Dengue Training For Frontliners 2023: Lecture 1 – Introduction & Clinical Course

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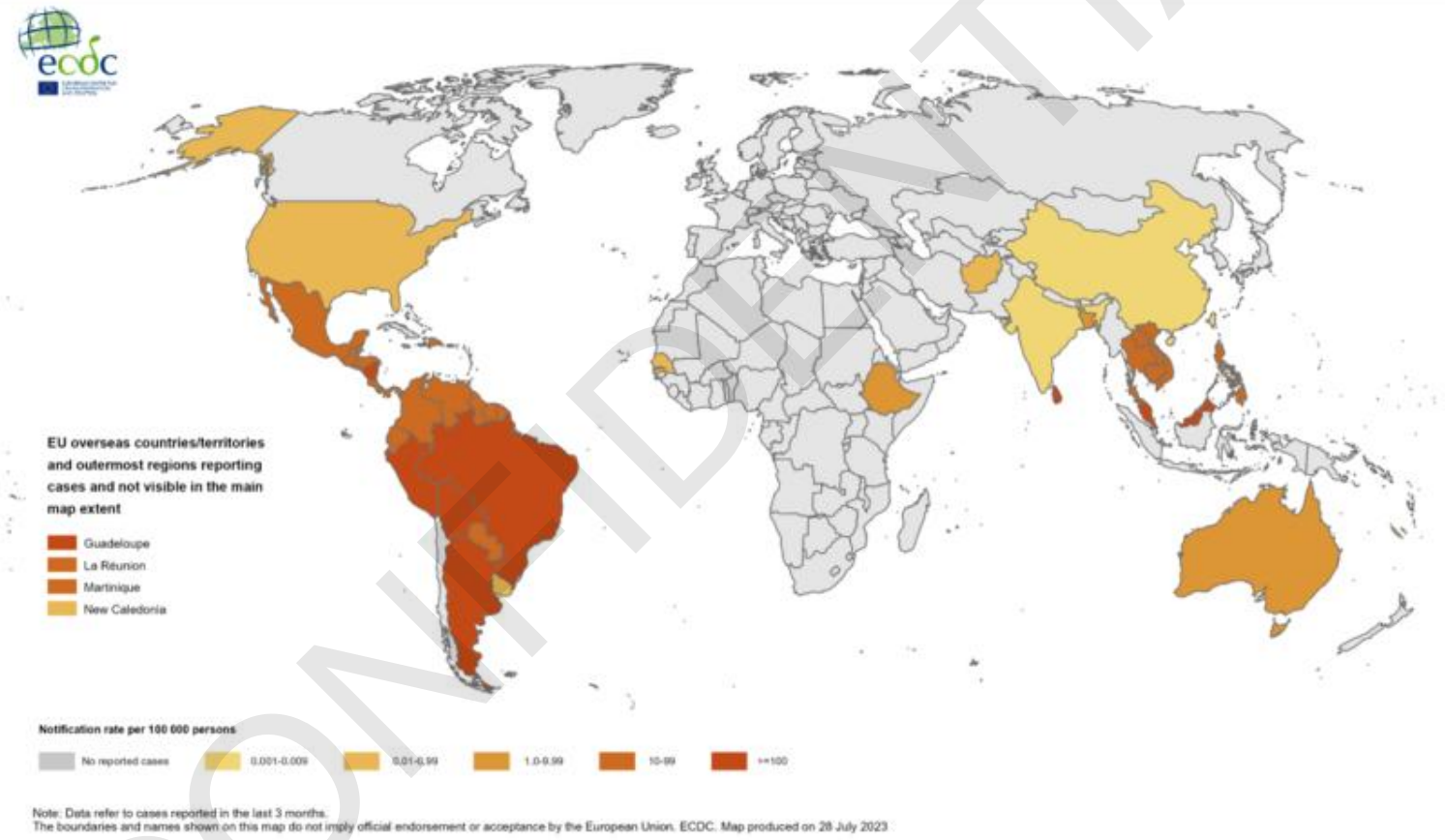
8 June 2023

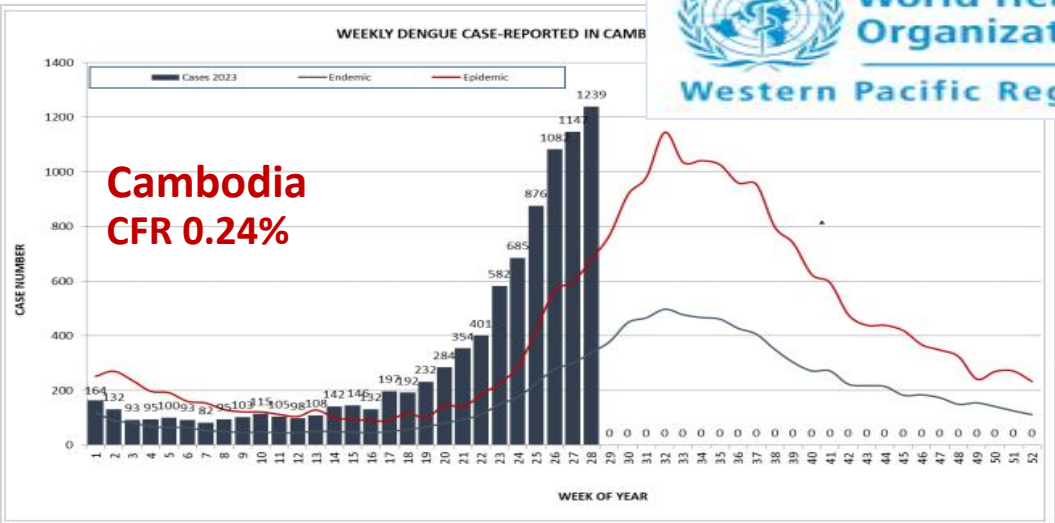


Geographical distribution of dengue cases reported worldwide

World Health Organization
Western Pacific Region

Dengue Situation Update 677

03 August 2023

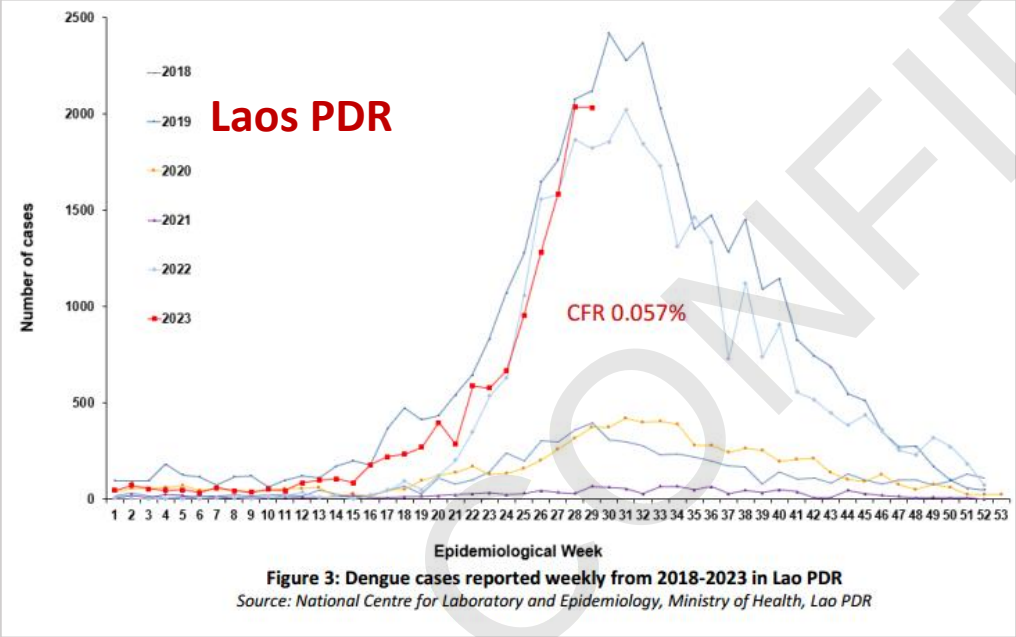


Cambodia
CFR 0.24%

Figure 1: Dengue cases reported weekly in 2023 vs Mean and Mean+2SD during 2015-2020 *excluding 2019 in Cambodia;
Source: National Dengue Surveillance System (NDCP/CNM/MOH)

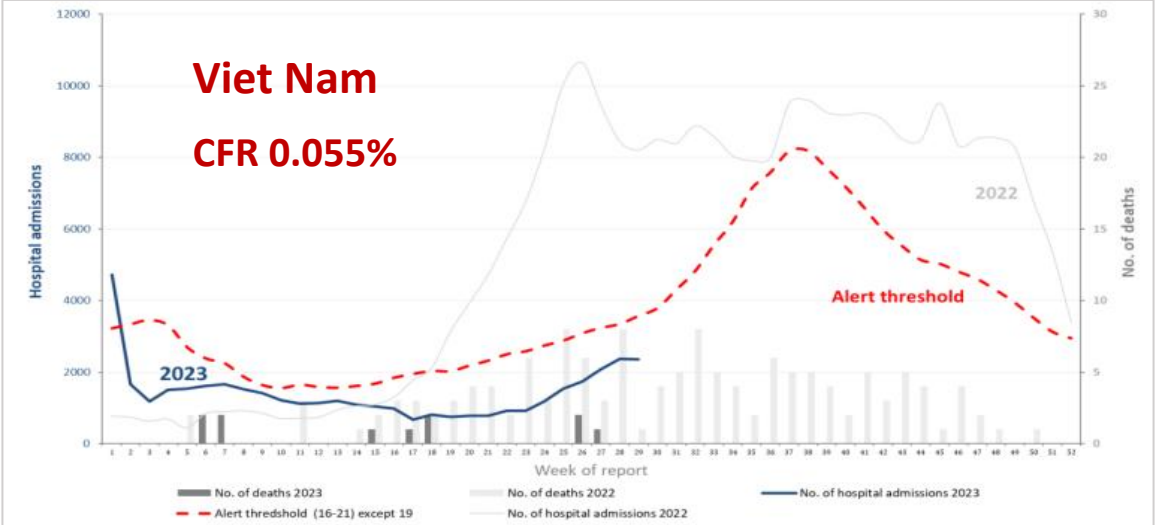
Philippines
CFR 0.4%

Figure 5: Dengue cases reported weekly from 2022 and 2023 in the Philippines
Source: Department of Health, the Philippines



Laos PDR
CFR 0.057%

Figure 3: Dengue cases reported weekly from 2018-2023 in Lao PDR
Source: National Centre for Laboratory and Epidemiology, Ministry of Health, Lao PDR



Viet Nam
CFR 0.055%

Figure 7: Number of dengue hospital admissions and deaths by weeks in 2022 compared to 2023, as of week 29 2023, Viet Nam
Source: General Department of Preventive Medicine, Ministry of Health, Viet Nam

MALAYSIA

KES MINGGUAN DENGGI 2022 & 2023

Tahun 2023 (Minggu 25 sehingga 3 Ogos 2023)

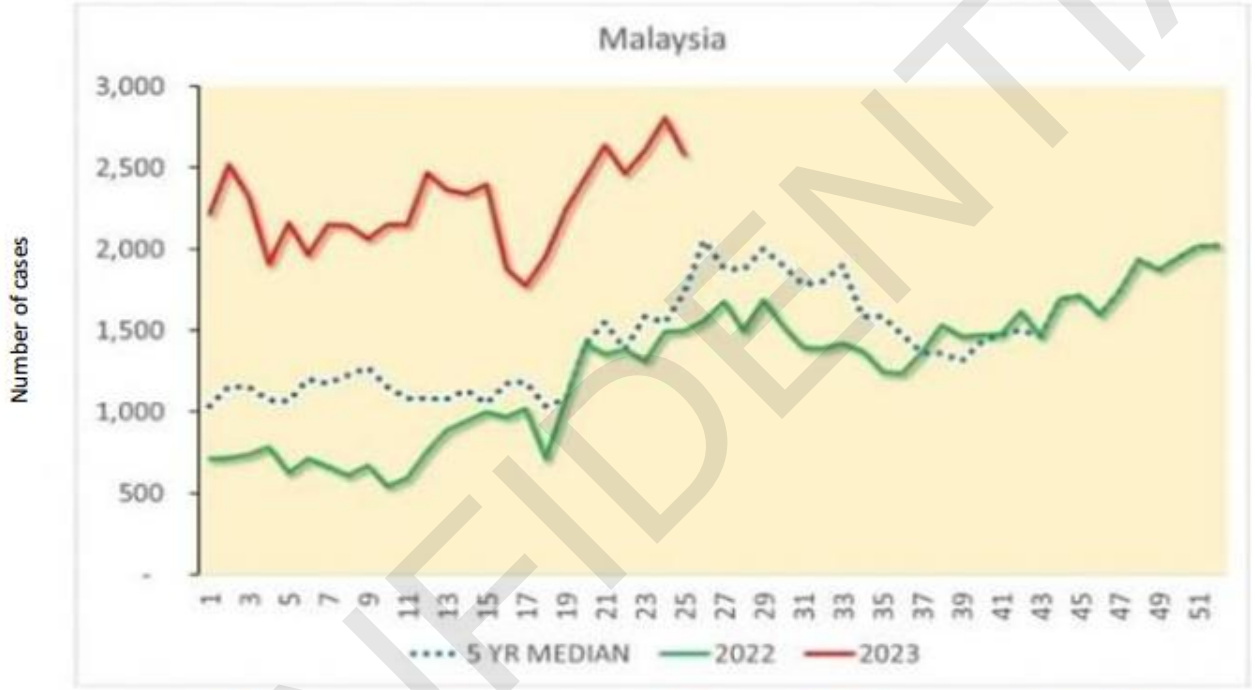


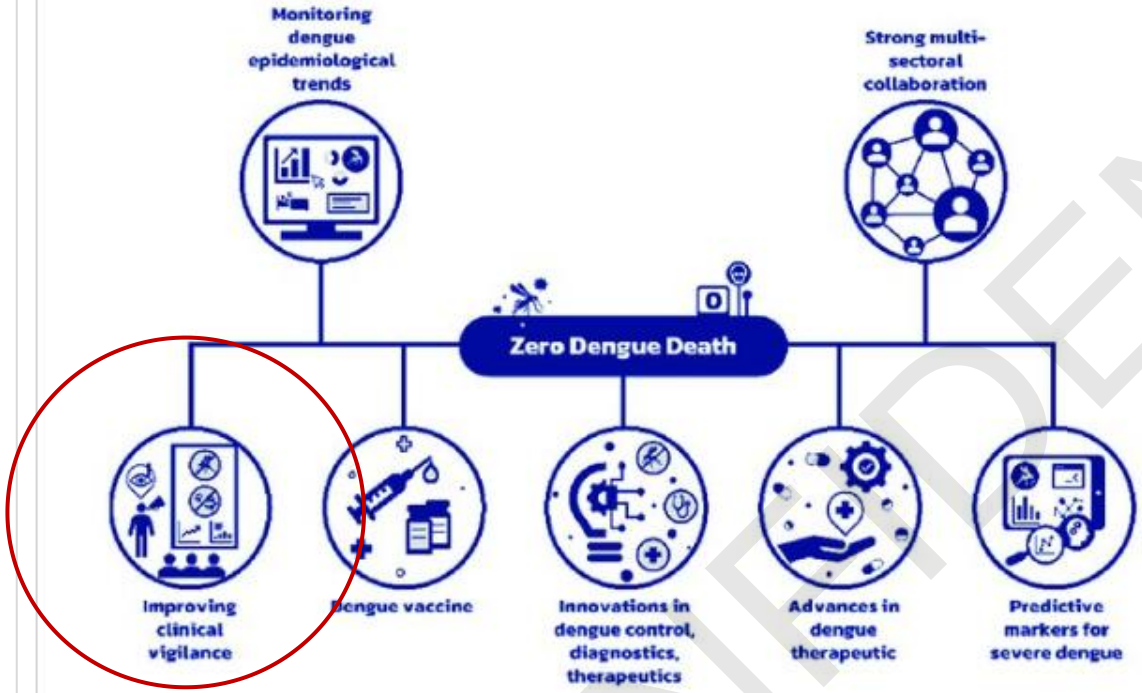
Figure 4: Dengue cases reported weekly from 2022, 2023, and median 2018-2022 in Malaysia

Source: Department of Health, Malaysia

As of 3rd **Aug 2023**, Week 25: 56,721 cases, 39 deaths, **CFR 0.07%**

As of 31 **Aug 2019**, Week 38: 90,936 cases, 132 deaths, **CFR 0.15%**

Preventable dengue deaths to ZERO



Figure

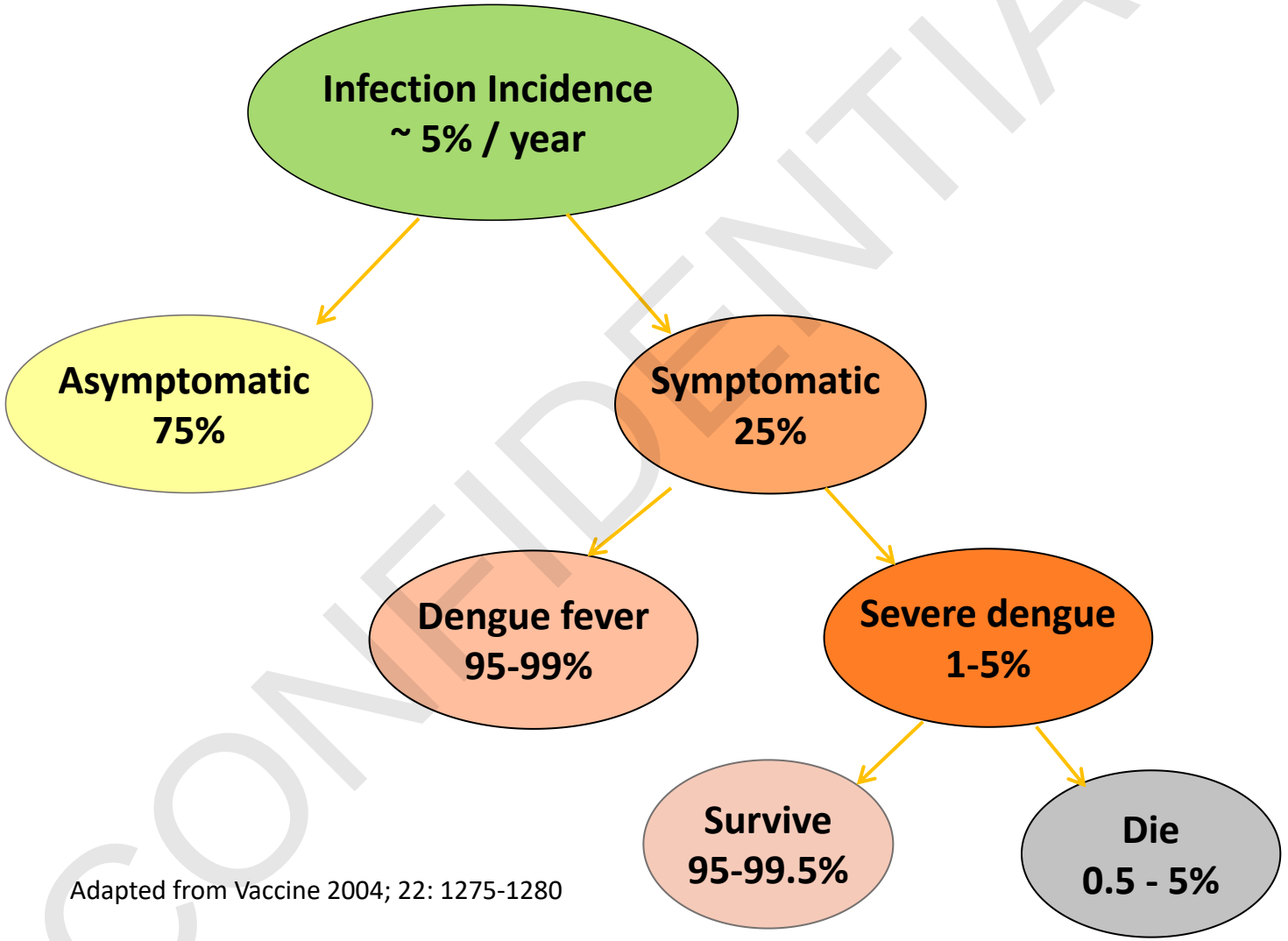
Caption

Figure 1. Strategy to reduce preventable dengue deaths to zero.

5th Asian Dengue Summit: Strategy to reduce **preventable dengue deaths to ZERO**:

IMPROVING CLINICAL VIGILANCE → **STRENGTHENING PRIMARY CARE**

Natural History of DENV Infections



Adapted from Vaccine 2004; 22: 1275-1280

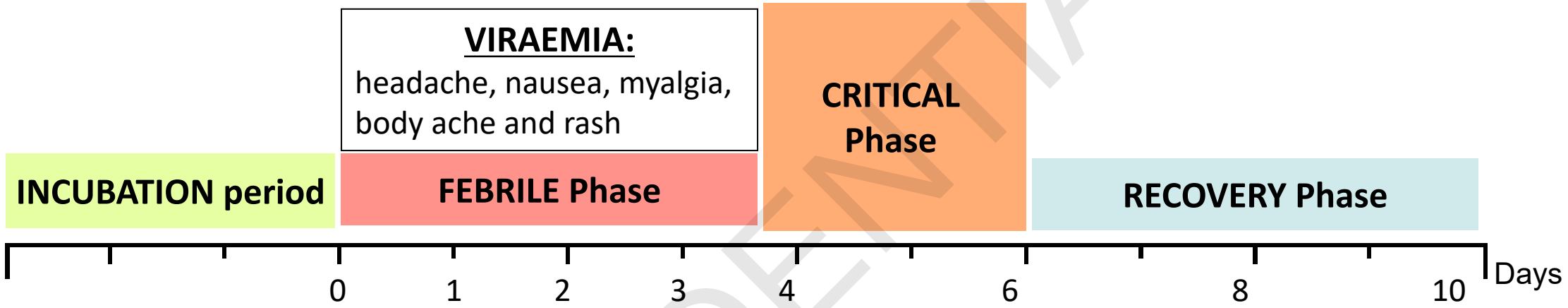
Clinical course of dengue

Dengue is a systemic and dynamic disease.

PLATELET COUNT

Dengue is NOT JUST a PLATELET count disease

Clinical course of dengue



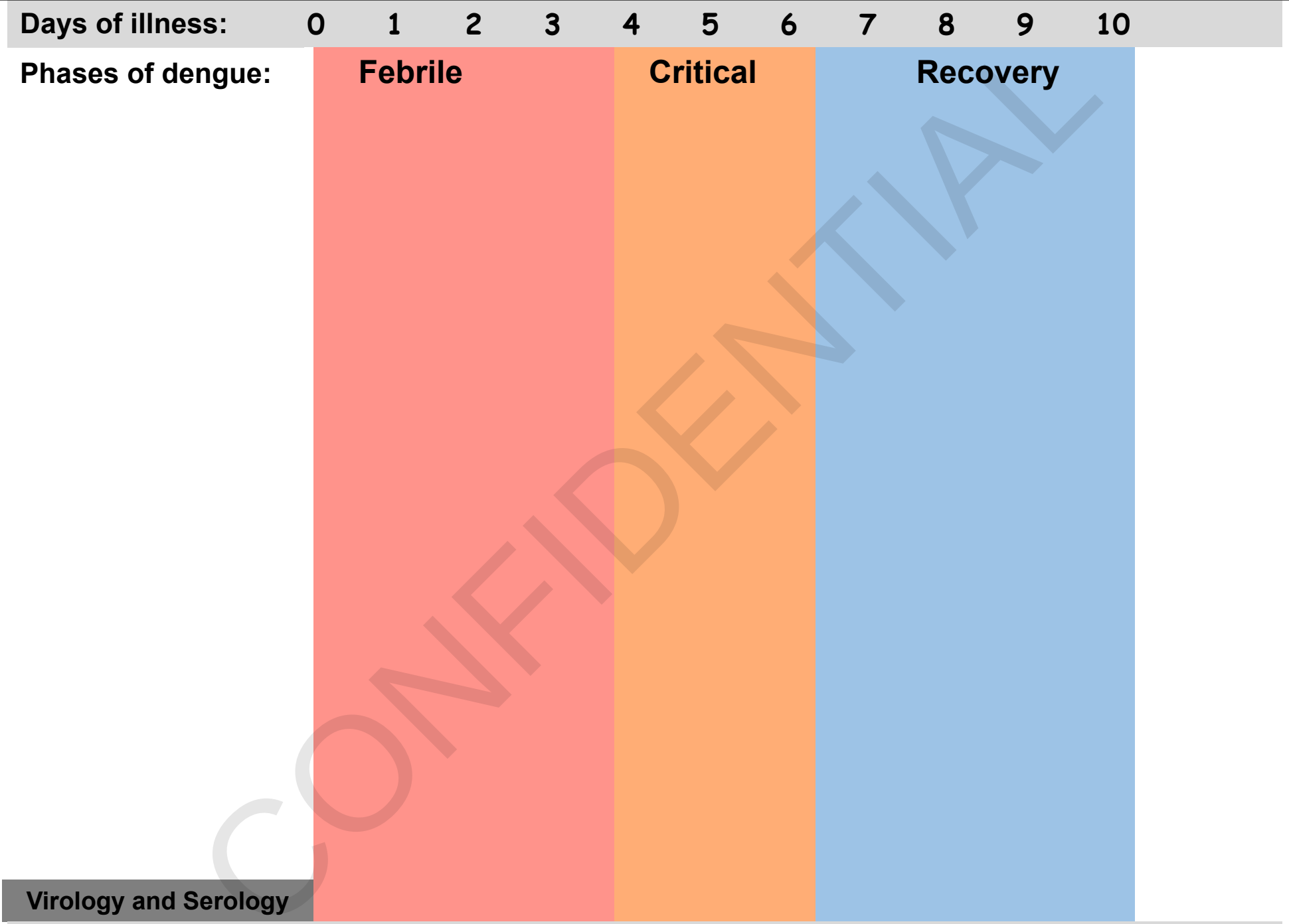
After the incubation period, the illness begins abruptly.

It is characterized by **3 phases**:

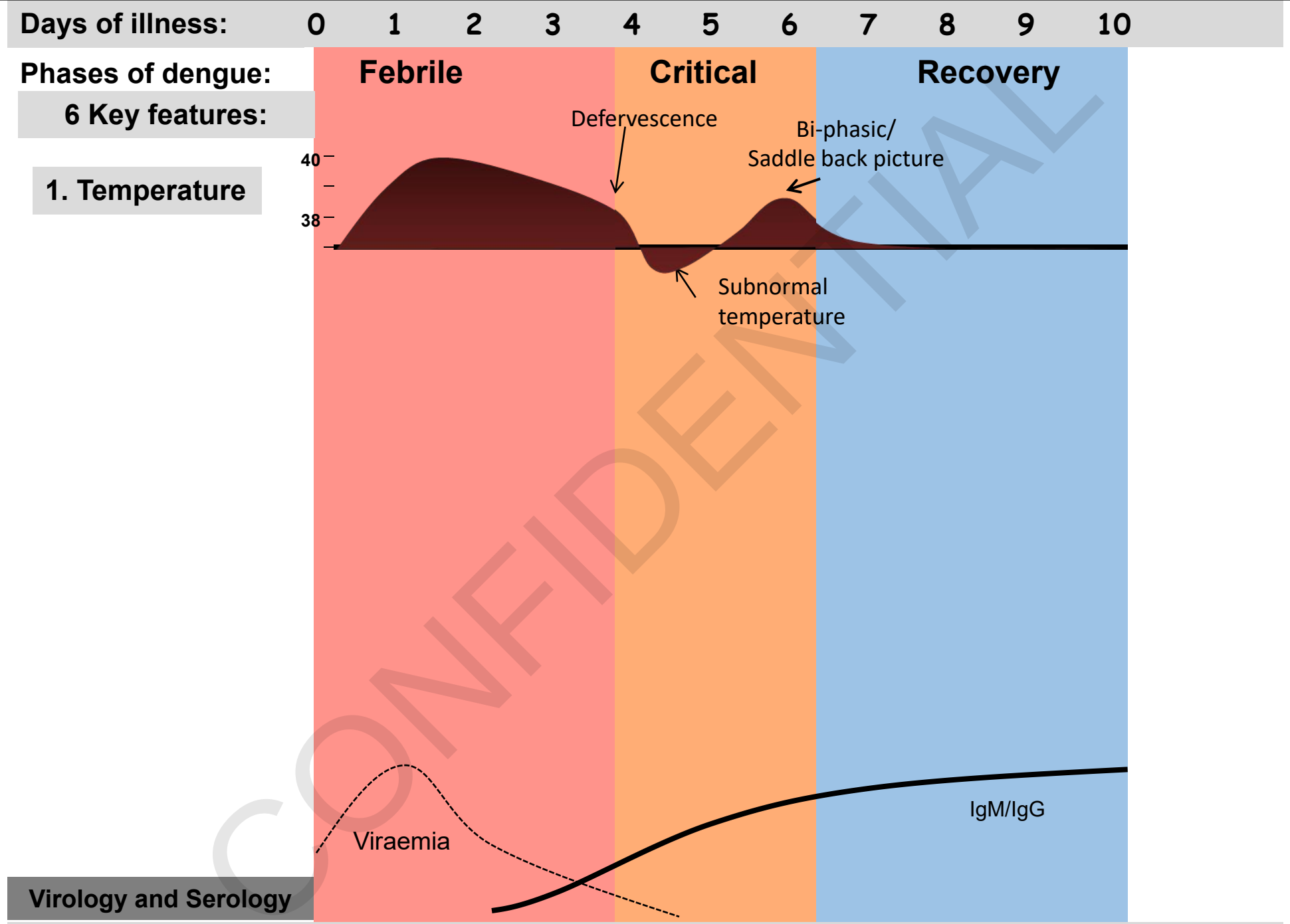
FEBRILE PHASE – commences at symptom onset

CRITICAL PHASE – **PLASMA LEAKAGE** commences around time of defervescence, (when body temperature drops to less than 38°C) **+ BLEEDING.**

RECOVERY PHASE – commences when plasma leakage resolves, **REABSORPTION**



Adapted from WCL Yip, 1980 by Hung NT, Lum LCS, Tan LH



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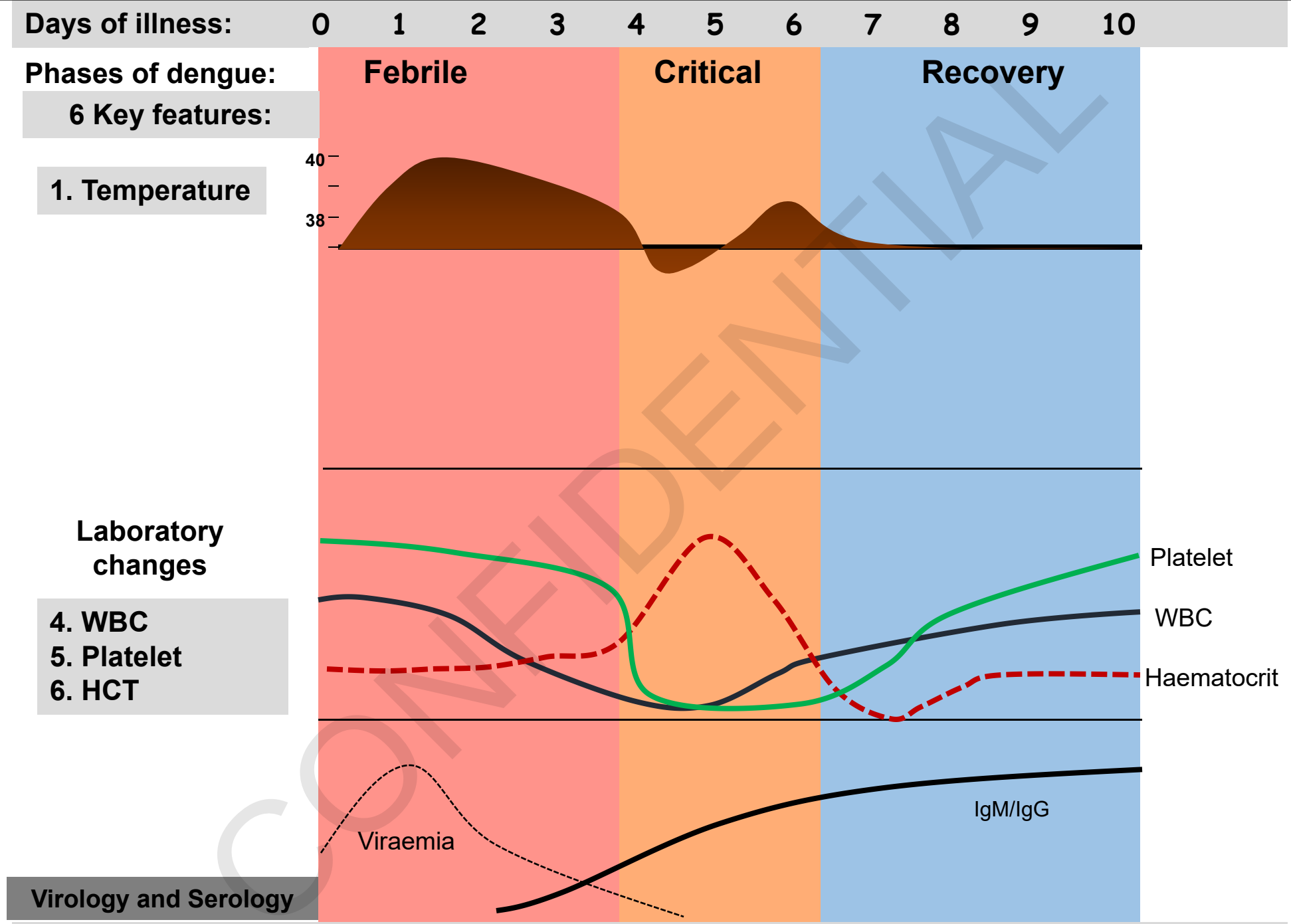

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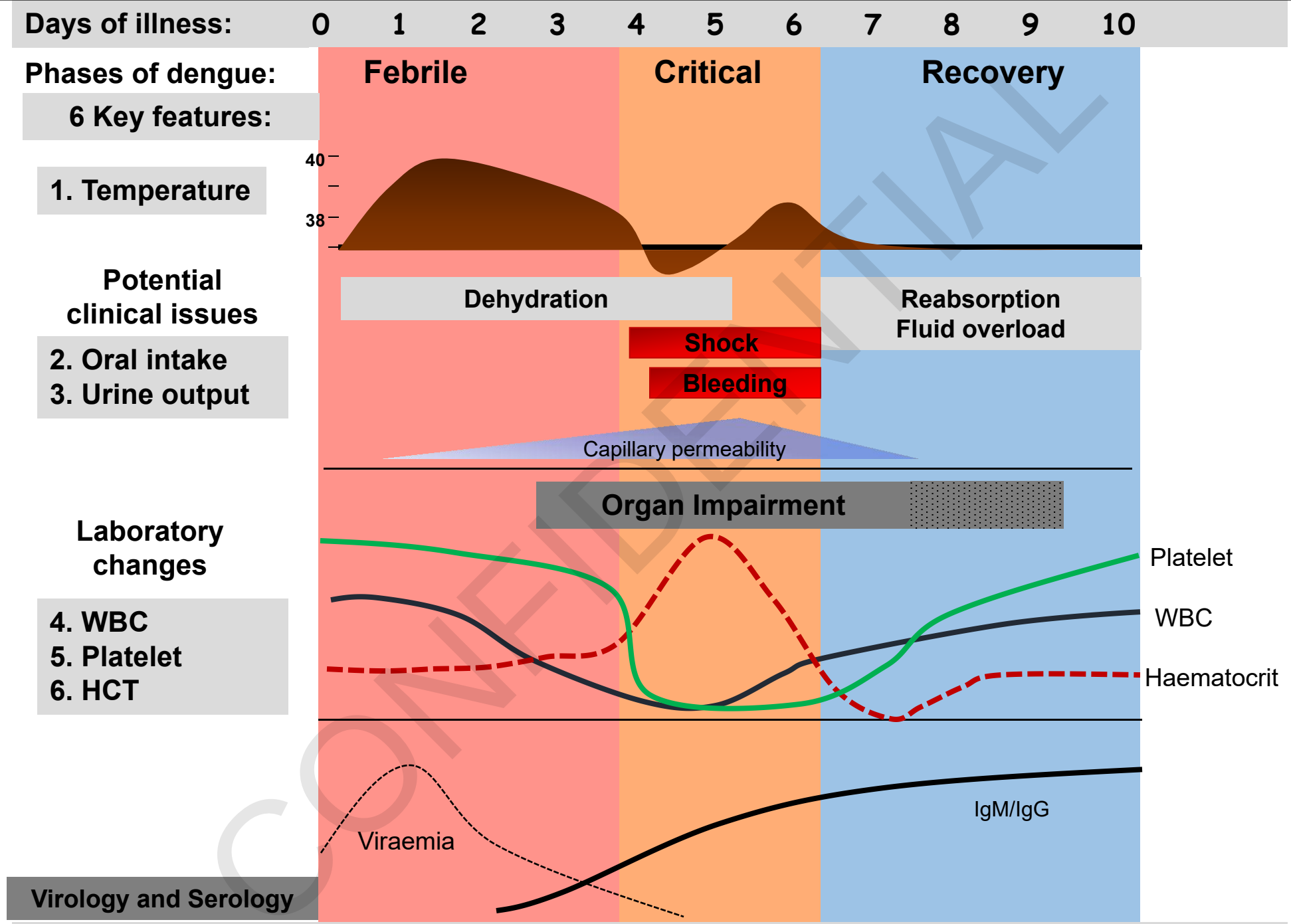


Adapted from WCL Yip, 1980 by Hung NT, Lum LCS, Tan LH

Vignette of febrile phase

- Usually lasts 2 to 7 days (minimum 72 hours)
- **High fever**; may be modified by antipyretics
- Common symptoms: **Anorexia**, myalgia, headache, retro-orbital pain, aches, rash
- **Difficult to differentiate** dengue from viral febrile illness
- **Normal CBC** in first 1 to 2 days of fever

Quality of life may be affected[1]

- Changes in behaviour and mood
- Inability to focus and concentrate on work and self-care

Children

Nausea and vomiting may be prominent

[1] Lum et al. Quality of Life of Dengue Patients. *Am J Trop Med Hyg*, 2008.

TRANSITION from febrile phase to critical phase

- Usually, day 4 to day 7 of illness
- Could be as early as day 3 or as late as day 7 or 8
- Coincides with defervescence

Development of warning signs:

Identify dengue patients already in shock or at risk of developing shock

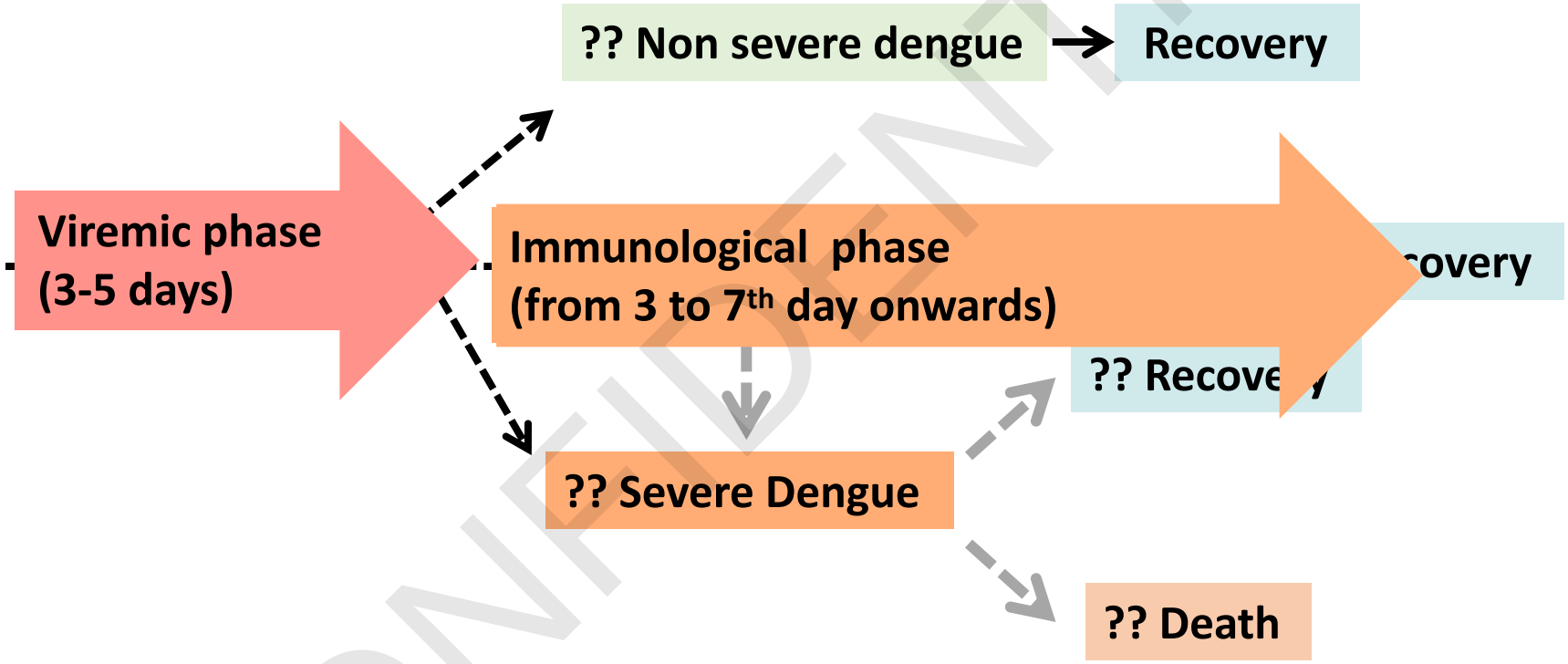
Clinical Warning Signs

1. **Severe abdominal pain**
2. **Persistent vomiting**
3. Mucosal bleed
4. Lethargy; restlessness
5. Liver enlargement >2cm
6. Clinical fluid accumulation

Laboratory Warning Signs

1. Leukopenia
2. **Rapid decrease platelet count**
3. **Rising haematocrit**

Difficult to predict course of dengue during febrile phase …



Pearls and pitfalls: abdominal pain

What is "significant" abdominal pain?

- Severe enough to be patient's **chief complaint**
- Could be mistaken as **surgical condition**

What does significant abdominal pain signify?

Severe abdominal pain is associated with increased vascular permeability and/or shock in the defervescence phase.

Pitfall: Most common diagnosis

Gastritis – because patient has not eaten for several days!

Acute Cholecystitis – because gall bladder is enlarged!

Pearls: persistent vomiting

What is persistent vomiting?

- Three or more times per day
- Patient is NOT able to tolerate oral fluids.

What does persistent vomiting signify?

Important sign of plasma leakage

Pearls: lethargy

When is lethargy is more than usual?

- Patient is confined to bed for most of the day.
- Patient sleeps most of the time.
- Patient is uninterested in food or television.
- Patient is too weak to walk to toilet.

Remember: restlessness = severe shock + cerebral hypoperfusion

Pearls: mucosal bleeding

Mucosal bleeding

Mucosal bleeding = warning of more severe manifestations

Fluid accumulation

Volume of fluid accumulation
= severity of vascular permeability + fluid therapy

Mild fluid accumulation: undetectable

Pearls: laboratory warning signs

Leucopenia

- Occurs 24 hours before rapid decrease in platelet count
- Not predictive of plasma leakage
- Good indicator that patient could have dengue

Rapid decrease in platelet count + rising trend in haematocrit

- Occur shortly before or at defervescence
- May precede changes in blood pressure and pulse pressure
- Indicate an increase in vascular permeability

NOTE: Changes in haematocrit may be masked by IV fluid therapy

What happens during the critical phase?

Increased vascular permeability

↓

Significant plasma leakage

↓

Development of warning signs

↓

Deterioration in patient's condition

How long does plasma leakage last?

24 – 48 hours

What could happen without treatment?

DEATH

Shock occurs when critical volume of plasma is lost through leakage.

Shock is often preceded by warning signs.

Body temperature may be sub-normal when shock occurs.

The total white cell count (instead of leukopenia) may increase in patients with severe bleeding at this stage.

46-year-old female – Day 1

History: **High fever**

Muscle ache

Headache

Poor appetite

PE: **Temp 39.3°C**

BP: 120/76 mmHg

PR 88/min

RR 16/min

Throat: not inflamed

No rash

CVS/Resp system/Abdomen - normal

CBC	D1
HB	13.5
HCT	39
WBC	7.2
PLT	235

Diagnosis : Acute Febrile Illness

	D1	D2
HB	13.5	13.1
HCT	39	38
WBC	7.2	5.3
PLT	235	151

Urine examination	
Protein	Nil
Red cells	2
White cells	5
Bacteria	+
Ketones	3+

Doctor's diagnosis: Urinary tract infection

Do you agree? What does the urine picture show?

	D1	D2	D3
HB	13.5	13.1	12.8
HCT	39	38	34
WBC	7.2	5.3	4.2
PLT	235	151	123

Vomiting and feeling unwell after 3rd day of illness

	D1	D2	D3	D4
HB	13.5	13.1	12.8	
HCT	39	38	34	
WBC	7.2	5.3	4.2	
PLT	235	151	123	

Dengue Fever **with warning signs**

Admitted to medical ward for intravenous fluid therapy

Vomiting and feeling unwell after 3rd day of illness

		D2	D3	D4	D5
HB	13.5	13.1	12.8	15.2	13.9
HCT	39	38	34	48	42
WBC	7.2	5.3	4.2	3.1	2.8
PLT	235	151	123	74	17

Vomiting and feeling unwell after 3rd day of illness

		D2	D3	D4	D5	D6	D7
HB	13.5	13.1	12.8	15.2	13.9	12.5	12.4
HCT	39	38	34	48	42	38	37
WBC	7.2	5.3	4.2	3.1	2.8	4.1	5.3
PLT	235	151	123	74	17	15	35

Vomiting and feeling unwell after 3rd day of illness

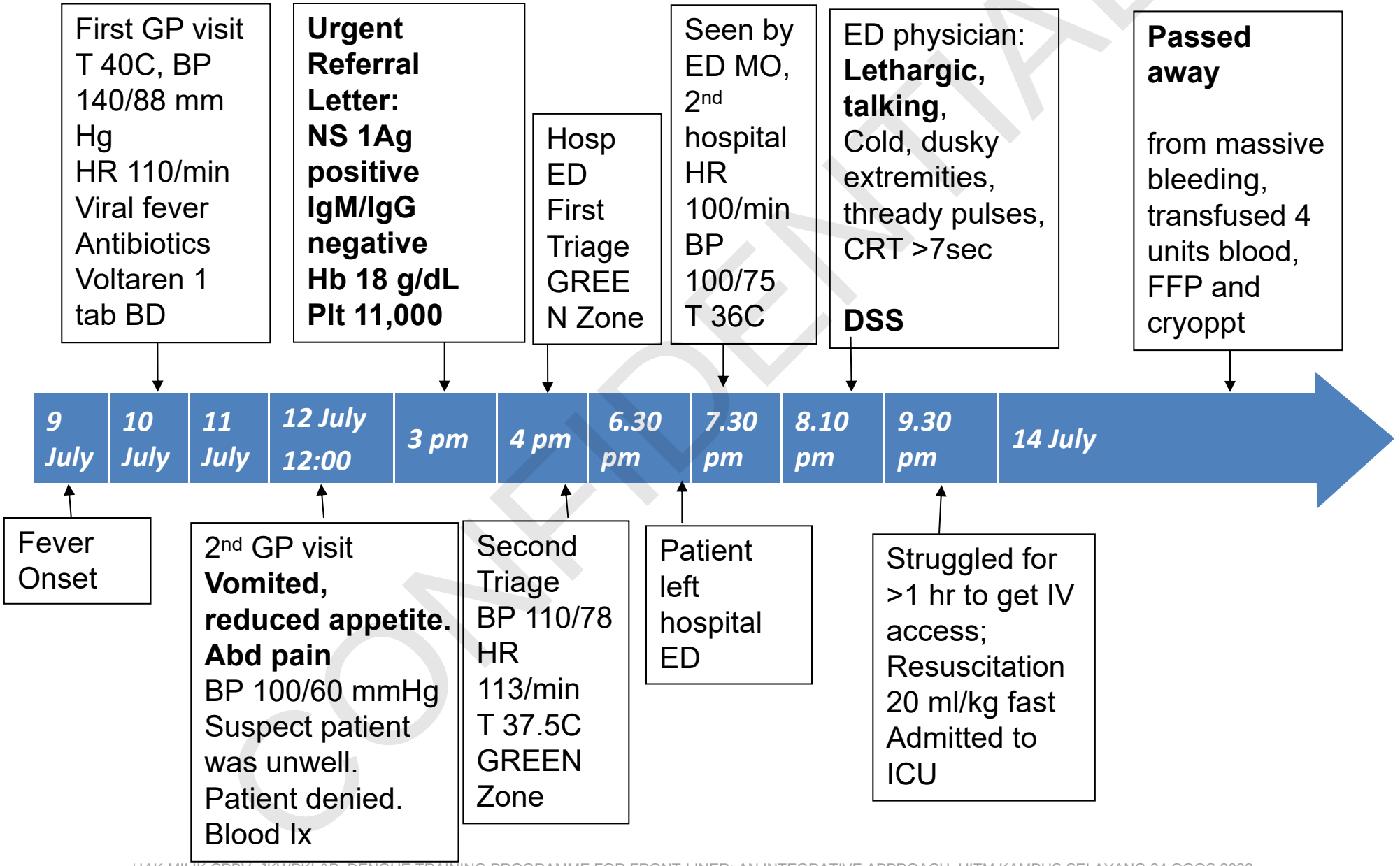
	D1	D2	D3	D4	D5	D6	D7
HB	13.5	13.1	12.8	15.2	13.9	12.5	12.4
HCT	39	38	34	48	42	38	37
WBC	7.2	5.3	4.2	3.1	2.8	4.1	5.3
PLT	235	151	123	74	17	15	35

When would you do laboratory confirmation of dengue diagnosis?

When was illness undifferentiated? What test would be most suitable ?

What tests would you order: D3, D4, D5, D6-7?

Case Timeline – 32-year-old man, no co-morbid conditions



Pearls and pitfalls: dengue shock

Dengue shock presents as a physiologic-time continuum

Compensated shock in the early stage
(normal or elevated blood pressure)

→

Decompensated shock in the late stages
(hypotension & unrecordable blood pressure)

Identification and treatment of **early shock** will improve clinical outcome.

Delayed treatment leads to **severe bleedin**g and organ impairment.

Severe bleeding will exacerbate the shock state and if unrecognized will cause **refractory and irreversible shock** with a very poor outcome.

Pitfall: Why is it easy to miss dengue shock?

Even in the severe shock state, the patient appears deceptively **"normal" or "stable"** with **a lucid conscious level**.

A careful physical examination is critical to recognizing a patient in shock before the stage of cardiovascular collapse.

Vasculopathy in dengue

Capillary fragility:

- Spontaneous skin petechiae
- Positive tourniquet test
- Spontaneous mucosal bleeding
- Prolonged bleeding after venipuncture

Plasma leakage:

- Light microscopy – **no structural changes in capillary walls**

Vascular Leak (VL)

- The most serious complication in dengue
- Critical determinant of disease severity is hypovolaemia, 2^{o} to ↑systemic vascular permeability and plasma leakage.

- When does **Vascular Leak** occur?

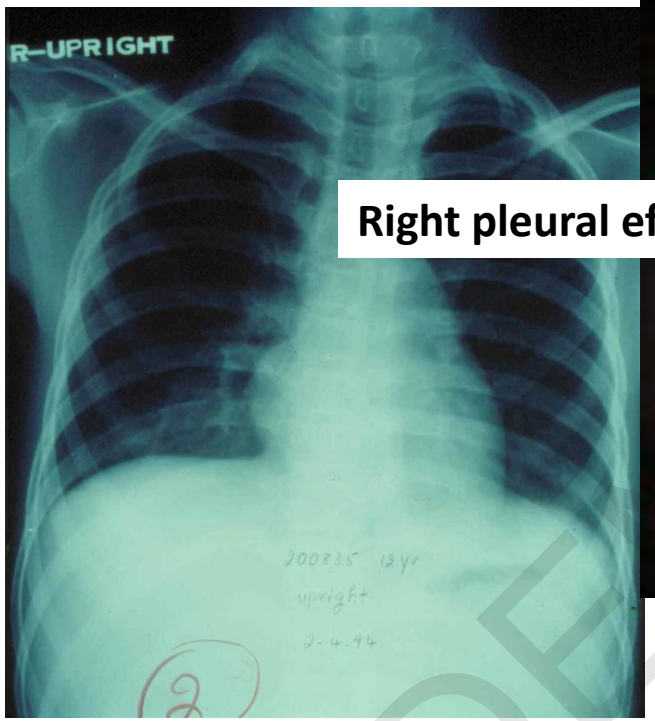
  Clinically significant plasma leakage during the critical period, coincides with defervescence, **when PC drops suddenly**

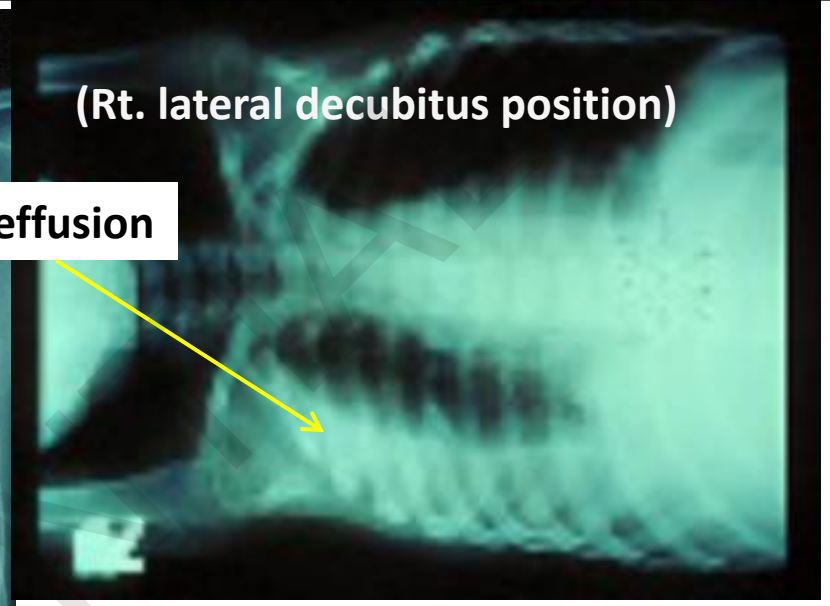
  If severe – leads to hypovolemic shock

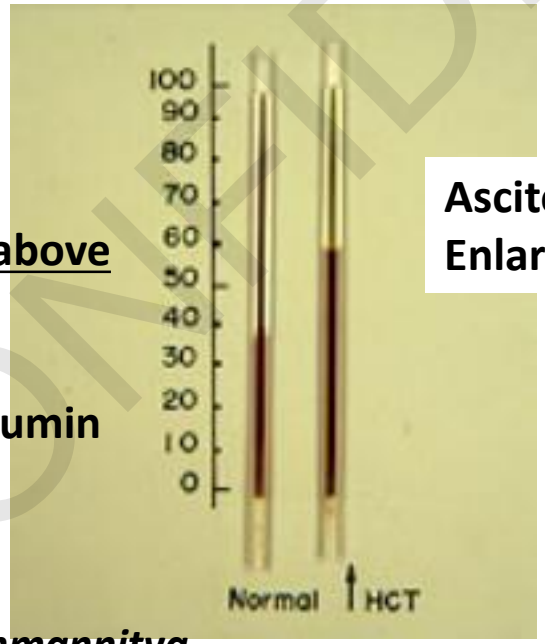
  Mild degrees of VL occur earlier in febrile phase (ultrasound)

- **Self-limiting condition** – **lasts for 24 to 48 hours**
  – reabsorption of extravasated fluid

Evidence of plasma leakage in Dengue,







Rising hematocrit above the baseline

Reduced serum albumin

Ascites
Enlarged liver

Slides from Prof S. Nimmannitya

BLEEDING

- Mucosal bleeding – epistaxis, gum bleeding is common

- **Severe bleeding** is uncommon:

  Pathogenesis: complex, unclear

  NOT related to severity thrombocytopenia, not initiated by DIC

  Related to: **DURATION OF SHOCK &**

  TRAUMA – venipuncture sites, IM injections

  Occult bleeding in GIT – difficult to recognize

  Life-threatening, Refractory shock, terminal event

  HIGH RISK – Post-partum, prior gastric/duodenal ulcers, NSAIDs, Anti-platelet medications, Severe liver impairment

Do all dengue patients enter critical phase?

NOT all patients will experience the critical phase

Clinical course of patient without significantly increased vascular permeability:

- Fever subsides → general condition improves and appetite recovers
- May have leukopenia
- Mild to moderate thrombocytopenia

Vignette of recovery phase

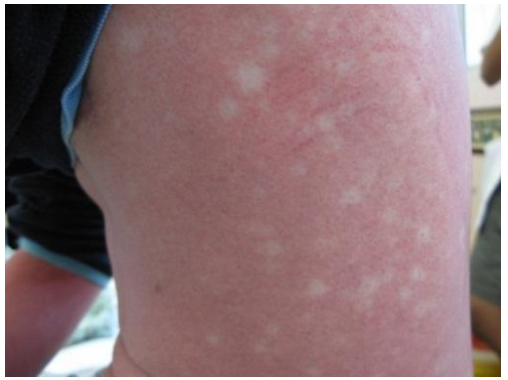
What happens in recovery phase?

Vascular permeability reverts to normal
→ Gradual reabsorption of extravascular fluid in next 48 to 72 hours

Clues to progression from critical phase to recovery phase

Clinical clues:

1. Improvement in general well-being and stable haemodynamic status
2. Diuresis
3. Biphasic fever
4. May have bradycardia
5. **Isles of white in a sea of red**



Source: Tan LH & Lum LCS

Laboratory clues:

1. HCT stabilizes.
   HCT may lower due to dilutional effect of reabsorbed fluid (haemodilution).
2. WBC usually starts to rise soon after defervescence.
3. **Thrombocytopenia persists longer than leucopenia**.

Summary of clinical problems during each phase

Febrile Phase

Dehydration

Contributing factors:
1. **Poor oral intake** from anorexia and nausea
2. **Insensible fluid loss** from high fever

High fever → Neurological disturbances

1. Hallucination
2. Febrile seizures

Critical Phase

Plasma leakage → hypovolaemia and shock

Severe haemorrhage

Organ impairment to liver, kidneys and other organs

Recovery Phase

Hypervolaemia with fluid overload because of inappropriate fluid management

NJ – 54 yr old female @ KK 1, Day 2

16 Feb – onset of fever

17 Feb – Walked into KK 1,
Fever for 2 days with **decreased oral intake**
Associated with myalgia
NO vomiting, **NO** abdominal pain, **NO** warning signs.

Phy exam: **Temp 39.2°C**, BP 137/62, HR – 108,
CVS and Lungs – normal

Management: Paracetamol 1 gm QID, CBC next morning

18 Feb – same clinic KK 1, Day 3 of fever

Dizziness, headache, decreased oral intake

NO URTI symptoms

NO vomiting, **NO** diarrhea, **NO** abd pain, **NO** chest pain, **NO** myalgia/arthralgia

Phy exam: Temp 37.9^{o}C, BP 134/70, PR 95, Good volume pulse, CRT <2 sec

CBC- WBC 3.1, Hb 13.7, HCT 39.6, Platelet 132

Management: Paracetamol – 1 g qid,
Notify as dengue,
Dengue alert card given,
Advice patient to seek medical help if worsening symptoms.
Repeat CBC next morning

19 Feb @ KK 2 – Day 4, late afternoon

Less oral intake, nausea

NO vomiting/diarrhoea, **NO** abd pain, **NO** URTI, **NO** bleeding.

Pink, good hydration, warm peripheries, CRT < 2 sec, Good pulse volume
Lungs, CVS, abdomen – normal
Temp 36.5^{o}C, BP 130/90, PR 92

TWC – 2.9, Hb 13.2, HCT 39.8, Platelet 88

Diagnosis: **DF, Day 4**, in defervescence, **NO warning signs**
Encourage fluid intake
Advice – go to nearest hospital if warning signs
Repeat CBC next day.

NJ – 54 yr old female

Time-line

Day 1 16 Feb	Day 2 17 Feb	Day 3 18 Feb	Day 4 19 Feb
Fever onset	Fever, Myalgia Headache	Dizziness, Headache	
	Decr oral intake **NO D,V,AP,WS**	Decr oral intake. **NO D,V,AP, WS**	Less oral intake, nausea **NO D, V, AP, WS**
	Temp 39.2°C Good perfusion	Temp 37.9°C Good perfusion	Temp 36.5°C Good perfusion
		WBC 3.1, HCT 39.6	WBC 2.9, HCT 39.8
		Hb 13.7, **Platelet 132**	Hb 13.2, **Platelet 88**
	Encourage oral fluid	Encourage oral fluid	Encourage oral fluid

NJ – 54 yr old female

20 Feb – KK 3 – Day 5, 9.45 am

Brought by daughter

Severe headache, dizziness, has not taken anything orally for past 2 days.

Lethargic looking, severely dehydrated, coated tongue, dry lips, no petechiae
Temp – 36.7^{o}C, BP 118/60, PR 120, Small pulse volume, CRT >2 sec
Lungs clear, abdomen – soft

CBC: WBC 2.6, HCT 46.2, Hb 15.2, Platelet 56

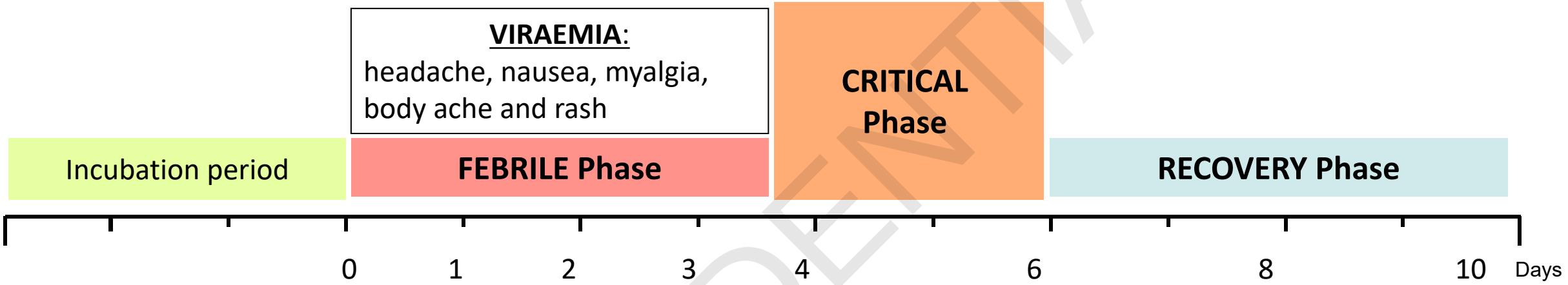
Dengue with dehydration and shock
Management: IV 500 ml NS, referred to nearest hospital.

NJ – 54 yr old female

Timeline

Day 1 16 Feb	Day 2 17 Feb	Day 3 18 Feb	Day 4 19 Feb	Day 5 20 Feb
Fever onset	Fever, Myalgia Headache Decr oral intake	Dizziness, Headache Decr oral intake	Less oral intake, nausea	Dizziness, not eaten anything for **past 2 days**.
	Temp 39.2^{o}C	Temp 37.9^{o}C	Temp 36.5^{o}C	Temp 36.7^{o}C
	Good perfusion	Good perfusion	Good perfusion	Poor perfusion
		WBC 3.1, HCT 39.6	WBC 2.9, HCT 39.8	WBC 2.6, HCT 46.2,
		Hb 13.7, Platelet 132	Hb 13.2, Platelet 88	Hb 15.2, Platelet 56
	Encourage oral fluid	Encourage oral fluid	Encourage oral fluid	**Dengue Shock Syndrome**

Clinical course of dengue



After the incubation period, the illness begins abruptly.

It is characterized by 3 phases:

FEBRILE phase – commences at symptom onset

CRITICAL phase – **PLASMA LEAKAGE,** around time of defervescence* (when temperature <38°C and remains below this level) **+ BLEEDING**

RECOVERY phase – when plasma leakage resolves, **REABSORPTION**

Dynamic phases & Clinical problems of dengue

Viremic phase (3-5 days)

Immunological phase, (from 3 to 7th day onwards)

Clinical Problems:
- High fever, nausea:
- **Dehydration**, Electrolyte Imbalance
- Ketosis
- **Co-morbid conditions**

Clinical Problems:
- Hypovolemia – **Plasma Leakage ± Severe Bleeding**
- Organ Impairment

- **Dehydration & Electrolyte Imbalance**
- **Co-morbid conditions**
- **?Paracetamol/ NSAIDS toxicity**

Clinical Problems:
Fluid Overload
Respiratory Distress/Failure