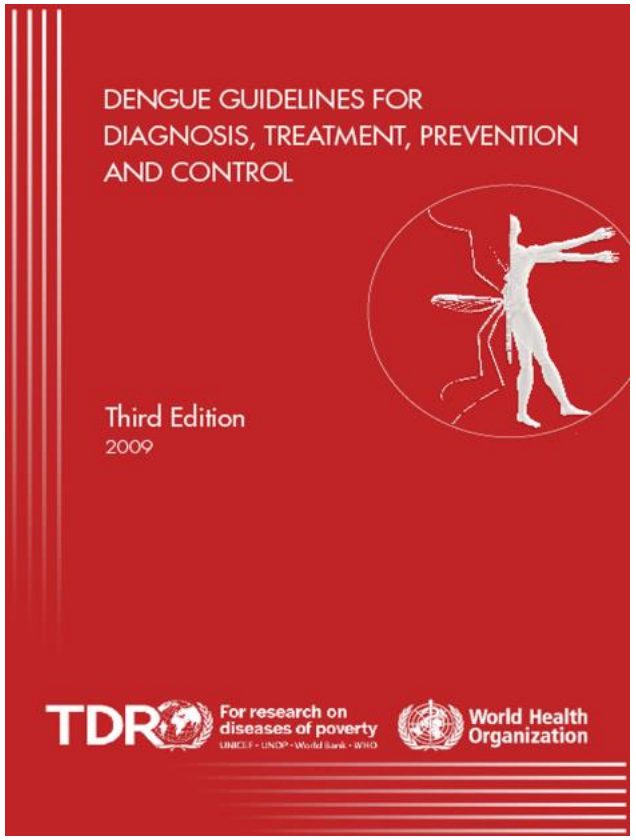
2. **DENV-1 exhibits higher viremia** levels compared to DENV-2 and DENV-3, and

3. **Primary infection is associated with higher and more prolonged detectable viremia** than secondary infection in DENV-1, while this pattern was not consistent across other serotypes.

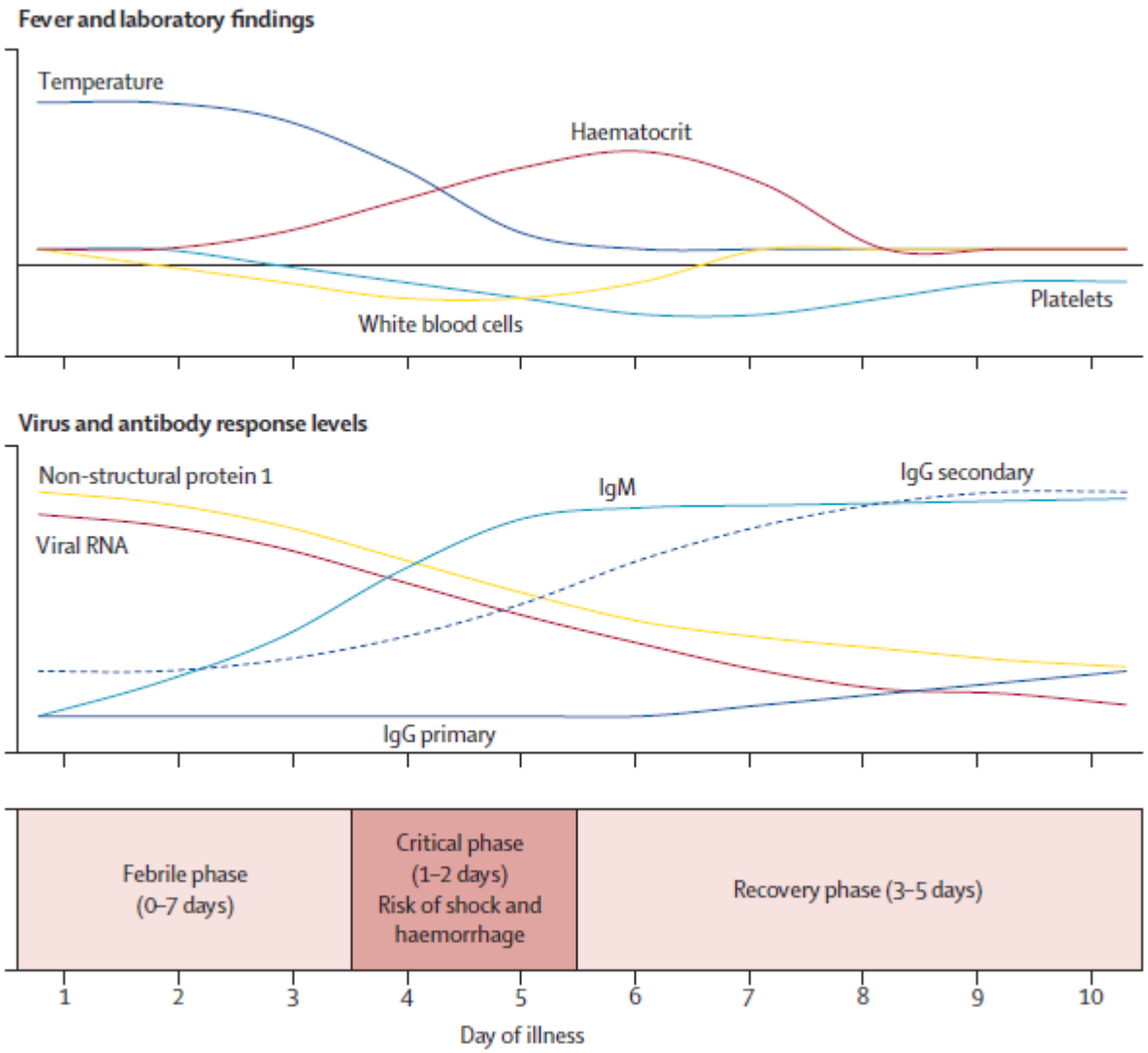
3. **Higher 1-4 day viremia was associated with a decrease in platelet count from day 6**

Vuong Elife 05.2024


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
Viraemia
IgM/IgG
Serology and virology
Course of dengue illness: Febrile Critical Recovery Phases

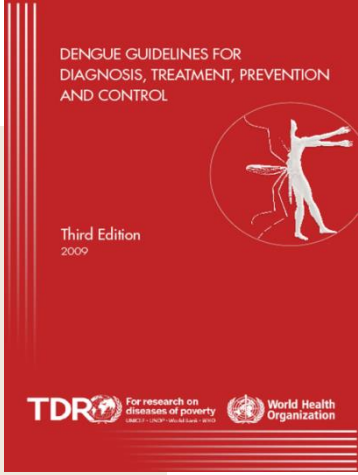

DENGUE GUIDELINES FOR DIAGNOSIS, TREATMENT, PREVENTION AND CONTROL
Third Edition
2009
TDR
For research on diseases of poverty
World Health Organization

Dengue diagnostics by day since symtoms'onset



Gabriela Paz-Bailey, Lancet

Dengue case classification by severity



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

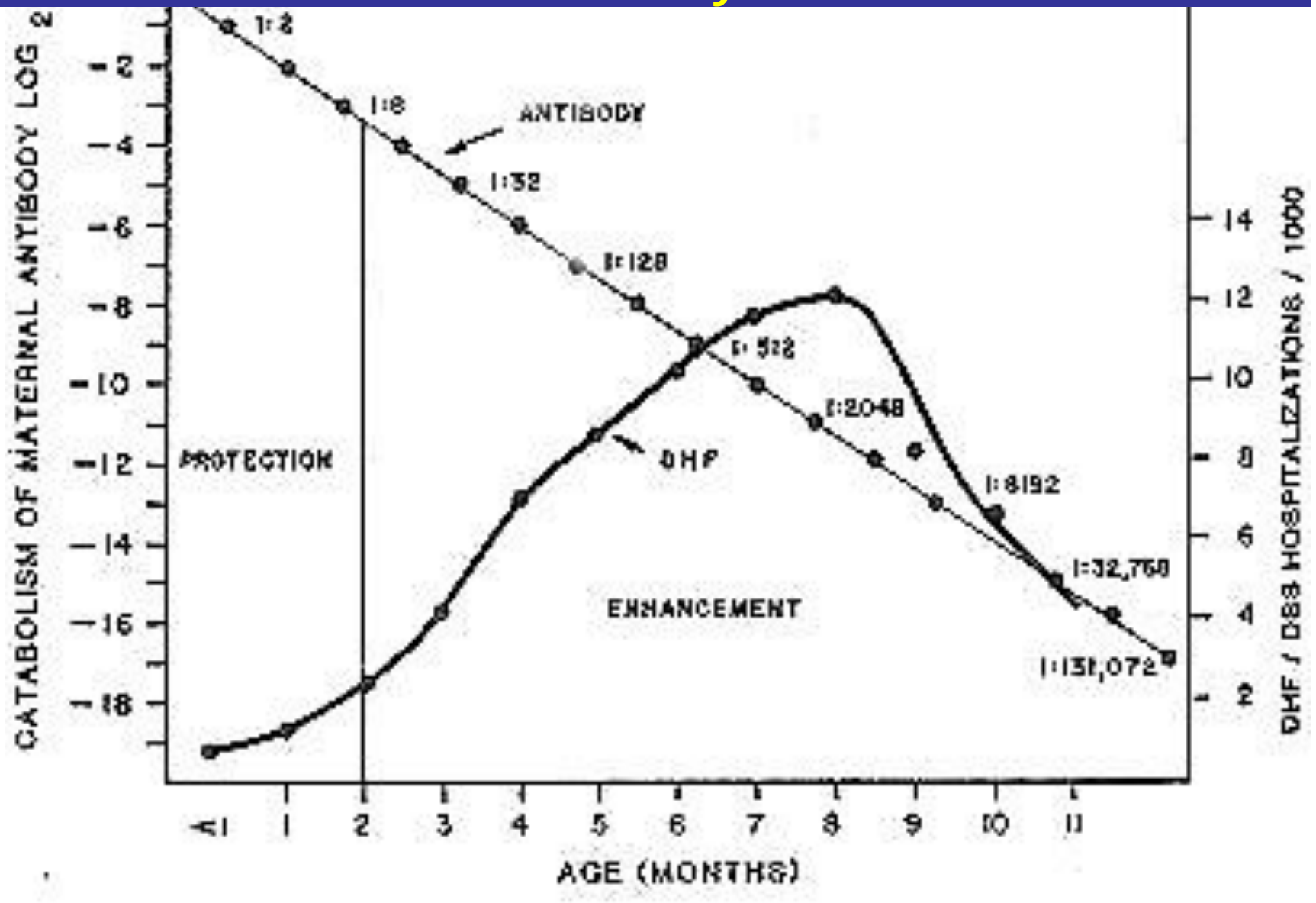
WHO/TDR 2009

Original sin and ADE create the perfect storm in the children <1 y

- The children receive low level IgG from the mother, and is protected up to month 6, after the reducing low titer determine the possible Antibody dependent enhancement of the cellular viral infection and it can determine in the children the paradoxical production of pro-inflammatory cytokine (TNFα, IL6, IL8, ICAM-1 …) and / or complement activation (by NS1) :

The perfect storm

Disease severity in infants to loss of maternal antibody



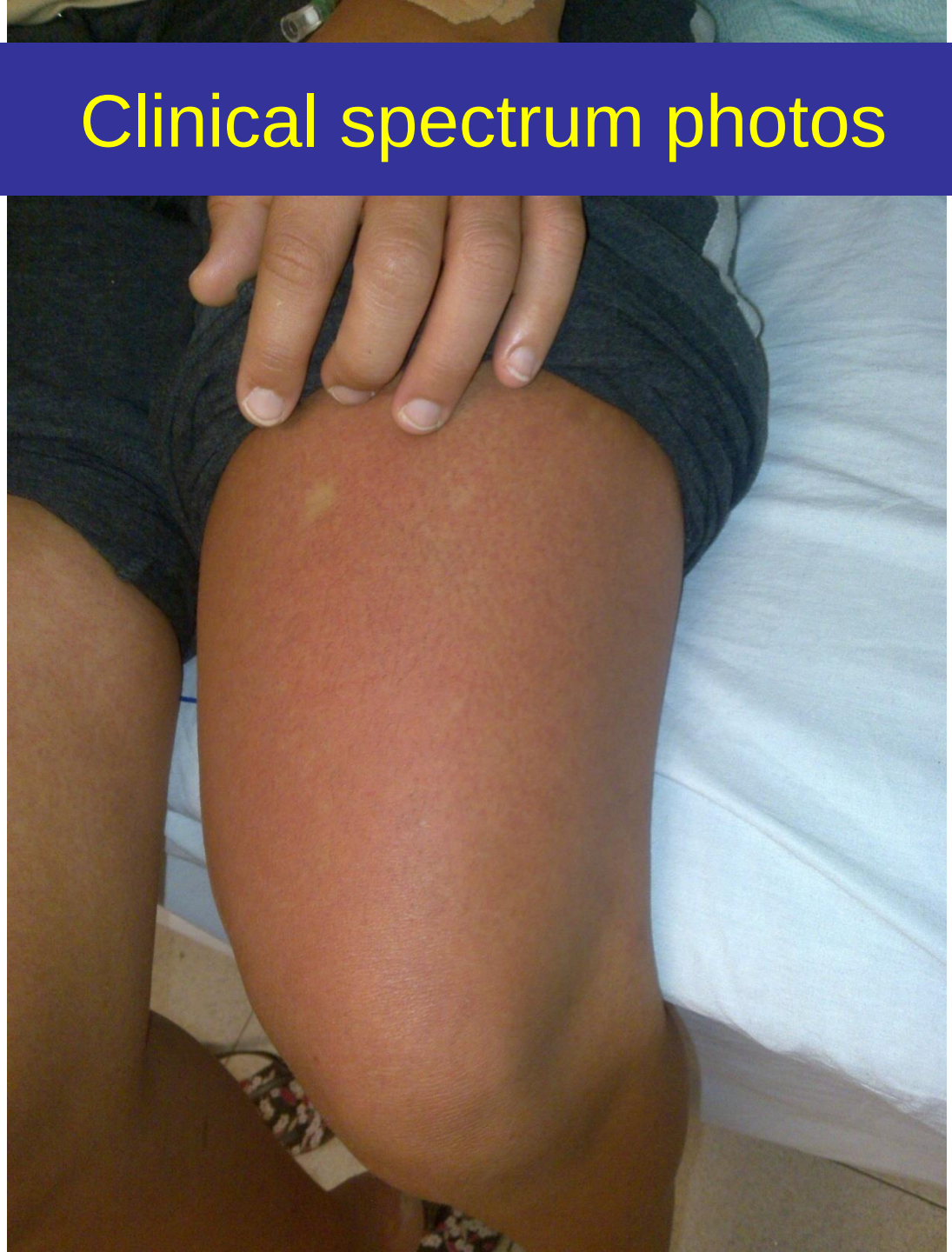
Increased vascular permeability

- Paradoxical production of pro-inflammatory cytokine (TNFα …) and / or complement activation (by NS1)
- is the main feature distinguishing severe from not severe dengue
  - apparent around the 4th to 5th day of illness
  - leads to the plasma leakage syndrome
  - reabsorption of fluid occurs between the 6th and the 7th day

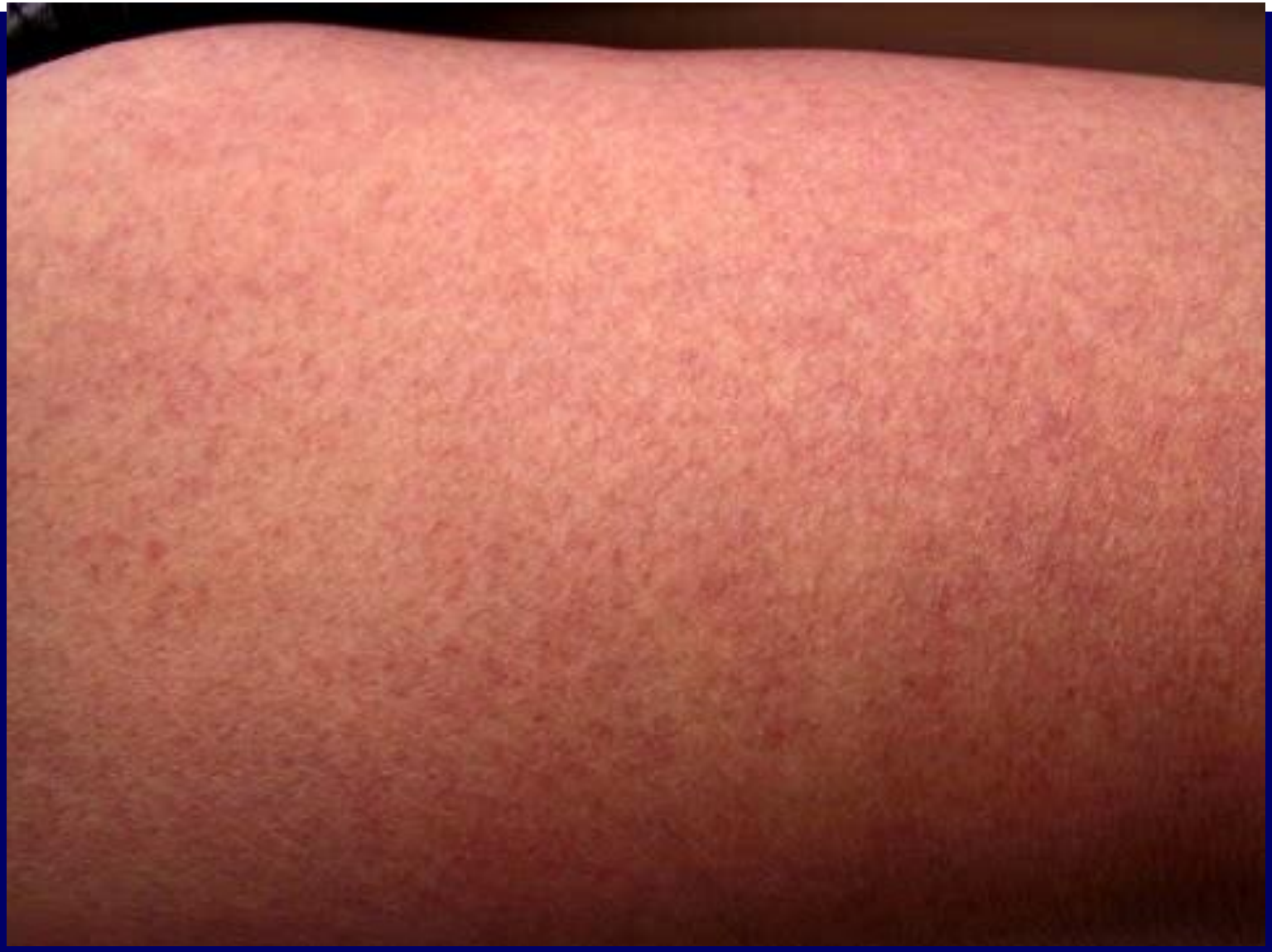
Careful attention to fluid balance is mandatory to prevent fluid overload

Clinical spectrum photos

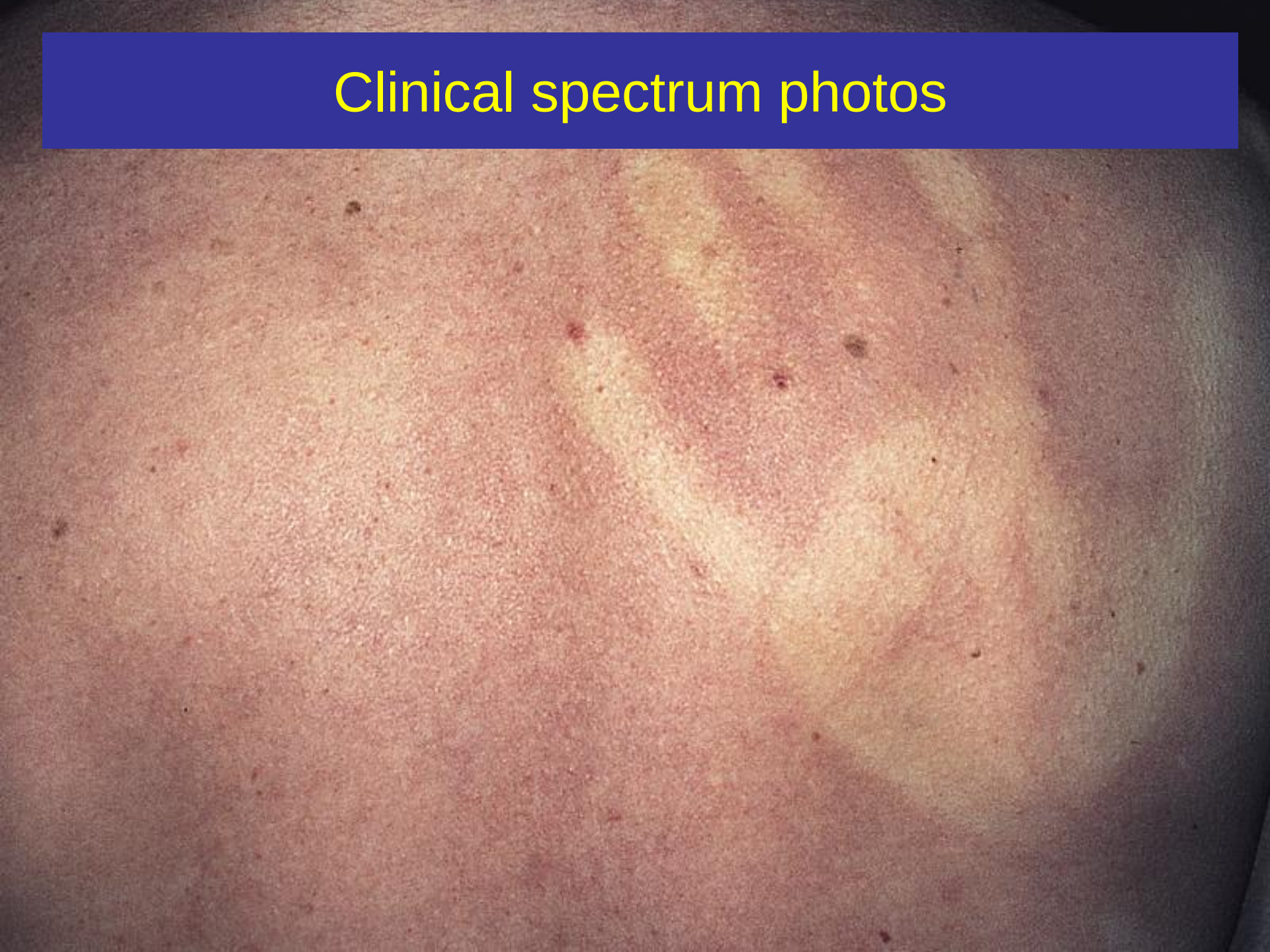
Clinical spectrum photos



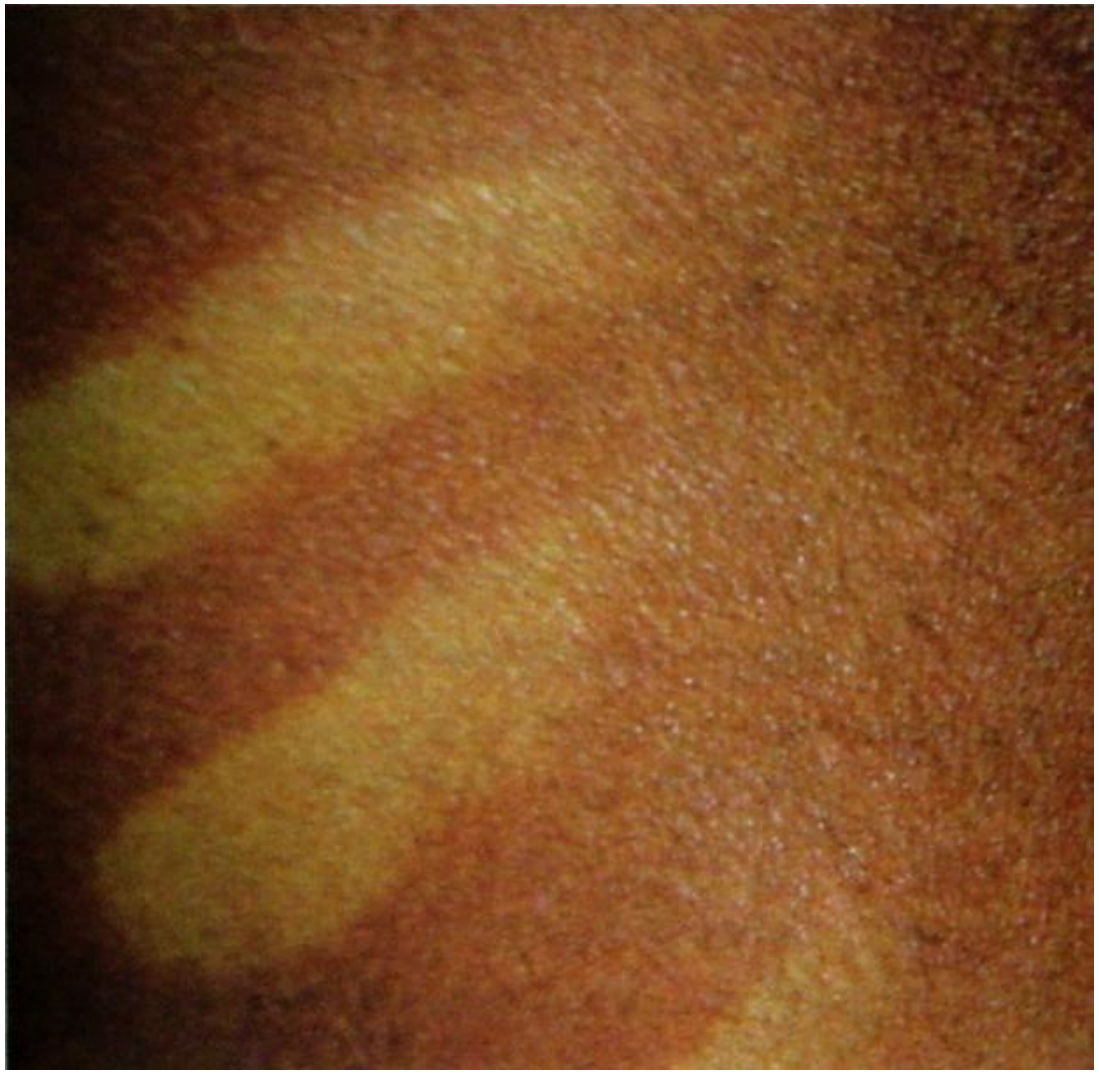
Clinical spectrum photos



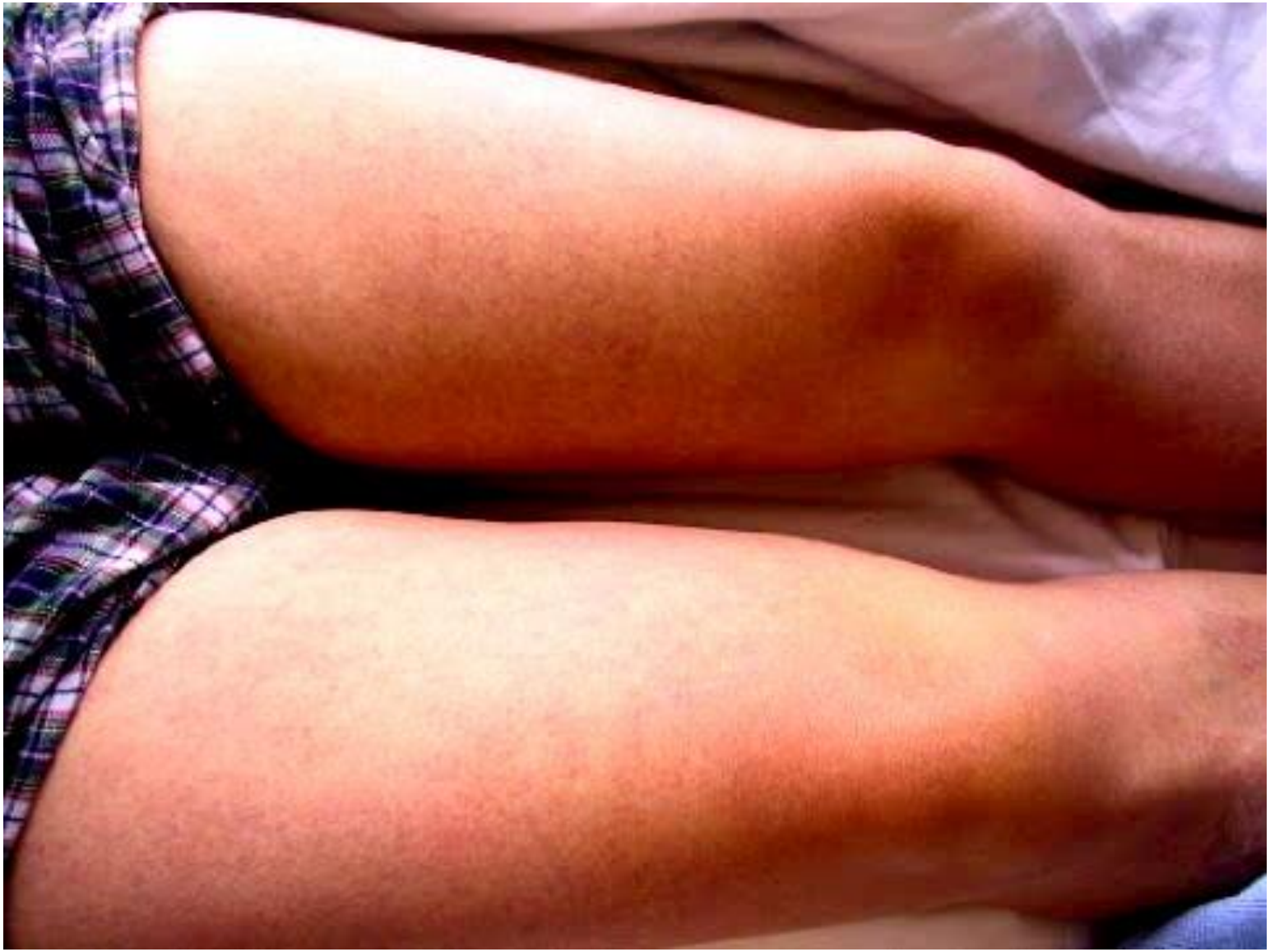
Clinical spectrum photos



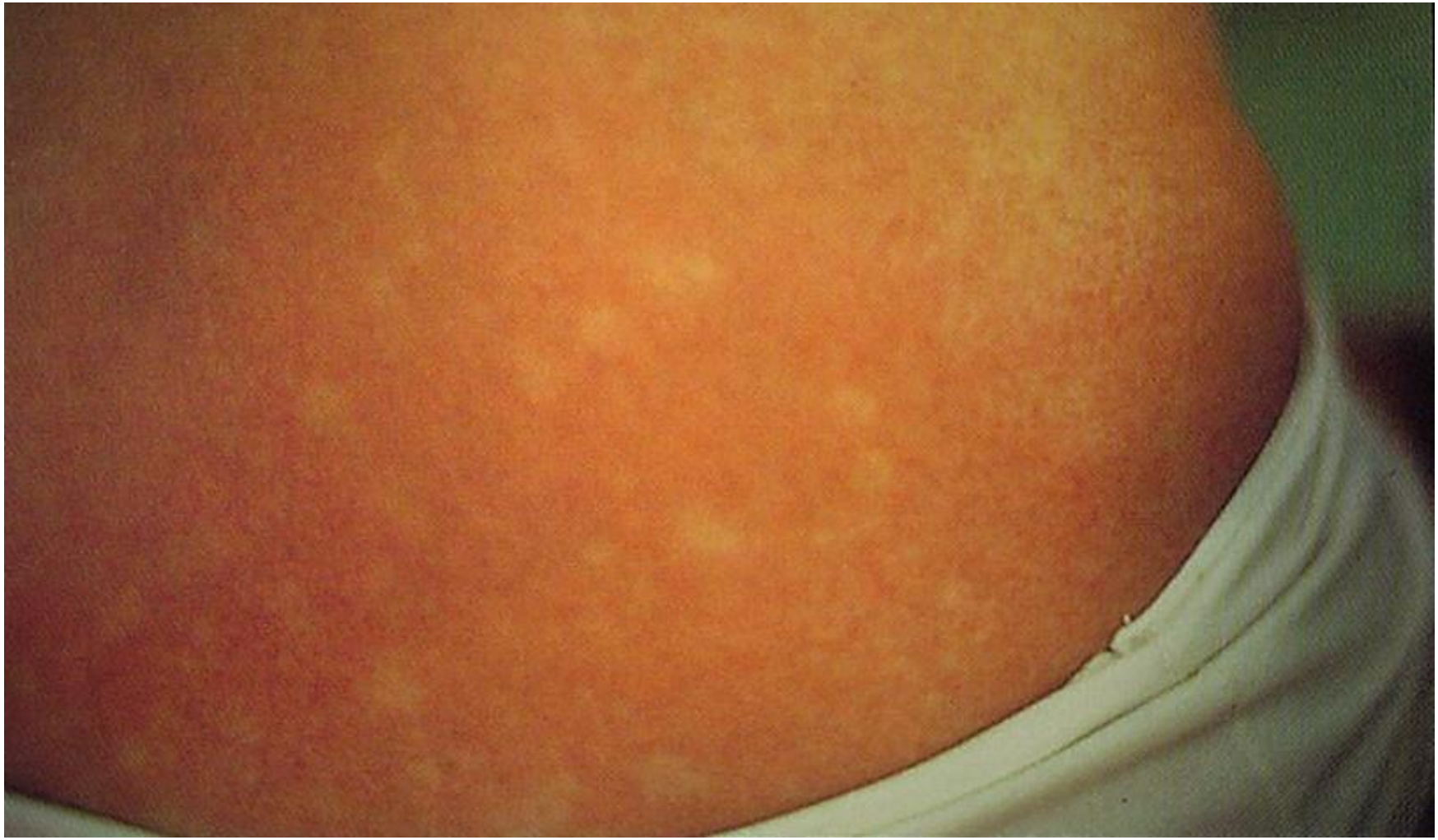
Clinical spectrum photos



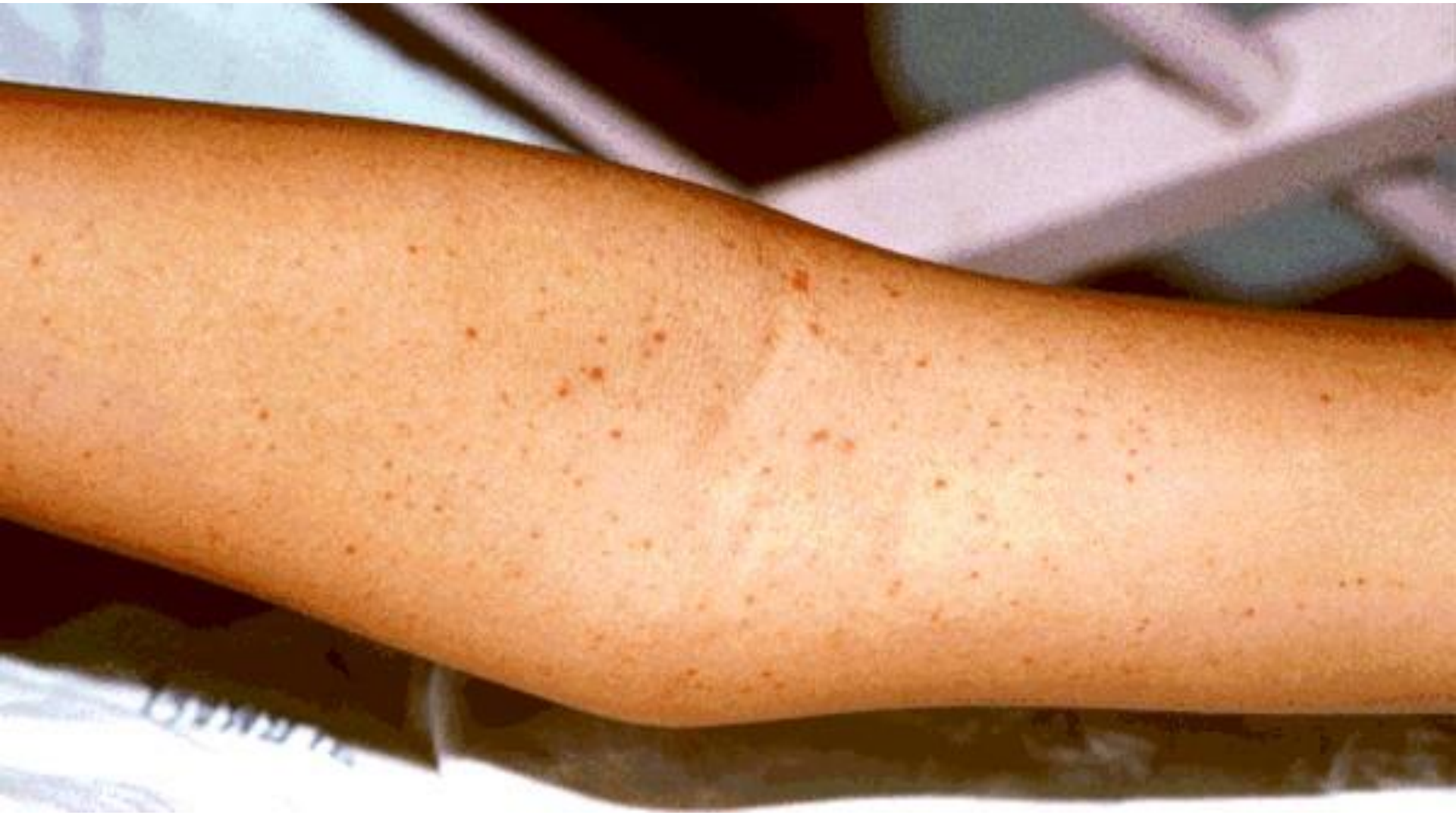
Clinical spectrum photos



Clinical spectrum photos



Clinical spectrum photos



DENGUE GUIDELINES FOR DIAGNOSIS, TREATMENT, PREVENTION AND CONTROL

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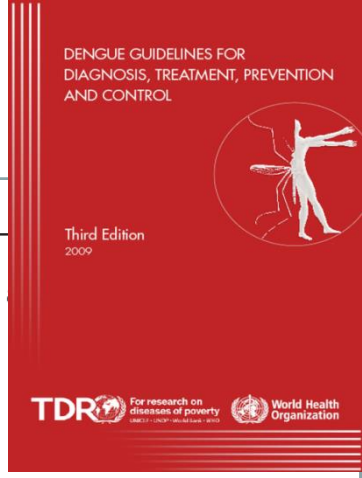
World Health Organization

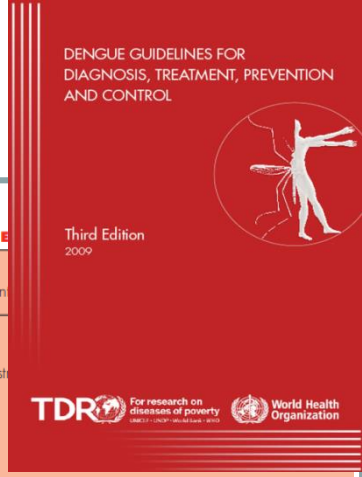
Dengue case classification by severity



Severity classification	Definition
Dengue without warning signs	A person who lives in or has traveled in the previous 14 days to areas with dengue transmission … fever usually for 2 to 7 days, and 2 or more of the following clinical manifestations: **1.** Nausea or vomiting **2.** Exanthema **3.** Headache or retro-orbital pain **4.** Myalgia or arthralgia **5.** Petechiae or positive tourniquet test **6.** Leukopenia
Dengue with warning signs	Any case of dengue that presents one or more of the following signs as, or preferably after, fever drops: **1.** Intense and sustained abdominal pain, or tenderness of the abdomen **2.** Persistent vomiting **3.** Fluid accumulation **4.** Mucosal bleed **5.** Lethargy or restlessness **6.** Postural hypotension (lipothymia) **7.** Liver enlargement >2 cm below the costal margin **8.** Progressive increase in hematocrit
Severe dengue	Any case of dengue that has one or more of the following clinical manifestations: **1.** Shock or respiratory distress due to severe plasma leakage. **2.** Severe bleeding: as assessed by the attending physician. **3.** Severe organ involvement (liver damage, myocarditis, etc.)

WHO Dengue guideline, 2009

Dengue diagnostics, treatment and fup monitoring by severity



MANAGEMENT

DENGUE WITHOUT WARNING SIGNS ↓ **DENGUE WITH WARNING SIGNS** **SEVERE DENGUE**

Group A
(May be sent home)

Group criteria
Patients who do not have warning signs
AND
who are able:
- to tolerate adequate volumes of oral fluids
- to pass urine at least once every 6 hours

Laboratory tests
- full blood count (FBC)
- haematocrit (HCT)

Treatment
Advice for:
- adequate bed rest
- adequate fluid intake
- Paracetamol, 4 gram maximum per day in adults and accordingly in children.

Patients with stable HCT can be sent home.

Monitoring
Daily review for disease progression:
- decreasing white blood cell count
- defervescence
- warning signs (until out of critical period).

Advice for immediate return to hospital if development of any warning signs, and
- written advice for management (e.g. home care card for dengue).

Group B
(Referred for in-hospital care)

Group criteria
Patients with any of the following features:
- co-existing conditions such as pregnancy, infancy, old age, diabetes mellitus, renal failure
- social circumstances such as living alone, living far from hospital

Laboratory tests
- full blood count (FBC)
- haematocrit (HCT)

Treatment
- Encouragement for oral fluids. If not tolerated, start intravenous fluid therapy 0,9% saline or Ringer's Lactate at maintenance rate.

Monitoring
Monitor:
- temperature pattern
- volume of fluid intake and losses
- urine output (volume and frequency)
- warning signs
- HCT, white blood cell and platelet counts.

OR: Existing warning signs

Laboratory tests
- full blood count (FBC)
- haematocrit (HCT)

Treatment
Obtain reference HCT before fluid therapy. Give isotonic solutions such as 0.9 % saline, Ringer's Lactate. Start with 5–7 ml/kg/hr for 1–2 hours, then reduce to 3–5 ml/kg/hr for 2–4 hr, and then reduce to 2–3 ml/kg/hr or less according to clinical response.

Reassess clinical status and repeat HCT:
- if HCT remains the same or rises only minimally -> continue with 2–3 ml/kg/hr for another 2–4 hours;
- if worsening of vital signs and rapidly rising HCT -> increase rate to 5–10 ml/kg/hr for 1–2 hours.

Reassess clinical status, repeat HCT and review fluid infusion rates accordingly:
- reduce intravenous fluids gradually when the rate of plasma leakage decreases towards the end of the critical phase.

This is indicated by:
- adequate urine output and/or fluid intake
- HCT deceases below the baseline value in a stable patient.

Monitoring
Monitor:
- vital signs and peripheral perfusion (1–4 hourly until patient is out of critical phase
- urine output (4–6 hourly)
- HCT (before and after fluid replacement, then 6–12 hourly)
- blood glucose
- other organ functions (renal profile, liver profile, coagulation profile, as indicated).

Group C
(Require emergency treatment

Group criteria
Patients with any of the following features:
- severe plasma leakage with shock and/or fluid accumulation with respiratory dist
- severe bleeding
- severe organ impairment

Laboratory tests
- full blood count (FBC)
- haematocrit (HCT)
- other organ function tests as indicated

Treatment of compensated shock
Start IV fluid resuscitation with isotonic crystalloid solutions at 5–10 ml/kg/hr over 1 hour. Reassess patients' condition.

If patient improves:
- IV fluids should be reduced gradually to 5–7 ml/kg/hr for 1–2 hours, then to 3–5 ml/kg/hr for 2–4 hours, then to 2-3 ml/kg/hr for 2–4 hours and then reduced further depending on haemodynamic status;
- IV fluids can be maintained for up to 24–48 hours.

If patient is still unstable:
- check HCT after first bolus;
- **if HCT increases**/still high (>50%), repeat a second bolus of crystalloid solution at 10–20 ml/kg/hr for 1 hour;
- if there is improvement after second bolus, reduce rate to 7–10 ml/kg/hr for 1–2 hours and continue to reduce as above;
- **if HCT decreases**, this indicates bleeding and need to cross-match and transfuse blood as soon as possible.

Treatment of hypotensive shock
Initiate IV fluid resuscitation with crystalloid or colloid solution at 20 ml/kg as a bolus for 15 minutes.
If patient improves:
- give a crystalloid/colloid solution of 10 ml/kg/hr for 1 hour, then reduce gradually as above.

If patient is still unstable:
- review the HCT taken before the first bolus;
- **if HCT was low** (<40% in children and adult females, <45% in adult males) this indicates bleeding, the need to cross-match and transfuse (see above);
- **if HCT was high** compared to baseline value, change to IV colloids at 10–20 ml/kg as a second bolus over 30 minutes to 1 hour; reassess after second bolus.
- **If patient is improving** reduce the rate to 7–10ml/kg/hr for 1–2 hours, then back to IV cystalloids and reduce rates as above;
- **if patient's condition is still unstable**, repeat HCT after second bolus.
- **If HCT decreases**, this indicates bleeding (see above);
- **if HCT increases**/remains high (>50%), continue colloid infusion at 10–20 ml/kg as a third bolus over 1 hour, then reduce to 7–10 ml/kg/h 1–2 hours, then change back to crystalloid solution and reduce rate as above.

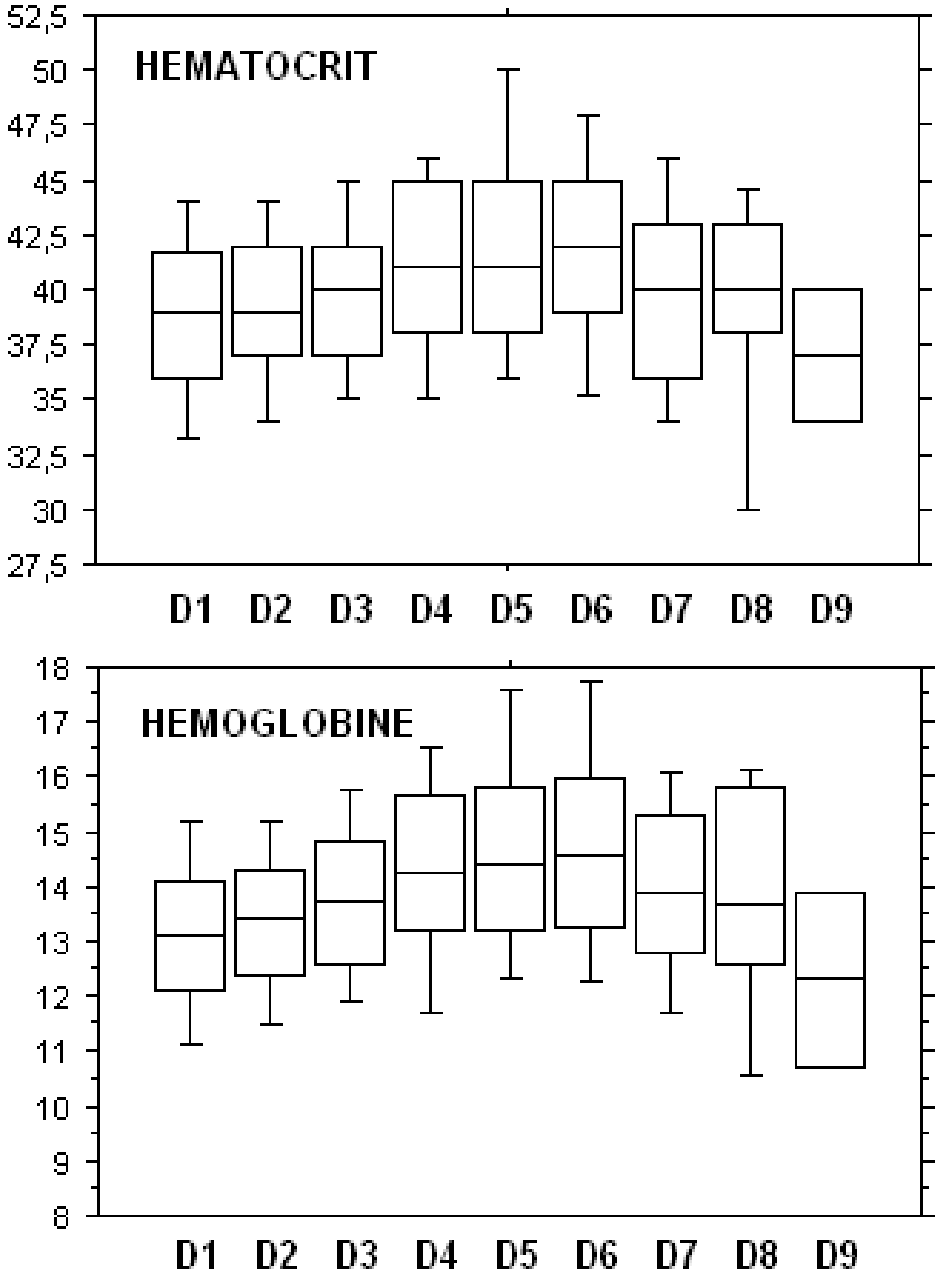
Treatment of haemorrhagic complications
Give 5–10 ml/kg of fresh packed red cells or 10–20 ml/kg of fresh whole blood.

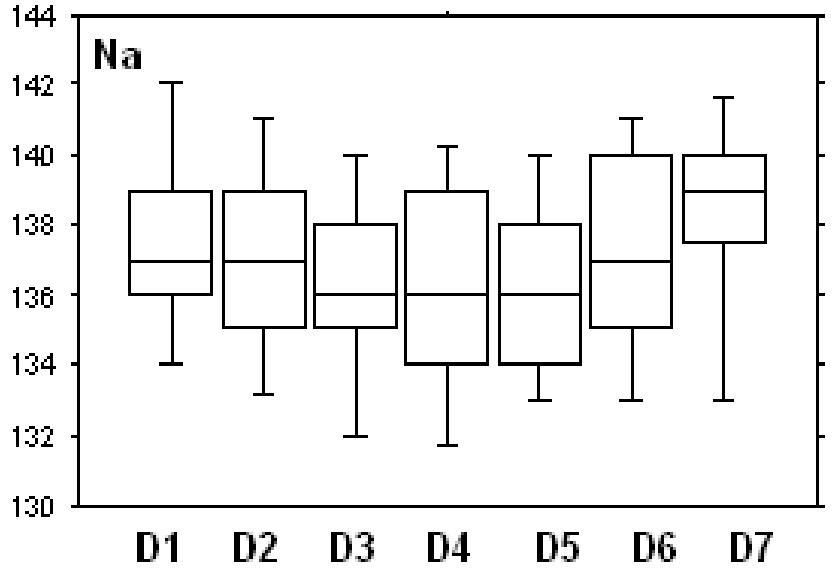
WHO Dengue guideline, 2009

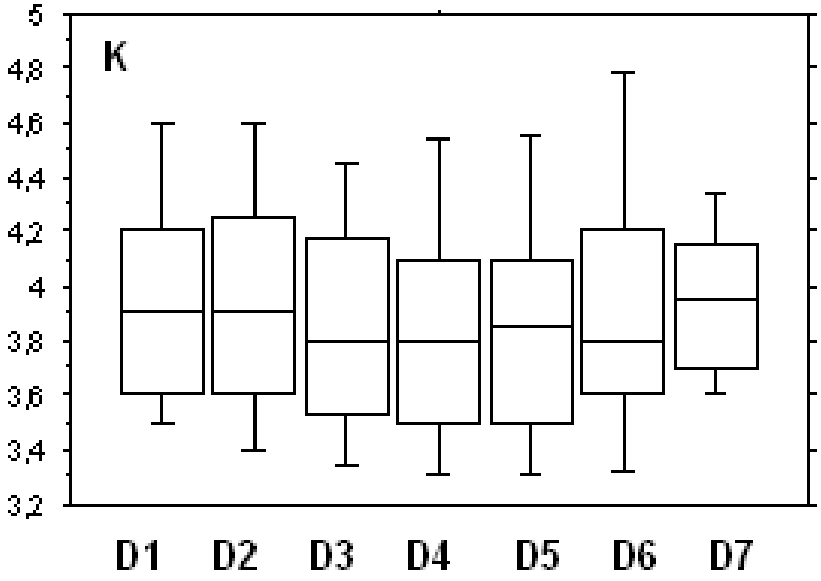
Diagnosis of plasma leakage

- **Hemoconcentration** (as defined by WHO): increased hematocrit > 20% from baseline value OR despite fluid administration (= increased hemoglobin)
- Evidence of **pleural effusion and/or ascites** (Xray, Ultrasounds +++)
- Miscelaneous: ***hypo proteinemia***, **hypo albuminemia**, **pulmonary edema**

Data recorded in 560 consecutive dengue patients in Martinique at the time of admission on the ED, according to the time elapsed since the onset of fever




Na
144
142
140
138
136
134
132
130
D1
D2
D3
D4
D5
D6
D7


K
5
4,8
4,6
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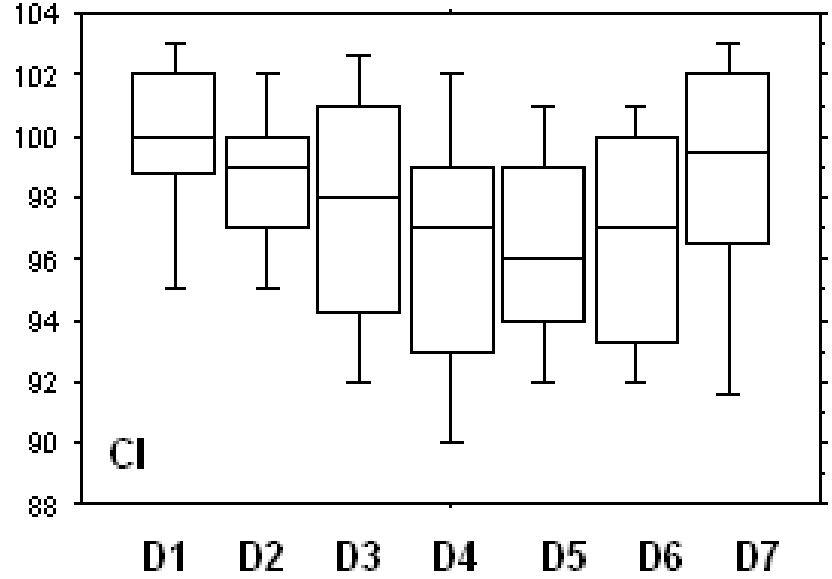
Cl
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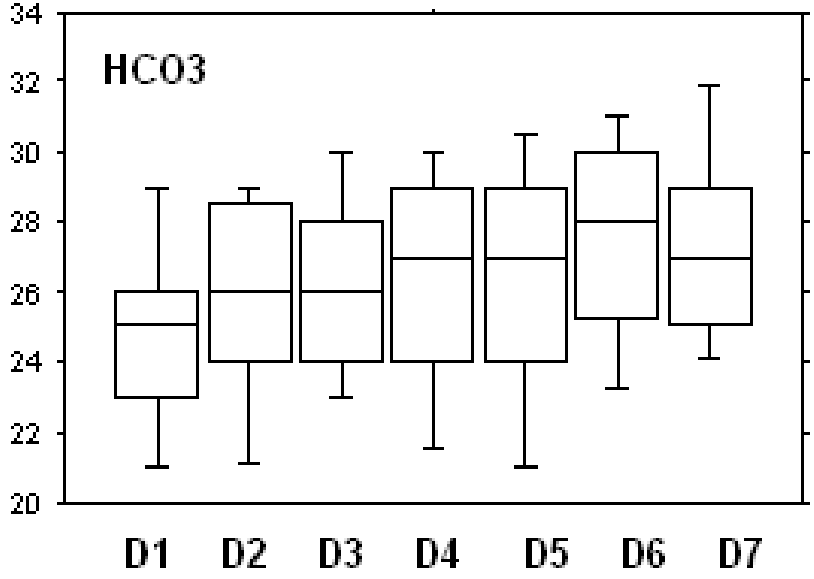
HCO3
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32
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28
26
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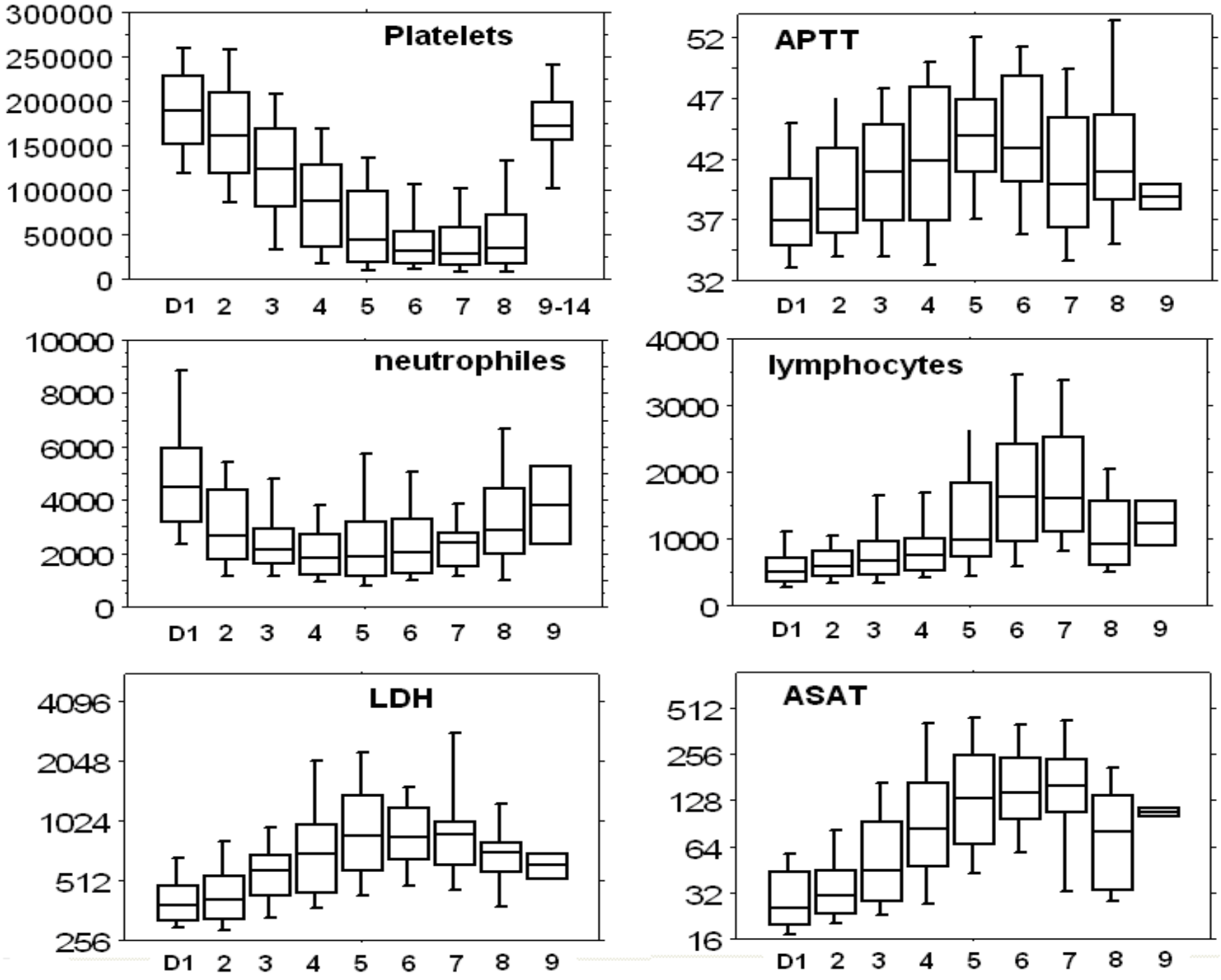

Platelets
300000
250000
200000
150000
100000
50000
0
D1 2 3 4 5 6 7 8 9-14
APTT
52
47
42
37
32
D1 2 3 4 5 6 7 8 9
neutrophiles
10000
8000
6000
4000
2000
0
D1 2 3 4 5 6 7 8 9
lymphocytes
4000
3000
2000
1000
0
D1 2 3 4 5 6 7 8 9
LDH
4096
2048
1024
512
256
D1 2 3 4 5 6 7 8 9
ASAT
512
256
128
64
32
16
D1 2 3 4 5 6 7 8 9

DF with no warning sign

- **Encourage oral fluids**. If not tolerated, start intravenous fluid therapy of 0.9% saline or Ringer's lactate with or without dextrose at maintenance rate.
- For obese and overweight patients, use the ideal body weight for calculation of fluid infusion
- Patients may be able to take oral fluids after a few hours of intravenous fluid therapy. Thus, it is necessary to revise the fluid infusion frequently. Give the minimum volume required to maintain good perfusion and urine output.
- **Intravenous fluids are usually needed only for 24–48 hou**rs.
- Patients should be monitored by health care providers for temperature pattern, volume of fluid intake and losses, urine output, warning signs, haematocrit, and white blood cell and platelet counts

DF with warning sign -1

- **Monitor vital signs (1–4 hourly) urine output (4–6 hourly),** haematocrit (before and after fluid replacement, then 6–12 hourly), blood glucose, and other organ functions and encourage oral fluids.
- Give only isotonic solutions 0.9% NACl or Ringer's lactate start with **5–7 ml/ kg/hour for 1–2 hours, then reduce to 3–5 ml/kg/hr for 2–4 hours, and then reduce to 2–3 ml/kg/hr** or less according to the clinical response
- **Reassess the clinical status and repeat the haematocrit**. If the haematocrit remains the same or rises only minimally, continue with the same rate (2–3 ml/kg/hr) for another 2–4 hours.
- **If the vital signs are worsening and haematocrit is rising rapidly, increase the rate to 5–10** ml/kg/hour for 1–2 hours.

Care of hospitalized patients (4)
Management / case report (adults)

- Hypotensive patients (<90/60 mmHg) without other direct indicators of clinical severity (alert, normal respiratory rate, no pleural effusion, no metabolic acidosis)
  - **isotonic crystalloids infusion, 6 to 10 mL/kg/hour during 2 to 4 hours**
  - close monitoring, repeated clinical evaluations
  - repeated measurements of hematocrit, hemoglobin, lactatemia, blood gases

- **If improvement** (mean arterial pressure > 70 mmHg, urine output > 0.5 mL/kg/hour, and lactatemia < 4 mmol/L),
  - **reduce the flow to 3-5 mL/kg/hour for 8 to 12 hours** and achieve a strict fluid balance
  - close observation may be conducted on the Intermediate Care Unit
  - In the case of confirmed improvement, reduce to 50 mL/kg/day.

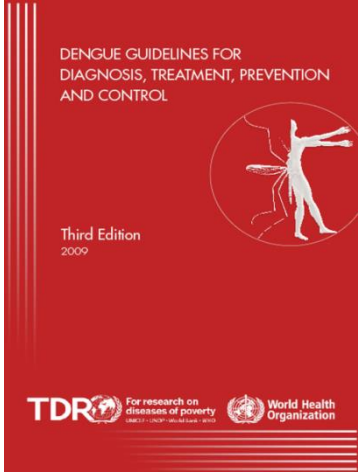


Figure 2.2 Algorithm for fluid management in compensated shock

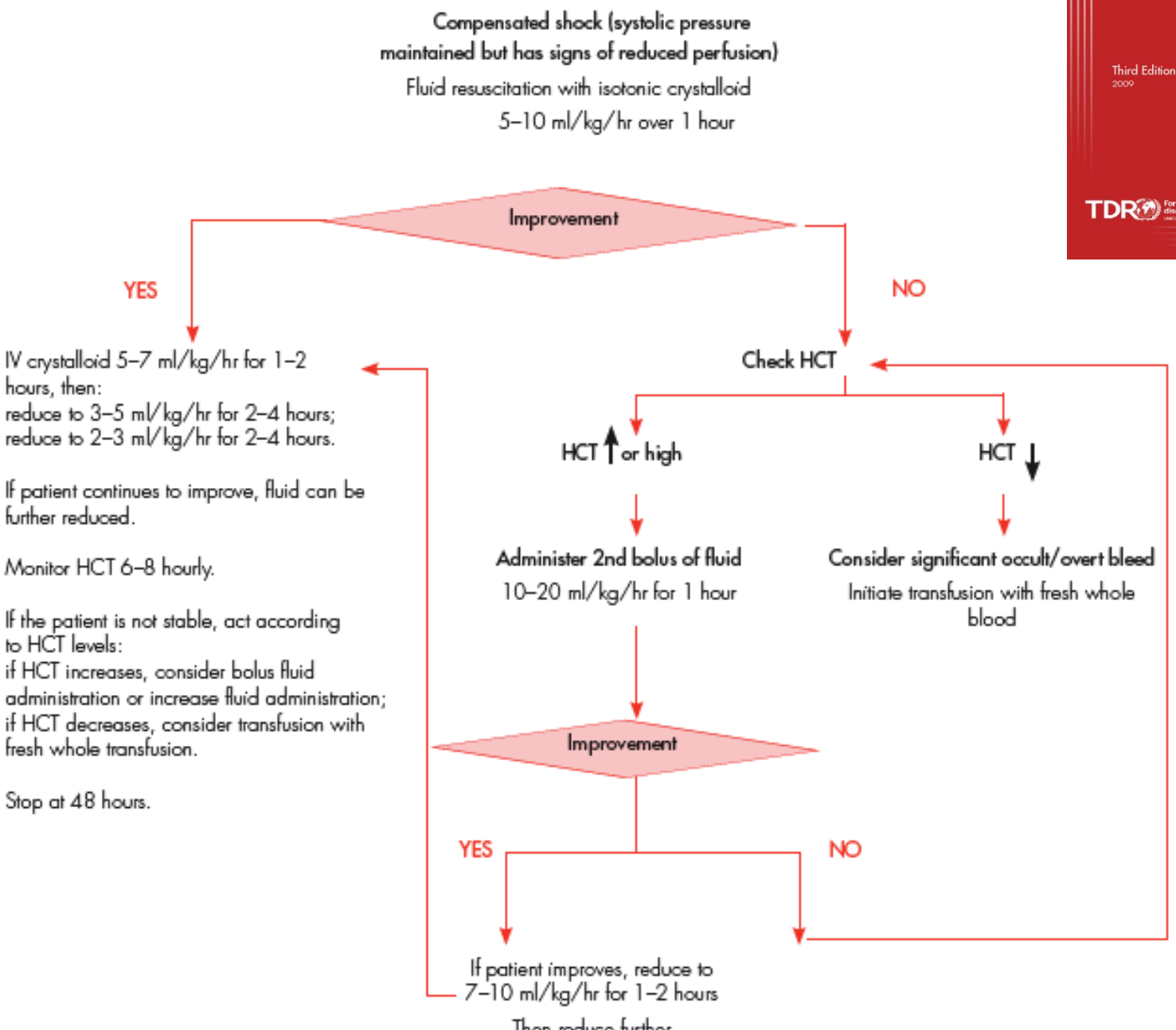
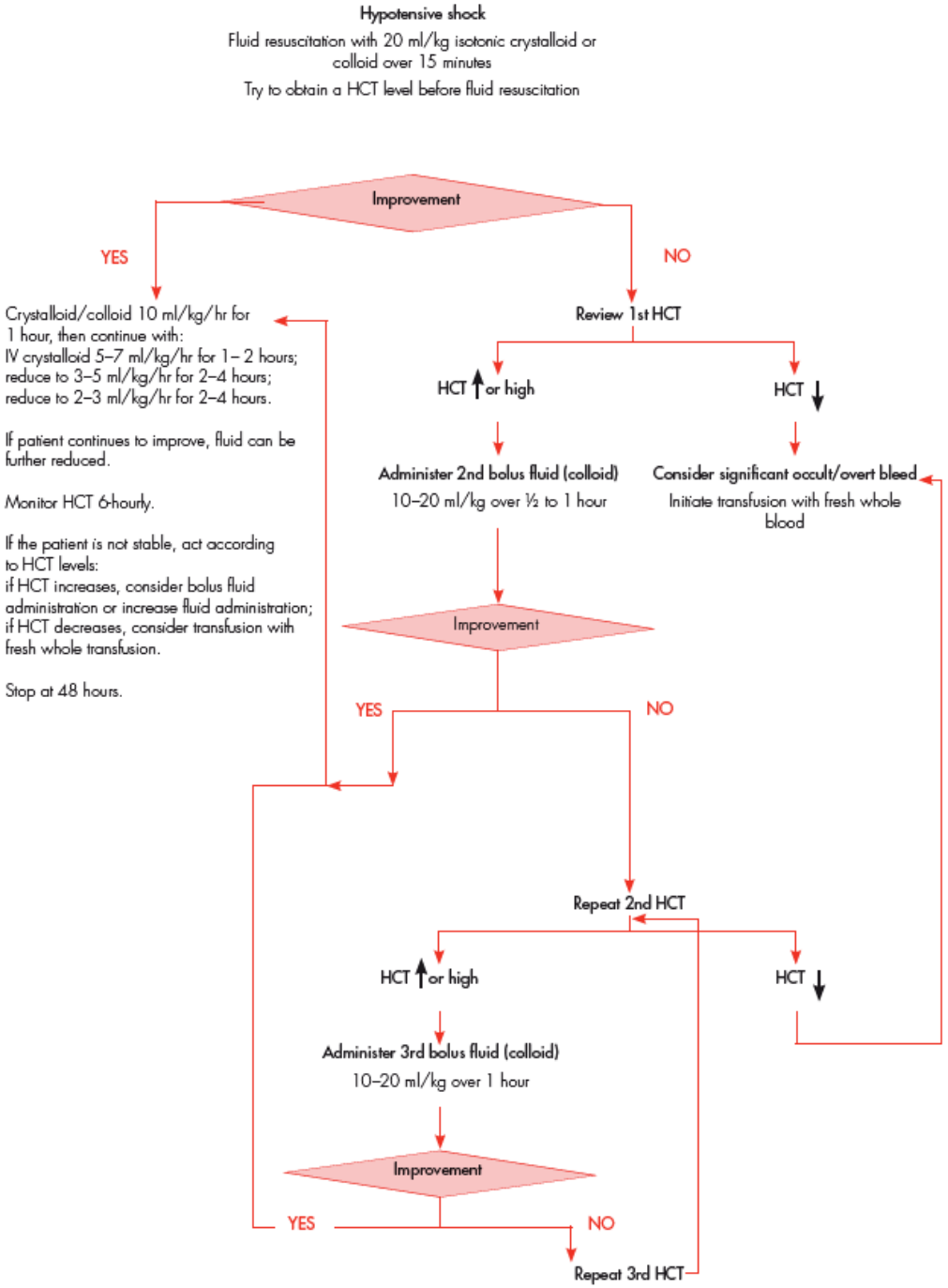
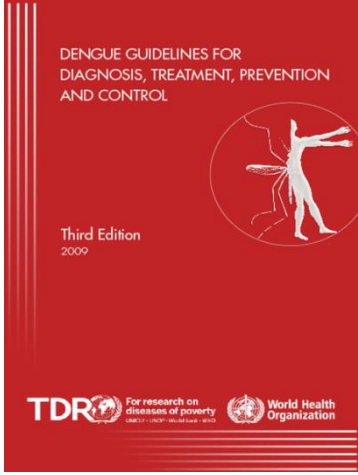


Figure 2.3 Algorithm for fluid management in hypotensive shock





Do not – Choosing wisely

- Most patients will experience only minor cutaneous and/or mucosal bleeding
- Prevention +++
  - **NO aspirin, NO NSAIDs,**
  - **NO steroids**
  - **NO IM injections**
  - **NO puncture of large** vessels, no **nasogastric tube**, no **urine catheterization or central line** unless absolute necessity
  - **NO hyper or over hydration**
  - in severely thrombocytopenic patients (<20,000 /mL):
    - Consider associated pathology or treatments
    - Prevention of trauma +++

Management of bleeding (cont'd)

- Severe bleeding (infrequent)
  - Gastrointestinal bleeding in adults with peptic ulcer or colonic diverticulosis, or previously treated with NSAIDs
  - Metrorrhagia (fibroma, spontaneous abortion)
  - Trauma
    - Accident (falls +++)
    - emergency surgery (delivery / cesarian section, spleen rupture, appendicitis, cholecystitis …)
    - **iatrogenic (IM, puncture of large vessels, urine catheter, nasogastric tube, lumbar puncture)**
  - Intracranial bleeding
- Clinically significant epistaxis: nasal package

Management of thrombocytopenia

- Peripheral destruction of platelets
- Decreased bone marrow production
- Impairment of platelet functions
- Typical evolution

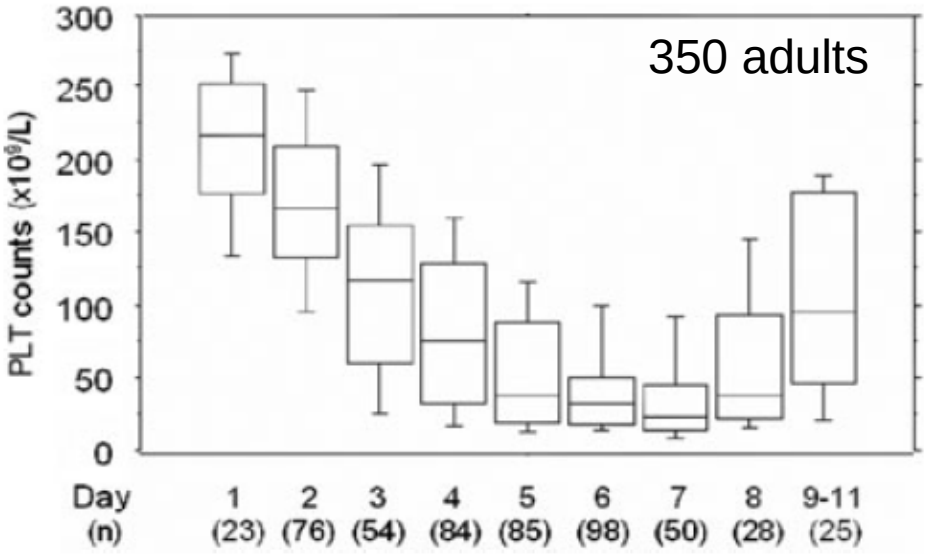
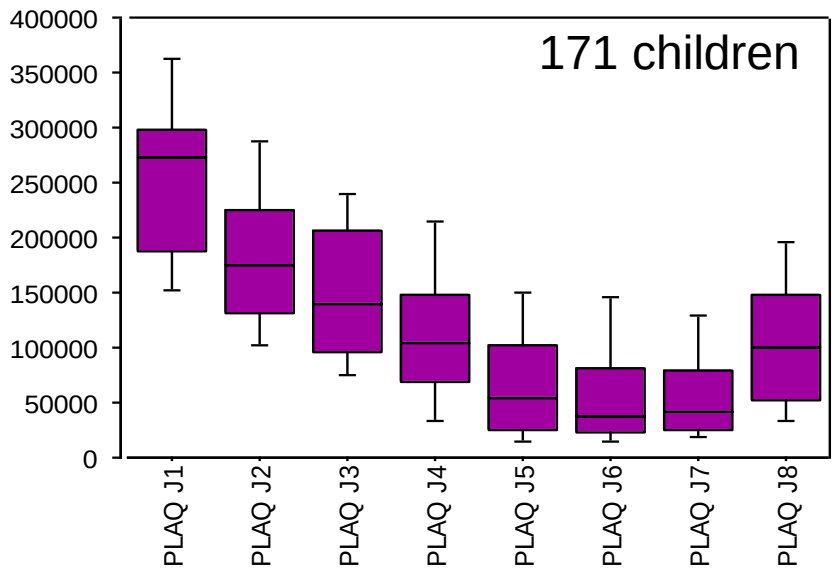
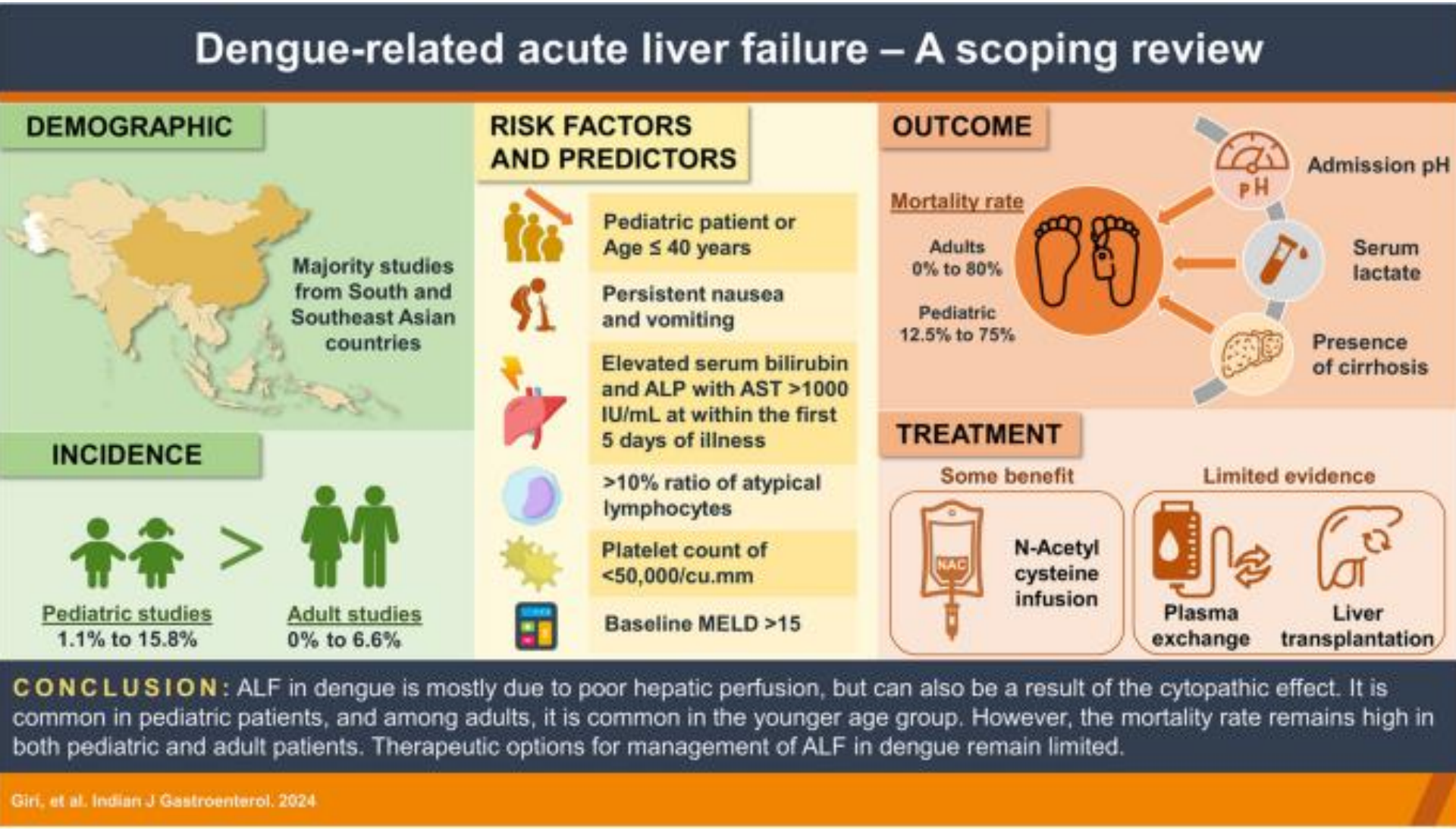


Fig. 2. PLT counts recorded in 350 patients with confirmed dengue infections and plotted against the time elapsed between the onset of fever (Day 1) and sampling



Y. Hatchuel,
University Hospital,Fort-de-France
(personal communication)

Management of LIVER toxicities



Management of LIVER toxicities

- In severe liver involvement (4-6% severe DF), mortality can rise to 50% owing to significant bleeding, hepatic encephalopathy, kidney injury, and metabolic acidosis.

- **Role of N-acetylcysteine in liver injury due to dengue fever**

Table 1. Research studies on efficacy of NAC in dengue fever with severe hepatitis.

Study	Study Type	Description	Treatment given	Time to recovery	Mortality	Remark
Ishtiaq et al. 2019[22]	Descriptive cross-sectional study	63 admitted patients with dengue-associate during 18-month period	NAC infusion PCV transfusion	Not specified	None	Possibly effective
Dissanayake et al. 2021[23]	Retrospective analysis	30 adults with severe DF and severe hepatitis	NAC infusion	mean length of hospital stay: 6.2 ± 1.27 days.	One patient	Effective with faster clinical and biochemical recovery
Sriphongphankul et al. 2021[24]	Retrospective cohort study	33 patients with DF associated ALF; 33/16 received NAC	NAC infusion	median duration of ALF was 5 days in the NAC group and 4 days in the non-NAC treatment ($p = 0.91$). The length of hospital stay in the NAC treatment group was 25 days vs. 22.7 days in the non- NAC treatment group	Two patients (one case of each group) had ALF resolution but died from other complications (one child with uncontrolled invasive aspergillosis pneumonia and acute renal failure in the NAC group and another child with intracranial bleeding in the non-NAC group).	Maybe beneficial in paediatric population

Gupta trop doc 2023

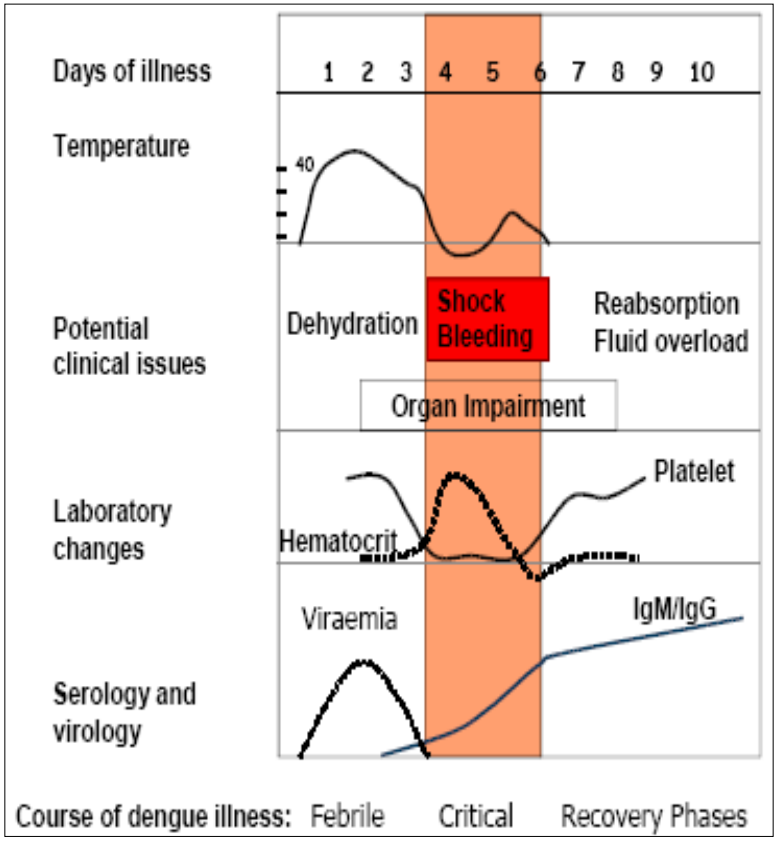
Discharge criteria (1)

Discharge of patients with severe forms of the disease

- patient feels much better and tolerates significant oral intake
- evidence of cessation of plasma leakage & clinically significant bleeding
- regression of fluid overload
- no fever for 48 hours
- Biology: increasing trend in platelet counts and stable hematocrit without iv fluids

Notice: 25% of dengue patients may have long-term fatigue syndrome

Discharge criteria (2)



Adapted from WCL Yip, Medical progress 1980

1) Precise timing toward the course of the disease
2) Examine the feasibility of follow up at home:
-no warning sign
-hydration via oral route
-good social environment
-flow chart of recommendations

Dengue

	Dengvaxia (CYD-TDV)[163]	Qdenga (TAK-003)[167]	TV003[168]
Manufacturer	Sanofi Pasteur	Takeda	US National Institutes of Health, Instituto Butantan, and Merck & Co
Status	Recommended by WHO for two patient groups: seropositive people aged 9–45 years, or all people regardless of serostatus in high seroprevalence areas (>80% seropositivity). Licensed in 20 countries. Recommended for seropositive children aged 9–16 years living in endemic areas in the USA[155]	Recommended by WHO to be considered for introduction in children aged 6–16 years in settings with high transmission intensity. Licensed in several countries, including Indonesia, Brazil, Argentina, the UK, and Germany	Ongoing phase 3 trial
Platform	Four chimeric viruses for each DENV serotype on a yellow fever virus backbone	Attenuated DENV-2 and three chimeric viruses for each of the four DENV serotypes	Attenuated DENV-1, DENV-3, and DENV-4, and a chimeric virus for DENV-2 on a DENV-4 backbone
Ages of trial participants	9–16 years	6–16 years	2–59 years
Doses	Three doses 6 months apart	Two doses 3 months apart	One dose
Prevaccination antibody screening recommended?	Yes	No	Unknown
Timeframe for efficacy endpoint	25 months for VCD and 60 months for hospitalisation	54 months for VCD and hospitalisation	24 months for VCD
Efficacy among seropositive people			
VCD: overall	76% (64% to 84%)	64% (58% to 69%)	89% (78% to 96%)
VCD: by serotype			
DENV-1	67% (46% to 80%)	56% (45% to 65%)	97% (81% to 100%)
DENV-2	67% (47 to 80%)	80% (73% to 86%)	84% (63% to 94%)
DENV-3	80% (67% to 88%)	52% (37% to 64%)	NR
DENV-4	89% (80% to 94%)	71% (40% to 86%)	NR
Hospitalisation: overall	79% (46% to 80%)	86% (79% to 91%)	NR
Hospitalisation: by serotype			
DENV-1	78% (55% to 90%)	67% (37% to 82%)	NR
DENV-2	82% (66% to 90%)	96% (90% to 98%)	NR
DENV-3	63% (18% to 83%)	74% (39% to 89%)	NR
DENV-4	89% (62% to 99%)	100% (NE)	NR
Efficacy among seronegative people			
VCD: overall	39% (–1% to 63%)	54% (42% to 63%)	74% (58% to 84%)
VCD: by serotype			
DENV-1	41% (–7% to 67%)	45% (26% to 60%)	86% (69% to 94%)
DENV-2	–21% (–136% to 38%)	88% (79% to 93%)	58% (21% to 78%)
DENV-3	52% (–6% to 78%)	–16% (–108% to 36%)	NR
DENV-4	65% (24% to 84%)	–106% (–629% to 42%)	NR
Hospitalisation overall	–41% (–168% to 93%)	79% (64% to 88%)	NR
Hospitalisation by serotype			
DENV-1	–37% (–219% to 41%)	78% (44% to 92%)	NR
DENV-2	–141% (–795% to 35%)	100% (NE)	NR
DENV-3	15% (–225% to 78%)	–88% (–573% to 48%)	NR
DENV-4	7% (–712% to 89%)	100% (NE)	NR

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