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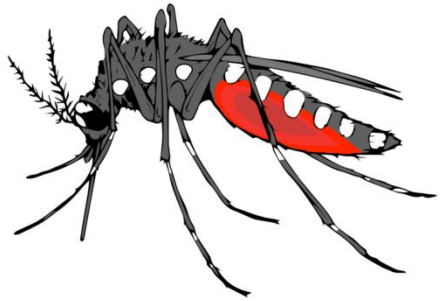

แนวทางการตรวจวินิจฉัยและดูแลรักษาโรคไข้เลือดออกในผู้ใหญ่

ศาสตราจารย์ แพทย์หญิงวิภา ธนาชาติเวทย์

ภาควิชาอายุรศาสตร์เขตร้อน คณะเวชศาสตร์เขตร้อน ม.มหิดล

WHO Consultant on Clinical Management of Dengue

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Outlines

- Facing the changes in dengue situation
- Stepwise approach for management of dengue in adults
- Management of dengue with comorbidities
- Hints to success management of dengue
- Dilemma on dengue vaccine

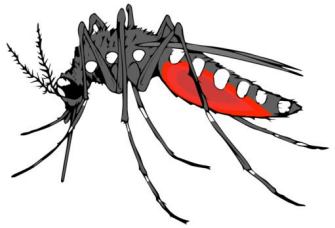
Introduction

- **Arbovirus infection :** Emerging or Re-emerging infectious diseases (ability to expand geographically and rapidly affect large population)
- **Emerging arbovirus infections :**
  - RNA genome : rapidly adapt to ever-changing host and environmental conditions
  - Global warming : increasing vectors
  - Degree of urbanization and migration : poor vector control in urban areas
  - Mass global travel : hyperendemic dengue activity in many tropical countries
- ***Arbovirus* (arthropod-borne virus) :**
  - Several families : **Flaviviridae**, Togaviridae, Bunyaviridae and Reoviridae
  - Arthropod vectors : **mosquitoes**, ticks, and sand flies

Becham JD *et al.* Continuum (Minneap Minn) 2015;21:1599-1611.
Muller DA *et al.* JID 2017;215:S89-95.
Kulkarni MA, *et al.* Global Health. 2022; 18(1):1.

Current arboviruses in Thailand

Arboviruses	Vector	Disease
Dengue virus	*Aedes aegypti* & *Aedes albopictus*	Dengue virus infection
Chikungunya virus	*Aedes aegypti* & *Aedes albopictus*	Chikungunya fever
Zika virus	*Aedes aegypti*	Zika virus infection



Raksakoon C and Potiwat R. Pathogens. 2021;10(1):80. doi: 10.3390/pathogens10010080.

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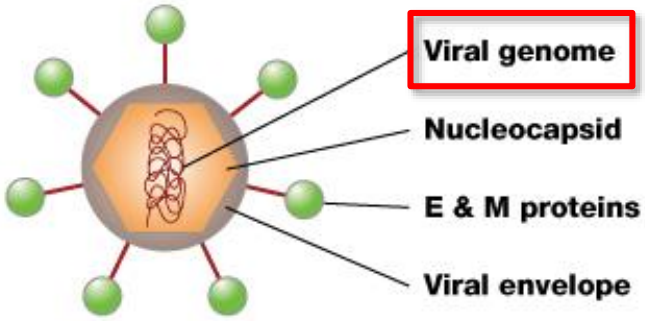
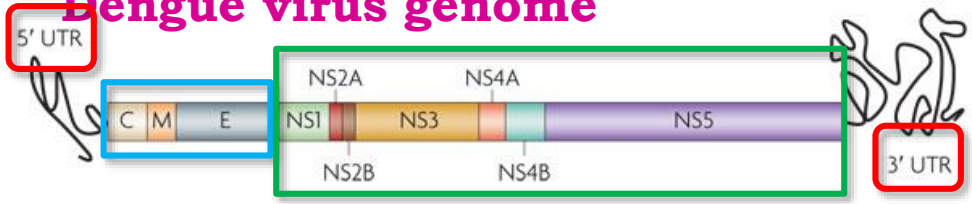
Dengue virus structure



Dengue virus genome



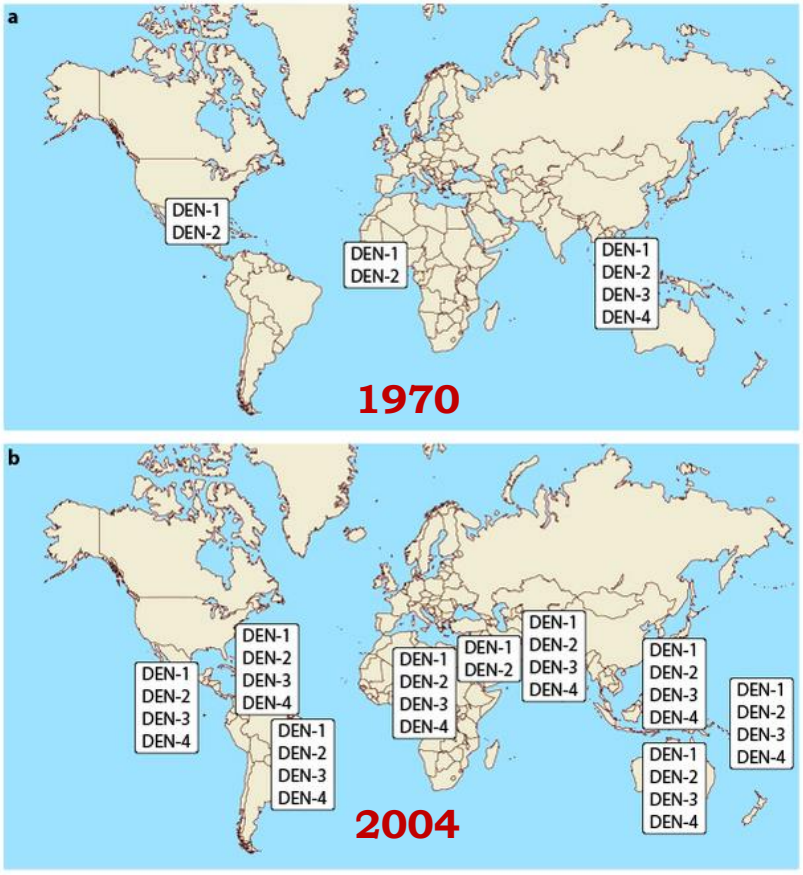
Dengue virus genome encodes

: 3 structural proteins
(capsid [C], membrane [M], and envelope [E])

: 7 nonstructural proteins
(NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5)

4 Serotypes : DENV 1-4
(genetic similar, antigenic distinct)

Change in Distribution of Dengue Serotypes (1970 and 2004)



https://www.nature.com/scitable/topicpage/dengue-viruses-22400925/

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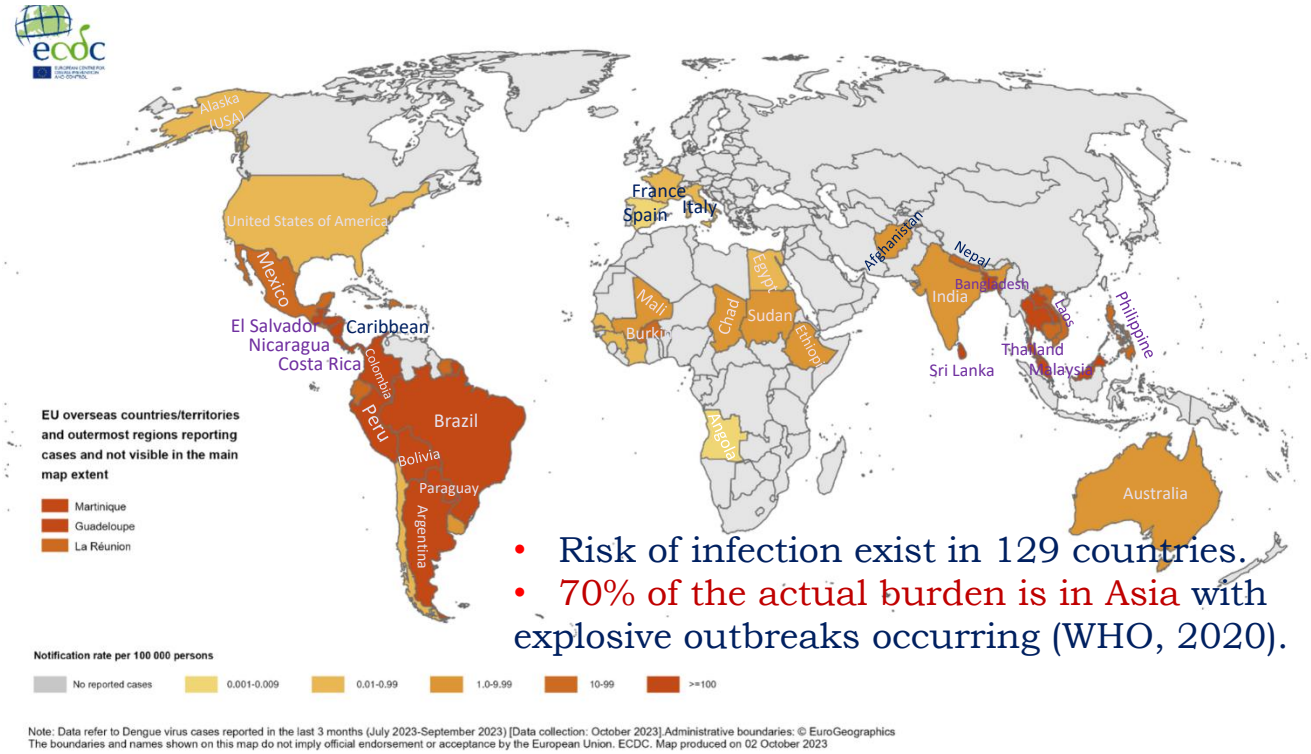
Three-month dengue virus disease case notification rate per 100,000 population (August-October 2023)

In 2023, Over 4.2 million cases **(>8-fold increase)** and over 4000 dengue-related deaths **(>4-fold increase)** have been reported from 79 countries/territories globally (WHO, 2020).



- Risk of infection exist in 129 countries.
- 70% of the actual burden is in Asia with explosive outbreaks occurring (WHO, 2020).

https://www.ecdc.europa.eu/en/publications-data/geographical-distribution-dengue-cases-reported-worldwide-2020

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สถานการณ์โรคไข้เลือดออกเสียชีวิต พ.ศ. 2566

กองโรคติดต่อนำโดยแมลง กรมควบคุมโรค

190 ราย
เสียชีวิตสะสม
มีใน รง. 506 แล้ว 181 ราย

0.12 ร้อยละ
อัตราป่วยตาย

ชาย 91 ราย
หญิง 99 ราย
อัตราส่วนเพศชาย:หญิง = 1:1.1

AGE

น้อยที่สุด 0 ปี

มัธยฐาน 28 ปี

มากที่สุด 91 ปี

	กลุ่มอายุ	ป่วย (ราย)	เสียชีวิต (ราย)	อัตราป่วยตาย (%)
1.	0-4 ปี	20,385	11	0.05
2.	5-14 ปี	53,703	38	0.07
3.	15-24 ปี	33,179	31	0.09
4.	25-34 ปี	21,691	44	0.20
5.	35-44 ปี	12,324	27	0.22
6.	45-54 ปี	7,568	15	0.20
7.	55-64 ปี	5,648	14	0.25
8.	65 ปีขึ้นไป	4,207	10	0.24

ข้อมูลจากรายงานการเฝ้าระวังโรคทางระบาดวิทยา (506) และโปรแกรมตรวจสอบข่าวการระบาด กรมควบคุมโรค **ณ วันที่ 12 มกราคม 2566**

จัดทำโดย กลุ่มเฝ้าระวังสถานการณ์และสื่อสารความเสี่ยง กองโรคติดต่อนำโดยแมลง กรมควบคุมโรค โทร. 0 2590 3151, 3133 Email: dvbdresponse@ddc.mail.go.th

https://ddc.moph.go.th/dvb/pagecontent.php?page=1269&dept=dvb

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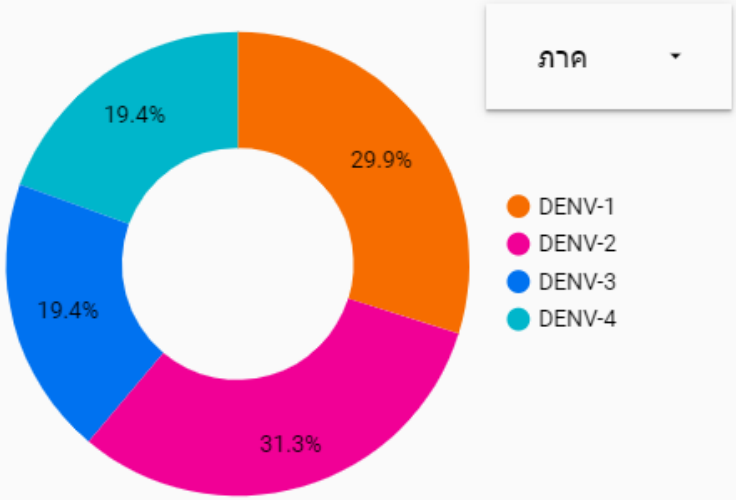
สถานการณ์โรคไข้เลือดออกเสียชีวิต พ.ศ. 2566

กองโรคติดต่อนำโดยแมลง กรมควบคุมโรค

การส่งตรวจทางห้องปฏิบัติการ

	ผลการตรวจ	จำนวน (ราย)
1.	Positive	144
2.	Positive แต่ไม่ทราบผล serotype	1
3.	อยู่ระหว่างรอผลตรวจ	19
4.	Negative	13
5.	ไม่ได้ส่งตรวจ	13



ข้อมูลจากรายงานการเฝ้าระวังโรคทางระบาดวิทยา (506) และโปรแกรมตรวจสอบข่าวการระบาด กรมควบคุมโรค **ณ วันที่ 12 มกราคม 2566**

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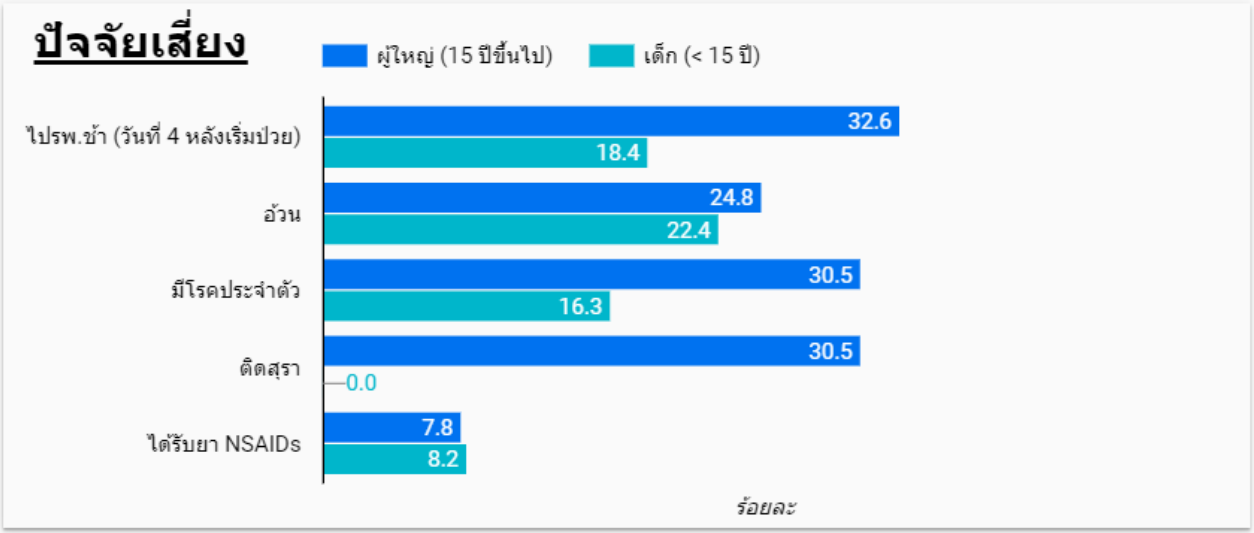
ปัจจัยเสี่ยง



49 ราย
เด็ก (< 15 ปี)

141 ราย
ผู้ใหญ่
(15 ปีขึ้นไป)

74%

Timeline ของผู้ป่วยโรคไข้เลือดออกเสียชีวิต (วัน)

	วันเริ่มป่วย	รักษาครั้งแรก	รักษาที่รพ.	วินิจฉัย Dengue	เสียชีวิต
Median		2	4	5	7
Min - Max		0 – 11	0 – 11	1 – 41	1 – 25

ข้อมูลจากรายงานการเฝ้าระวังโรคทางระบาดวิทยา (506) และโปรแกรมตรวจสอบข่าวการระบาด กรมควบคุมโรค **ณ วันที่ 12 มกราคม 2566**

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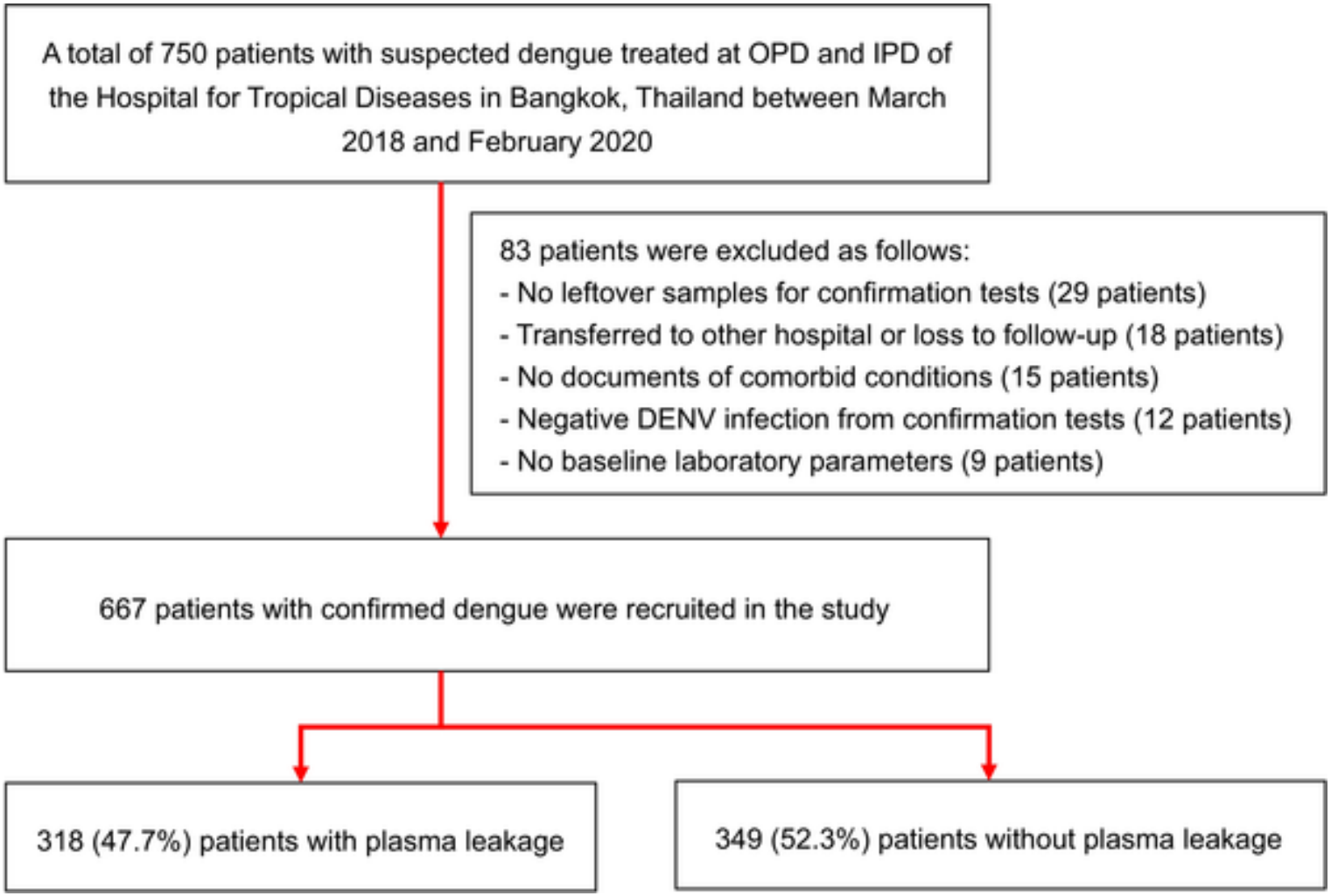
https://ddc.moph.go.th/dvb/pagecontent.php?page=1269&dept=dvb



Talukdar S, Thanachartwet V, Desakorn V, Chamnanchanunt S, Sahassananda D, *et al.* PLoS One 2021;16(7):e0255358. doi: 10.1371/journal.pone.0255358

Characteristic	Day 1 of fever onset				Day 2 of fever onset				Day 3 of fever onset				Day 4 of fever onset			
	Total	With PL	Without PL	P-value	Total	With PL	Without PL	P-value	Total	With PL	Without PL	P-value	Total	With PL	Without PL	P-value
Temp[a] (˚C)	n = 35	n = 17	n = 18		n = 99	n = 50	n = 49		n = 256	n = 131	n = 125		n = 419	n = 220	n = 199	
	39.0 (38.5–39.4)	39.0 (38.7–39.6)	38.7 (38.1–39.1)	0.134	38.9 (38.3–39.4)	39.0 (38.8–39.6)	38.8 (38.2–39.3)	0.066	38.5 (38.0–39.2)	38.7 (38.2–39.3)	38.3 (37.8–39.0)	<0.001	38.1 (37.5–38.8)	38.2 (37.8–39.0)	38.0 (37.8–38.6)	<0.001
MAP[a] (mmHg)	n = 35	n = 17	n = 18		n = 98	n = 50	n = 48		n = 256	n = 131	n = 125		n = 419	n = 220	n = 199	
	83 (79–96)	83 (78–97)	84 (80–92)	0.568	84 (77–93)	86 (79–95)	80 (76–92)	0.062	84 (76–94)	85 (78–96)	83 (75–93)	0.061	84 (76–92)	86 (77–92)	82 (75–91)	0.036
Cumulative fluid[a] (ml/day)	n = 4	n = 2	n = 2		n = 4	n = 2	n = 2		n = 123	n = 78	n = 45		n = 290	n = 184	n = 106	
	480 (119–765)	160 (78, 241)	750 (720, 780)	N/A	610 (396–1551)	610 (536, 683)	1095 (350, 1840)	N/A	500 (63–880)	540 (-42–922)	371 (130–708)	0.402	500 (-55–1105)	542 (-51–1238)	407 (-73–966)	0.199
WBC[a] ($\times 10^3$ cells/mm^3)	n = 27	n = 10	n = 17		n = 93	n = 48	n = 45		n = 256	n = 129	n = 127		n = 416	n = 218	n = 198	
	5.10 (4.10–7.00)	4.60 (4.00–6.48)	5.90 (4.00–7.70)	0.414	3.90 (2.90–5.50)	3.75 (2.65–5.10)	4.10 (3.35–5.65)	0.252	3.10 (2.48–4.20)	3.10 (2.55–4.10)	3.20 (2.40–4.20)	0.987	2.80 (2.30–3.80)	2.90 (2.30–3.82)	2.80 (2.20–3.72)	0.375
ALC[a] (cells/mm^3)	n = 19	n = 7	n = 12		n = 65	n = 34	n = 31		n = 196	n = 106	n = 90		n = 382	n = 198	n = 184	
	102 (41–141)	90 (45–108)	122 (0–176)	0.592	100 (32–202)	99 (0–207)	100 (44–207)	0.654	139 (76–224)	137 (76–212)	142 (76–236)	0.353	185 (92–331)	185 (93–390)	180 (89–306)	0.304
HCT rise[a] (%)	n = 27	n = 10	n = 17		n = 93	n = 48	n = 45		n = 257	n = 130	n = 127		n = 416	n = 218	n = 198	
	0.25 (0–7.63)	0.29 (0–9.74)	0 (0–6.42)	0.711	2.88 (0–7.32)	1.58 (0–7.59)	3.31 (0–7.13)	0.911	5.22 (1.03–11.58)	6.36 (1.37–13.36)	4.50 (0.74–9.58)	0.040	6.73 (2.76–12.20)	8.43 (4.70–15.01)	5.11 (1.13–9.36)	<0.001
PLT count[a] ($\times 10^3$/mm^3)	n = 27	n = 10	n = 17		n = 93	n = 48	n = 45		n = 257	n = 130	n = 127		n = 416	n = 218	n = 198	
	193 (154–215)	178 (148–215)	198 (158–214)	0.570	152 (116–181)	150 (110–172)	161 (126–207)	0.209	116 (75–146)	101 (64–142)	125 (90–156)	<0.001	85 (50–124)	73 (39–101)	106 (64–138)	<0.001
AST[a] (U/l)	n = 27	n = 10	n = 17		n = 93	n = 48	n = 45		n = 153	n = 96	n = 57		n = 237	n = 141	n = 96	
	21 (17–27)	22 (18–29)	19 (16–22)	0.219	37 (28–54)	38 (30–61)	28 (24–41)	0.012	50 (34–90)	60 (38–118)	36 (24–63)	<0.001	80 (47–154)	97 (57–178)	58 (39–91)	<0.001
ALT[a] (U/l)	n = 27	n = 10	n = 17		n = 93	n = 48	n = 45		n = 154	n = 97	n = 57		n = 237	n = 141	n = 96	
	22 (15–24)	22 (17–24)	20 (14–21)	0.125	30 (23–40)	32 (26–42)	23 (17–27)	<0.001	32 (21–56)	37 (25–76)	24 (16–37)	<0.001	51 (28–103)	54 (37–120)	38 (24–62)	<0.001
ALB[a] (g/dl)	n = 24	n = 10	n = 14		n = 66	n = 48	n = 18		n = 85	n = 58	n = 27		n = 128	n = 92	n = 36	
	4.8 (4.5–5.0)	4.8 (4.6–5.0)	4.5 (4.3–5.2)	0.349	4.7 (4.5–4.9)	4.7 (4.5–4.9)	4.5 (4.3–4.6)	0.008	4.4 (4.2–4.7)	4.4 (4.2–4.7)	4.4 (4.3–4.9)	0.656	4.2 (3.9–4.5)	4.0 (3.8–4.5)	4.3 (4.2–4.6)	0.001

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PLoS One 2021;16(7):e0255358. doi: 10.1371/journal.pone.0255358

Characteristic	Day 5 of fever onset				Day 6 of fever onset				Day 7 of fever onset				Day 8 of fever onset			
	Total	With PL	Without PL	P-value	Total	With PL	Without PL	P-value	Total	With PL	Without PL	P-value	Total	With PL	Without PL	P-value
Temp[a] (˚C)	n = 554	n = 296	n = 258		n = 580	n = 300	n = 280		n = 553	n = 283	n = 270		n = 389	n = 222	n = 167	
	37.7 (37.0–38.4)	37.8 (37.2–38.5)	37.5 (37.0–38.3)	0.013	37.2 (36.8–37.8)	37.2 (36.8–37.8)	37.0 (36.7–37.8)	0.103	36.8 (36.5–37.2)	36.9 (36.6–37.8)	36.8 (36.5–37.1)	0.022	36.6 (36.3–37.0)	36.6 (36.3–37.0)	36.6 (36.3–37.0)	0.948
MAP[a] (mmHg)	n = 554	n = 296	n = 258		n = 580	n = 300	n = 280		n = 554	n = 283	n = 271		n = 389	n = 222	n = 167	
	81 (74–90)	83 (75–91)	80 (74–88)	0.056	79 (72–87)	80 (73–87)	77 (71–85)	0.006	78 (72–86)	79 (73–88)	76 (71–84)	0.006	78 (72–87)	80 (73–89)	77 (71–83)	0.001
Cumulative fluid balance[a] (ml/day)	n = 456	n = 276	n = 180		n = 521	n = 296	n = 225		n = 547	n = 305	n = 242		n = 548	n = 305	n = 243	
	580 (-12–1349)	670 (100–1645)	296 (-162–966)	<0.001	630 (-192–1535)	915 (-36–1942)	291 (-482–1005)	<0.001	381 (-565–1470)	600 (-362–1910)	232 (-653–982)	<0.001	250 (-711–1385)	420 (-664–1682)	100 (-780–936)	0.003
WBC[a] (×10^3 cells/mm^3)	n = 548	n = 293	n = 255		n = 566	n = 294	n = 272		n = 544	n = 280	n = 264		n = 383	n = 221	n = 162	
	3.00 (2.30–4.30)	3.10 (2.30–4.60)	2.90 (2.30–3.90)	0.231	3.80 (2.70–5.32)	4.20 (2.70–5.90)	3.55 (2.70–4.90)	0.014	4.90 (3.50–6.60)	5.10 (3.90–6.80)	4.30 (3.22–6.28)	0.002	5.20 (4.20–6.70)	5.30 (4.40–6.90)	4.80 (3.88–6.40)	0.017
ALC[a] (/mm^3)	n = 517	n = 284	n = 233		n = 556	n = 292	n = 264		n = 540	n = 279	n = 261		n = 380	n = 219	n = 161	
	297 (160–692)	333 (180–797)	270 (144–599)	0.016	711 (336–1270)	818 (401–1362)	582 (266–1071)	<0.001	912 (500–1516)	943 (574–1496)	876 (458–1602)	0.239	869 (518–1334)	910 (525–1334)	816 (510–1348)	0.591
HCT rise[a] (%)	n = 549	n = 294	n = 255		n = 567	n = 295	n = 272		n = 545	n = 281	n = 264		n = 384	n = 222	n = 162	
	7.61 (3.03–13.38)	10.59 (4.87–16.32)	5.50 (2.16–9.00)	<0.001	7.50 (3.01–12.27)	9.84 (4.52–16.11)	5.66 (1.70–9.09)	<0.001	5.22 (1.39–10.15)	6.84 (2.36–12.20)	3.78 (0.90–8.00)	<0.001	3.48 (0–7.69)	3.75 (0–9.06)	3.03 (0–6.94)	0.070
PLT count[a] (×10^3/mm^3)	n = 548	n = 293	n = 255		n = 566	n = 294	n = 272		n = 544	n = 280	n = 264		n = 383	n = 221	n = 162	
	61 (31–97)	46 (23–76)	82 (47–119)	<0.001	45 (25–74)	34 (19–55)	62 (36–94)	<0.001	50 (29–78)	39 (24–60)	67 (39–92)	<0.001	64 (40–90)	57 (35–89)	72 (48–94)	<0.001
AST[a] (U/l)	n = 269	n = 167	n = 102		n = 238	n = 152	n = 86		n = 179	n = 124	n = 55		n = 131	n = 95	n = 36	
	116 (58–212)	135 (79–270)	72 (42–132)	<0.001	128 (76–232)	154 (88–267)	107 (64–180)	0.002	141 (80–253)	152 (97–260)	89 (55–199)	0.003	142 (59–267)	165 (88–315)	72 (40–211)	0.004
ALT[a] (U/l)	n = 269	n = 167	n = 102		n = 238	n = 152	n = 86		n = 179	n = 124	n = 55		n = 130	n = 95	n = 35	
	62 (34–126)	72 (45–127)	42 (23–91)	<0.001	77 (47–153)	88 (50–176)	62 (38–102)	0.001	99 (50–178)	108 (56–181)	70 (34–159)	0.016	117 (65–230)	135 (70–228)	98 (52–246)	0.166
ALB[a] (g/dl)	n = 170	n = 125	n = 45		n = 165	n = 125	n = 40		n = 121	n = 98	n = 23		n = 75	n = 58	n = 17	
	4.0 (3.7–4.3)	3.9 (3.5–4.2)	4.3 (3.8–4.6)	<0.001	3.8 (3.4–4.1)	3.6 (3.3–4.0)	4.2 (4.0–4.6)	<0.001	3.7 (3.4–4.0)	3.6 (3.3–3.9)	4.2 (4.0–4.4)	<0.001	3.8 (3.4–4.2)	3.6 (3.4–4.0)	4.3 (4.2–4.8)	<0.001

Talukdar S, Thanachartwet V, Desakorn V, Chamnanchanunt S, Sahassananda D, *et al.*
PLoS One 2021;16(7):e0255358. doi: 10.1371/journal.pone.0255358

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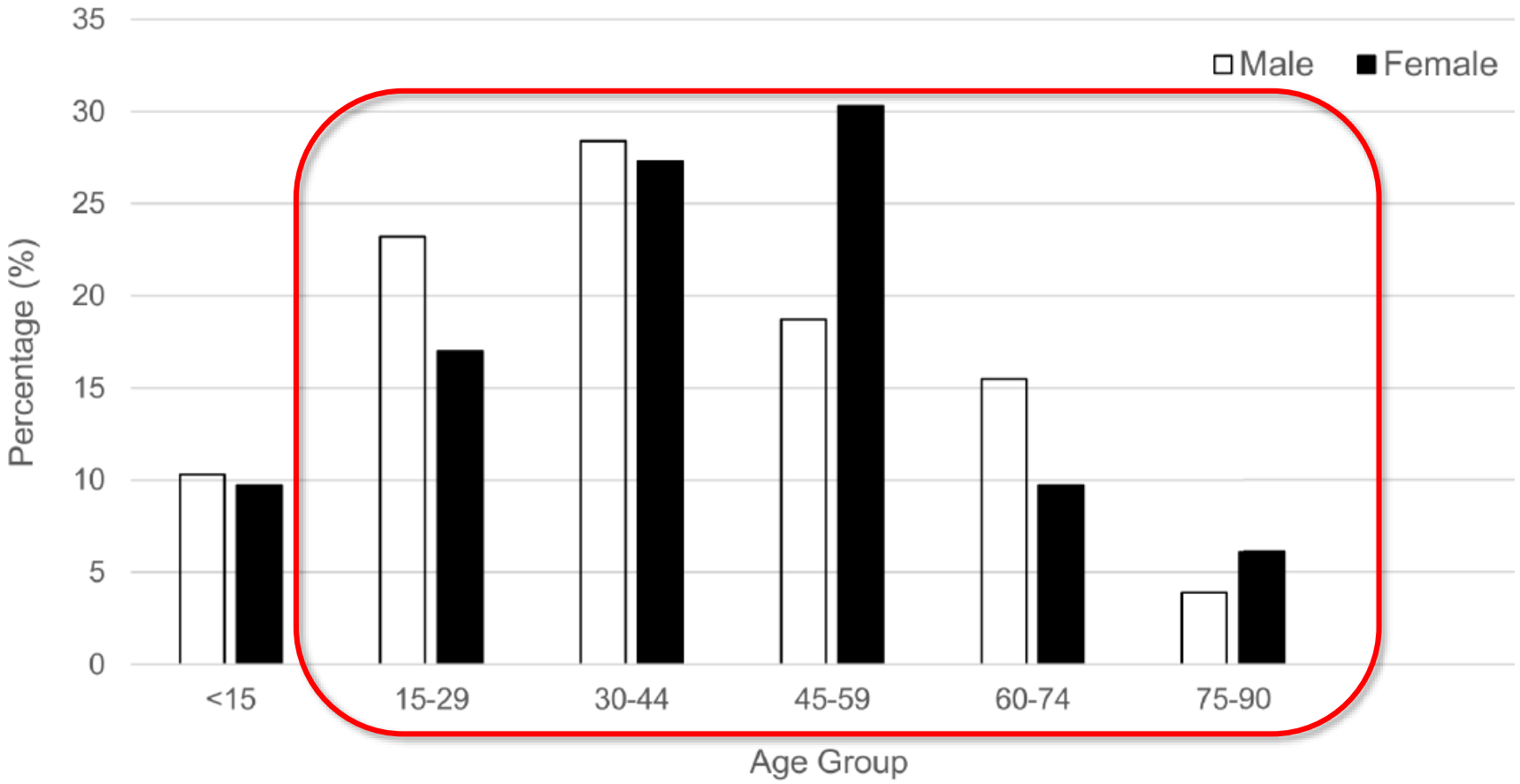
Problems in Management of Dengue in Thailand (2018)

- Diagnosis of dengue
  - → **Fluid management :** (**Over** > Under resuscitation)
- Recognition of plasma leakage
- Recognition of significant bleeding
  - → **Delayed blood transfusion**
- Detection of dengue shock syndrome
  - → **Improper fluid management & Delayed blood transfusion**

Courtesy of Professor Siripen Kalayanarooj

Mortality Distribution in Different Age Groups (322 Dengue Deaths in Malaysia, 2013-2014)



Woon YL *et al.* PLoS Negl Trop Dis 2016;10:e0004575.doi:10.1371/journal.pntd.0004575.

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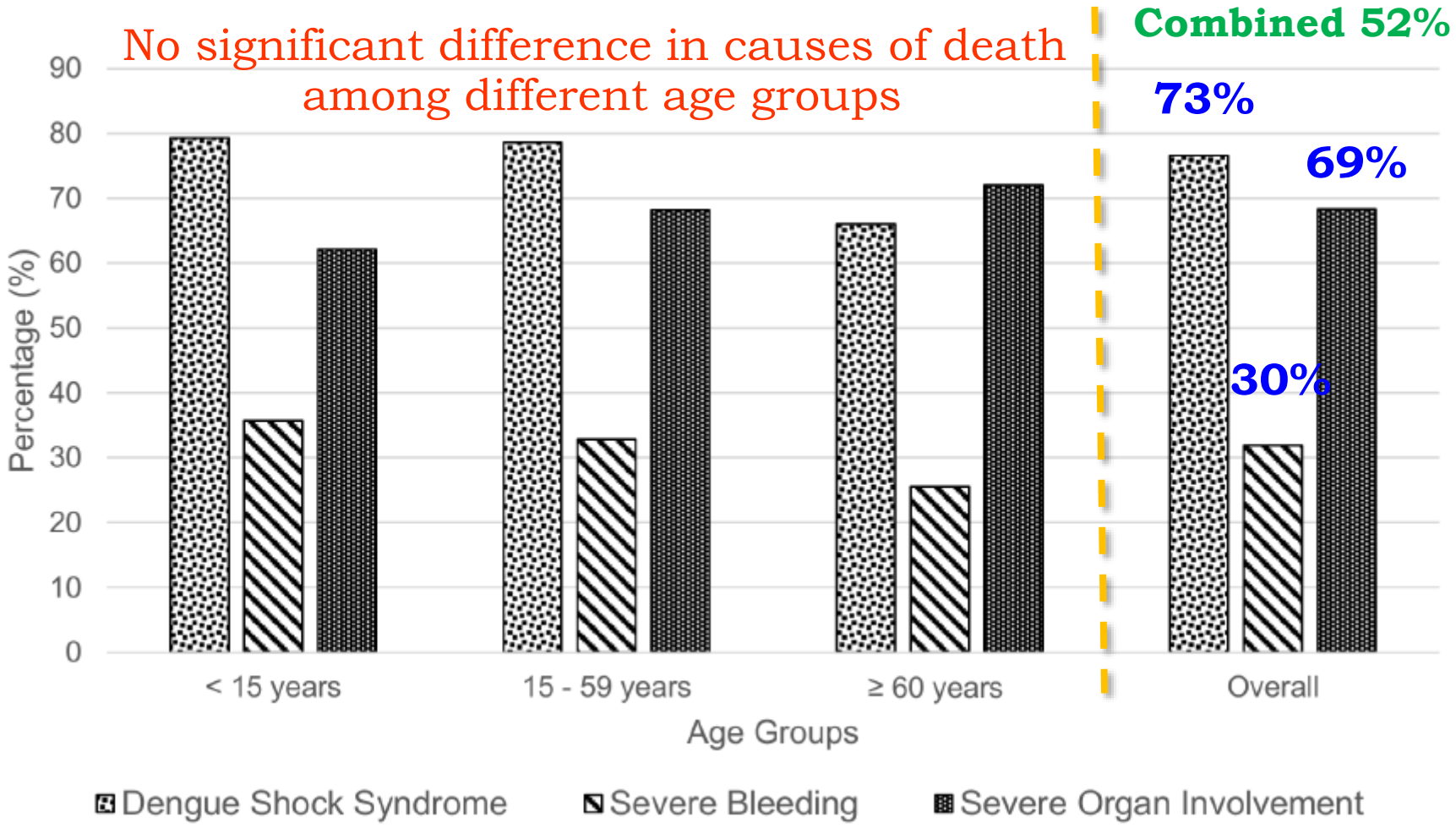
Causes of 322 Dengue Deaths in Malaysia, 2013-2014



Woon YL *et al.* PLoS Negl Trop Dis 2016;10:e0004575.doi:10.1371/journal.pntd.0004575.

Dengue Severity (Children vs. Adults)

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	Direct admit		Refer
	Children (n=402)	Adults (n=59)	Adults (n=51)
HCT ≥20%	351 (92%)*	39 (70%)	20 (53%)
Recurrent shock	147 (37%)*	5 (8%)	27 (61%)*
Bleeding	271 (67%)	59 (100%)*	51 (100%)*
- Skin bleeding	207 (52%)	21 (36%)	9 (18%)
- Mucosal bleeding	55 (14%)	35 (59%)*	30 (60%)*
- Severe bleeding	8 (2%)	3 (5%)	11 (22%)*
Acute liver failure	0	0	2 (4)*
Acute kidney injury	0	0	2 (4)*
Encephalopathy	1 (0.2%)	1 (2%)	7 (14)*

Trung DT *et al.* PLoS Negl Trop Dis 2012;6(6):e1679. doi: 10.1371/journal.pntd.0001679.

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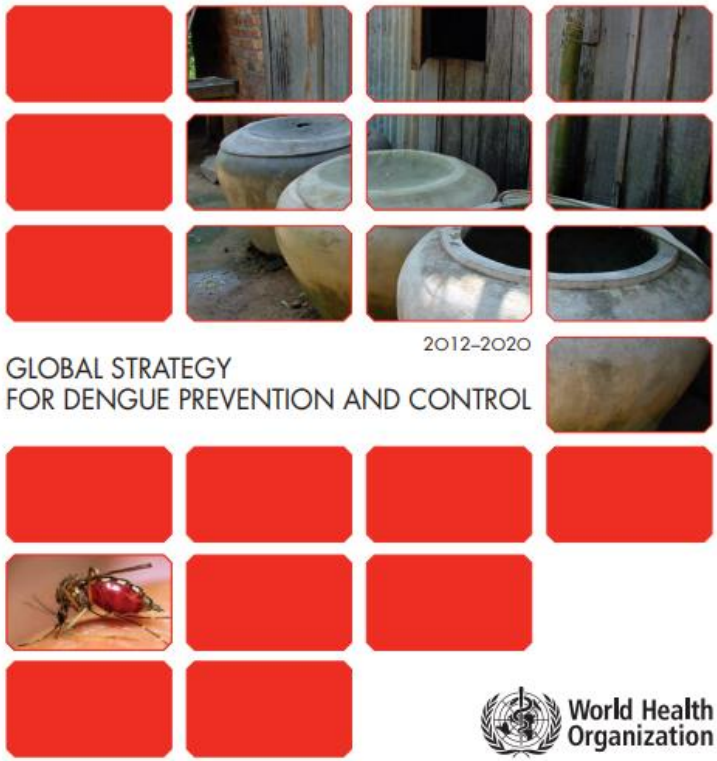
No Approved Therapy is Available !!!!!

- Prompt recognition and diagnosis is important for appropriate supportive care.
- Early diagnosis and access to proper medical care lowers fatality <1%.




https://www.who.int/denguecontrol/resources/9789241504034/en/
Muller DA *et al.* JID 2017;215:S89-95.



MORTALITY FROM DENGUE CAN BE REDUCED TO ALMOST ZERO BY IMPLEMENTING TIMELY, APPROPRIATE CLINICAL MANAGEMENT, WHICH INVOLVES EARLY CLINICAL AND LABORATORY DIAGNOSIS, INTRAVENOUS REHYDRATION, STAFF TRAINING AND HOSPITAL REORGANIZATION.

https://www.who.int/denguecontrol/resources/9789241504034/en/

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Stepwise Approach for Management of Dengue in Adults

- Diagnosis of dengue
- Risk factors for severe disease
- Evaluation of dengue severity
- Evaluation of disease phase
- Management

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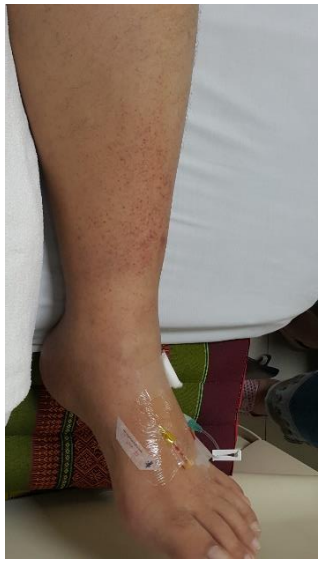
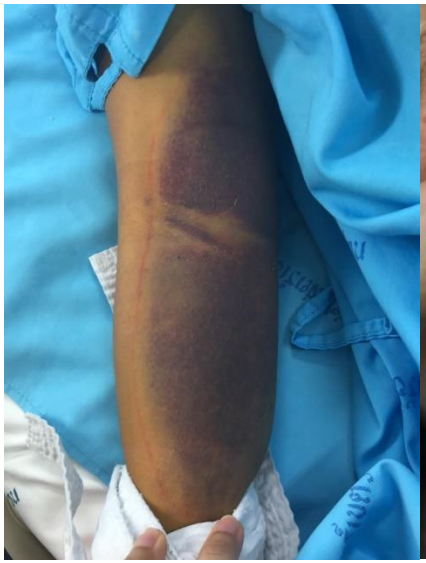
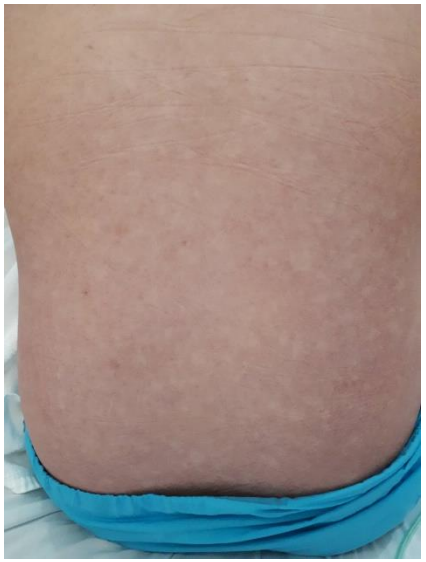
Clinical Diagnosis of Dengue

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Clinical Symptoms & Signs of Patients with Dengue

Variables	95% CI
Fever	98 (97-99)
Malaise	76 (64-85)
Headache	76 (70-81)
Asthenia	74 (46-91)
Body-ache	67 (55-77)
Lethargy	67 (33-90)
Chills	65 (58-72)
Myalgia	64 (58-70)
Back pain	57 (32-79)
Arthralgia	54 (46-61)

Variables	95% CI
Retro-orbital pain	35 (27-44)
Dizziness	23 (12-40)
Anorexia	48 (35-61)
Nausea	42 (34-50)
Vomiting	40 (35-45)
Abdominal pain	32 (28-37)
Diarrhea	21 (17-25)
Bleeding	26 (21-31)
Cough	23 (18-29)
Rash	30 (26-33)

Guo C *et al.* Front Cell Infect Microbiol 2017;7:317. doi: 10.3389/fcimb.2017.00317.

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Clinical Symptoms & Signs of Adults with Dengue

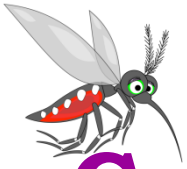
	Tantawichien T	Taylor WR et al.	Thomas L et al.	Thanachartwet V et al.
Country	Thailand	Vietnam	France	Thailand
Year	1997-1998	2008	2005-2010	2013-2015
Age (yr)	26.9	23.5	35.0	24.0
Fever (day)	5.2	5.0	3.0	4.0
Headache	38%	93%	84%	87%
Retro-orbital pain	-	40%	-	64%
Myalgia	26%	77%	75%	91%
Arthralgia	-	-	-	33%
Vomiting	47%	46%	-	16%
Abdominal pain	24%	28%	-	42%
Diarrhea	25%	34%	24%	32%
Cough	-	45%	21%	39%
Rash	28%	52%	-	44%
Hepatomegaly	21%	4%	-	23%

Associations between Symptoms & Signs with Dengue

Variables	OR	95% CI	P-value
Rash	2.8	1.7-4.4	<0.001
Petechiae	2.0	1.2-3.1	0.004
Lethargy	1.8	1.0-3.1	0.041
Conjunctival injection	1.5	1.0-2.3	0.045
TT +ve	4.9	1.1-22.0	0.040
Low WBC	4.4	1.8-11.2	0.002
Low PLT	3.3	2.2-5.0	<0.001

PPV 70-83%

Kalayanarooj S. Trop Med Health 2011;39:S83-7. doi: 10.2149/tmh.2011-S10.
Guo C *et al.* Front Cell Infect Microbiol 2017;7:317. doi: 10.3389/fcimb.2017.00317.



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Case Definition of Probable Dengue (WHO 1997, 2011)

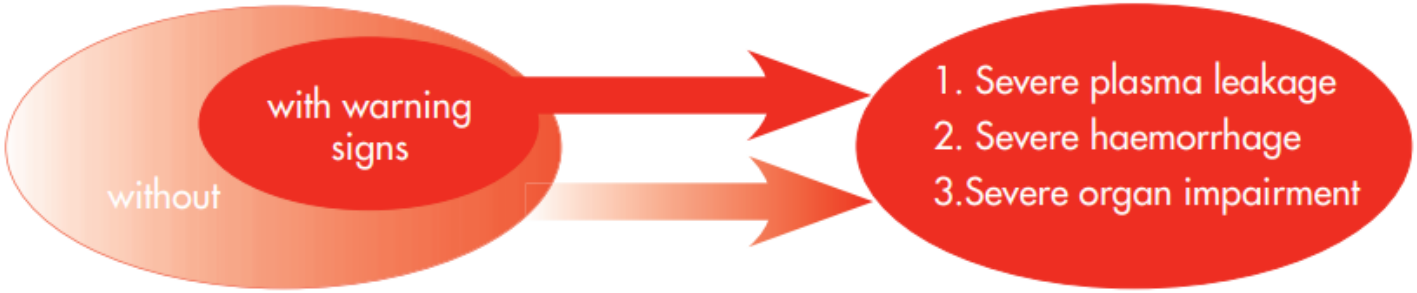
Acute febrile illness with ≥2 of the following signs and symptoms :

- ✓ Headache
- ✓ Retro-orbital pain
- ✓ Myalgia
- ✓ Arthralgia/bone pain
- ✓ Rash
- ✓ Hemorrhagic manifestations : petechiae, epistaxis, gum bleeding, hematemesis, melena, positive tourniquet test
- ✓ Leukopenia (WBC ≤5,000 cells/mm^3)
- ✓ Hemoconcentration 5-10%
- ✓ PLT ≤150,000/mm^3

WHO, 1997

Chaterji S *et al.* Am J Trop Med Hyg 2011;84:224-8.

Case Definition of Probable Dengue (WHO 2009)



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
- Leukopenia
- 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 enlargment >2 cm
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

*(requiring strict observation and medical intervention)

CRITERIA FOR SEVERE DENGUE

Severe plasma leakage

leading to:

- Shock (DSS)
- Fluid accumulation with respiratory distress

Severe bleeding

as evaluated by clinician

Severe organ involvement

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

WHO, 2009

Chaterji S *et al.* Am J Trop Med Hyg 2011;84:224-8.

Diagnostic Accuracy of Probable Dengue

WHO 1997, 2011

Acute febrile illness with ≥2 of the following signs and symptoms :

- ✓ Headache
- ✓ Retro-orbital pain
- ✓ Myalgia
- ✓ Arthralgia/bone pain
- ✓ Rash
- ✓ Hemorrhagic manifestations : petechiae, epistaxis, gum bleeding, hematemesis, melena, positive tourniquet test
- ✓ Leukopenia (WBC ≤5,000 cells/mm^3)
- ✓ Hemoconcentration 5-10%
- ✓ PLT ≤150,000/mm^3

- ○ Sensitivity 95%
- ○ Specificity 36%

WHO 2009

- Live in /travel to endemic area
- Fever ≥2 of the following criteria
  - ✓ Nausea/vomiting
  - ✓ Rash
  - ✓ Aches and pains
  - ✓ TT positive
  - ✓ Leukopenia
  - ✓ Any warning signs

- ○ Sensitivity 80%
- ○ Specificity 57%

Chaterji S *et al.* Am J Trop Med Hyg 2011;84:224-8.

Initial Diagnoses at First Healthcare Contact of Fatal Dengue

	Children (<15 yrs)	Adults (15-59 yrs)	Elderly (≥60 yrs)
Dengue shock syndrome	3%	3%	9%
Dengue with WSs	6%	8%	4%
Dengue without WSs	6%	18%	16%
Acute pharyngitis and/or tonsillitis	34%	16%	5%
Non-specific (viral) febrile illness	31%	28%	21%
Sepsis	3%	3%	9%
Acute gastroenteritis	3%	4%	2%

Woon YL *et al.* PLoS Negl Trop Dis 2016;10:e0004575.doi:10.1371/journal.pntd.0004575.

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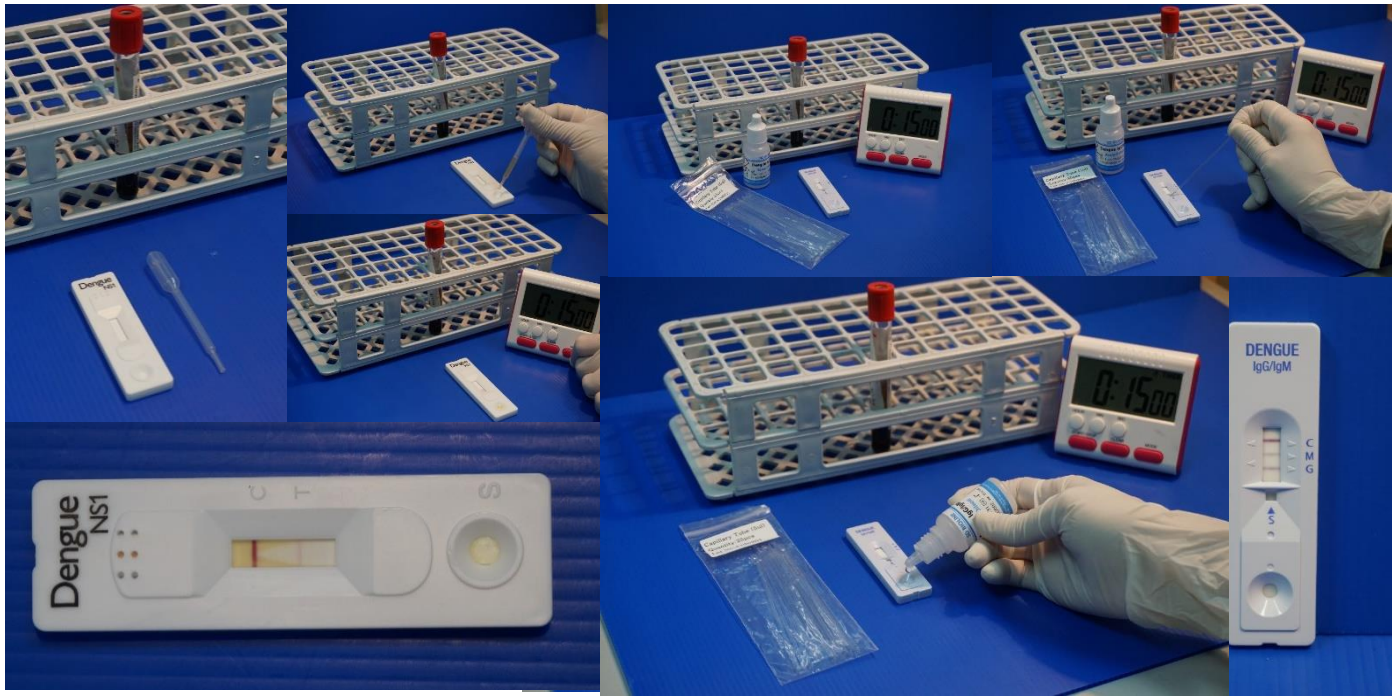
Laboratory Diagnosis of Dengue



Lab. Investigations of Adults with Dengue

	Tantawichien T	Taylor WR et al.	Thomas L et al.	Thanachartwet V et al.
Fever (days)	5.2	5.0	3.0	4.0
Hematology & Blood chemistries				
HCT (%)	-	42.5	-	41.6
WBC(cells/μL)	-	4,560	-	3,000
Platelets (/μL)	-	60,000	-	78,000
AST (U/L)	-	113	-	94
ALT (U/L)	-	67	-	65
Albumin (g/dL)	-	4.5	-	4.2
Complications				
DSS	-	-	14%	10%
Cutaneous bleeding	22%	-	-	28%
Mucosal bleeding	42%	20%	17%	42%
Ascites	4% (U/S)	29% (U/S)	-	-
Pleural effusion	11% (U/S)	16% (CXR)	-	-
Acute kidney injury	-	-	12%	10%

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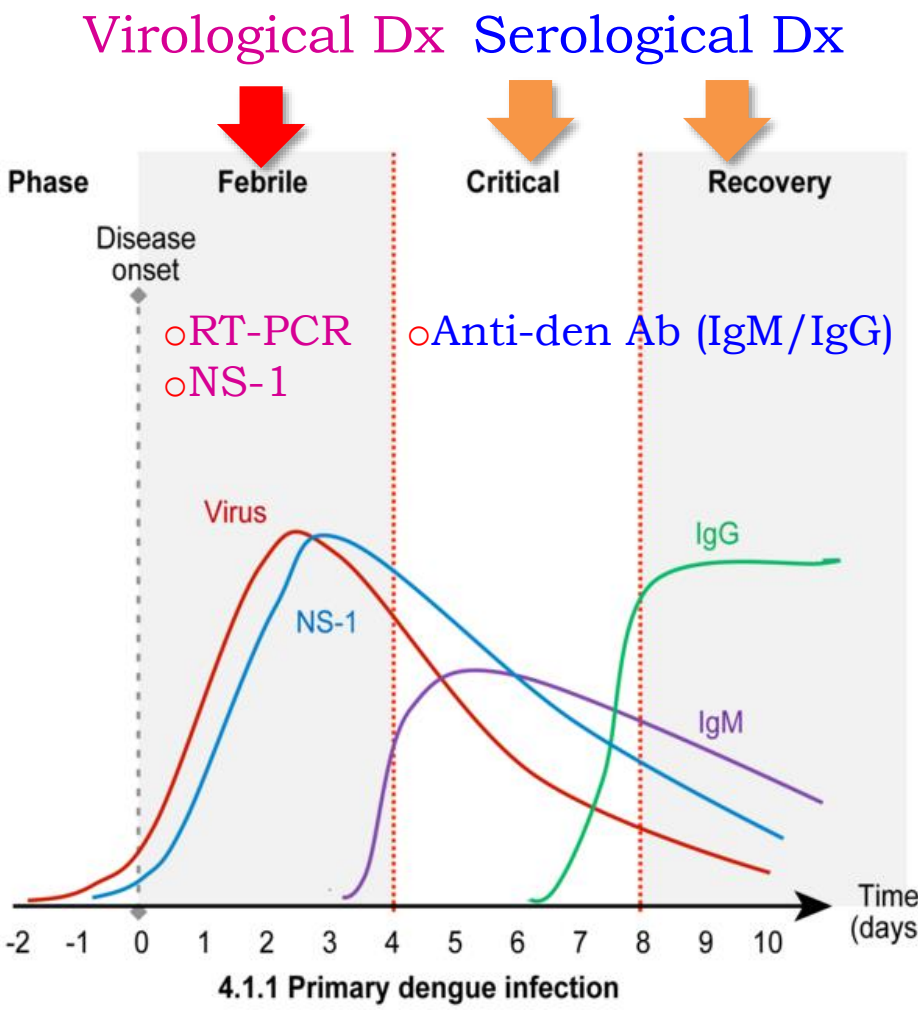
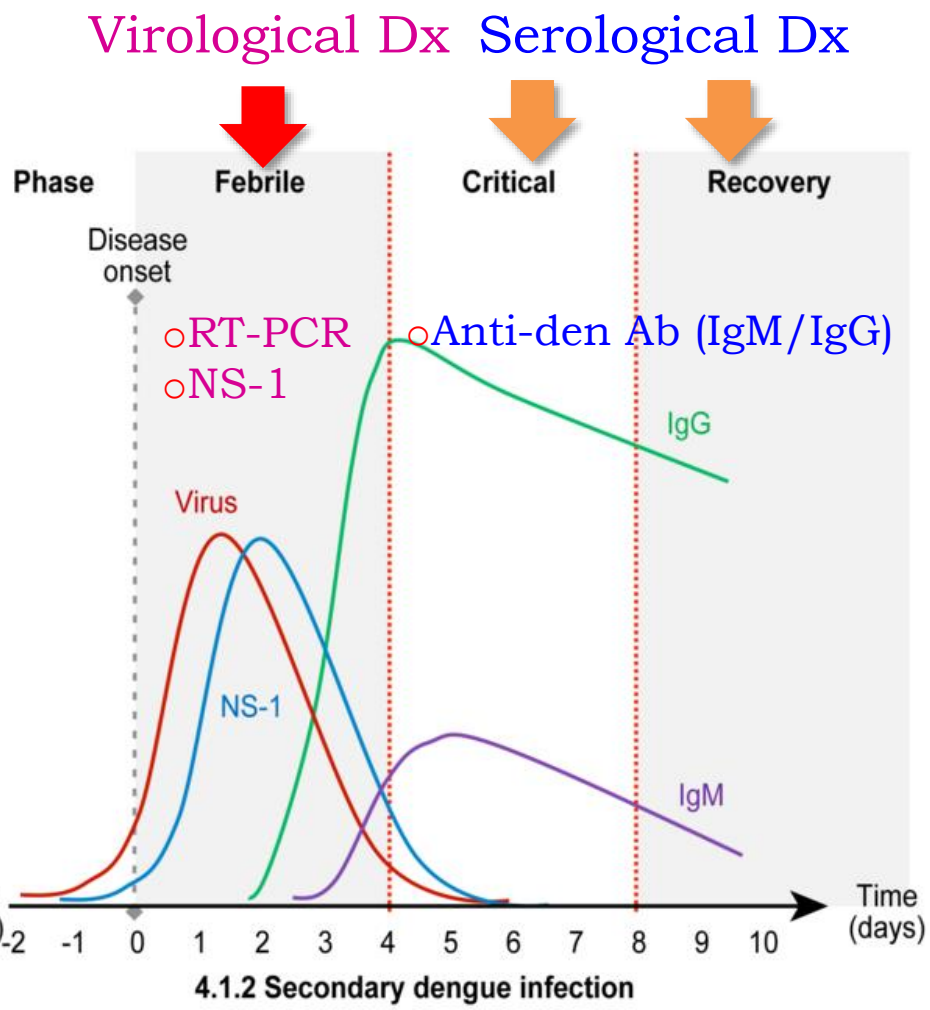
Comparison of Laboratory Findings between Fatal and Non-fatal DHF in Adults

Variable	Fatal (n=10)	Non-fatal (n=299)	*P-value*
Initial Lab findings			
WBC >12,000 cells/μL	1/10 (10%)	4/293 (1%)	0.155
Bandemia	3/8 (38%)	5/277 (2%)	0.001
Platelet count (/μL)	35,000	93,000	0.088
Pre-fatal Lab findings			
WBC >12,000 cells/μL	6/9 (67%)	4/293 (1%)	0.020
Bandemia	4/6 (67%)	5/277 (2%)	0.592
Platelet count (/μL)	17,000	93,000	<0.001

Lee IK *et al.* PLoS Negl Trop Dis. 2012;6(2):e1532. doi: 10.1371/journal.pntd.0001532.

Confirmation Tests for Dengue





วิภา ธนาชาติเวทย์. การดูแลรักษาเดงกีรุนแรงทางคลินิกในผู้ใหญ่; ๒๕๖๐. หน้า ๓๕-๔๖.
Muller DA *et al*. J Infect Dis. 2017;215:S89-95.

Laboratory Diagnostic Methods for Detection of Dengue

	Clinical sample	Diagnostic approach	Methodology	Time to Results
Viro. Dx	Acute serum (D1-5)	Nucleic acid detection	RT-PCR/ Real-time RT-PCR	1-2 d
		Ag detection	NS1 Ag rapid test	Mins
			NS1 Ag capture ELISA	1 d
Sero. Dx	Paired sera • acute serum (D1-5) • convalescent serum (D15-21)	IgM or IgG seroconversion	ELISA	1-2 d
			PRNT	>7 d
	Serum after D5	IgM detection	MAC-ELISA	1-2 d
			IgM rapid test	Mins
		IgG detection	IgG ELISA	1-2 d
			IgG rapid test	Mins

Adapted from WHO 2009; Muller DA *et al.* JID 2017:215;S89.

Confirmation Tests for Dengue

Virological diagnosis

RT-PCR

- Sensitivity 98-99%
- Specificity 100%

Dengue NS-1

- ELISA
  - Sensitivity 60-75%
  - Specificity 71-95%
- Rapid strip tests
  - Sensitivity 40-81%
  - Specificity 76-97%

Serological diagnosis

Anti-den Ab (IgM/IgG)

- ELISA
  - Sensitivity 96-99%
  - Specificity 78-91%
- Rapid strip tests
  - Sensitivity 6-96%
  - Specificity 69-92%

Definite diagnosis?
Primary/Secondary?

วิภา ธนาชาติเวทย์. การดูแลรักษาเดงกีรุนแรงทางคลินิกในผู้ใหญ่; ๒๕๖๐. หน้า ๓๕-๔๖.
Hunsperger EA *et al*. PloS Negl Trop Dis. 2014;8:e3171.

Rapid Diagnostic Tests for Dengue

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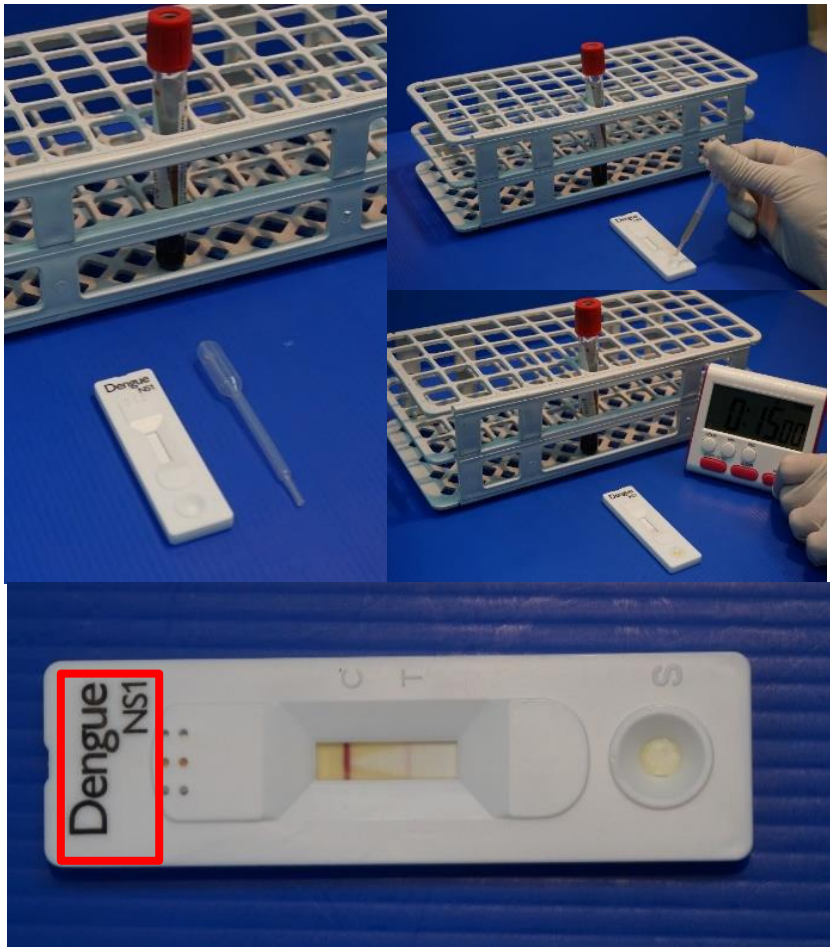
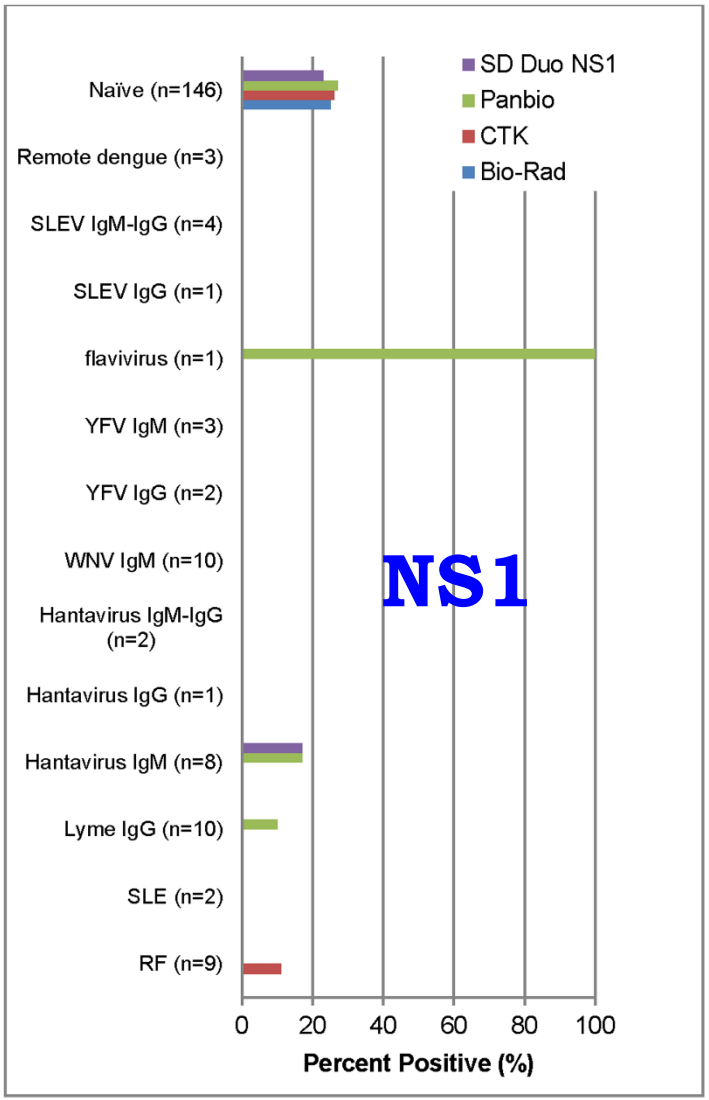
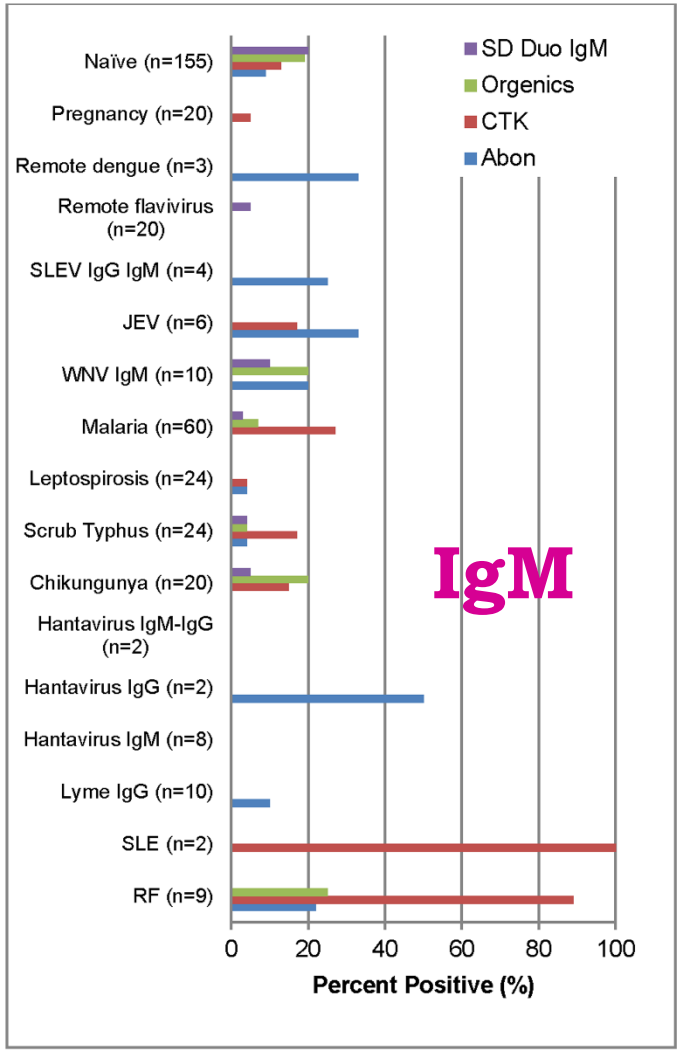


False Positive Rate of DENV RDT



NS1=non-structural protein 1, SLE=systemic lupus erythematosus, SLEV=St. Louis Encephalitis virus, RF=rheumatoid factor, YFV=yellow fever virus, WNV=West Nile virus



SLE=systemic lupus erythematosus, SLEV=St Louis Encephalitis virus, RF=rheumatoid factor, YFV=yellow fever virus, WNV=West Nile virus, JEV=Japanese

Hunsperger EA *et al.* PLoS Negl Trop Dis 2014;8:e3171.

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Stepwise Approach for Management of Dengue in Adults

- Diagnosis of dengue
- Risk factors for severe disease
- Evaluation of dengue severity
- Evaluation of disease phase
- Management

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Clinical factors for Predicting Dengue Severity in Adults

Character	Lee MS et al	Figueiredo MA et al	Pang J et al	Pozo-Aguilar JO et al	Thanachartwet V et al	Malhi TH et al	Lee IK et al
Country	Taiwan	Brazil	Singapore	Mexico	Thailand	Malaysia	Taiwan
Year	2000	2002-2005	2007-2008	2009	2012-2015	2008-2014	2002-2010
Severity	DHF	DHF	DHF	Severe dengue	Severe dengue	DHF	DSS/Severe dengue
Clinical factors							
Age (yrs.)	>65 [OR 1.9]	-	30-39 [OR 1.4] 40-49 [OR 1.3]	-	>40 [OR 5.2]	>40 [OR 4.1]	-
Underlying disease	DM [OR 1.9] HT [OR 1.7] CKD [OR 3.6]	DM [OR 2.7]	DM [OR 1.8] DM with HT [OR 2.2]	-	-	DM [OR 2.8]	DM for DSS [OR 7.4] DM for SD [6.2]

Pregnant woman, Obesity, Heart diseases, Hematologic diseases, Prolonged shock, Significant bleeding

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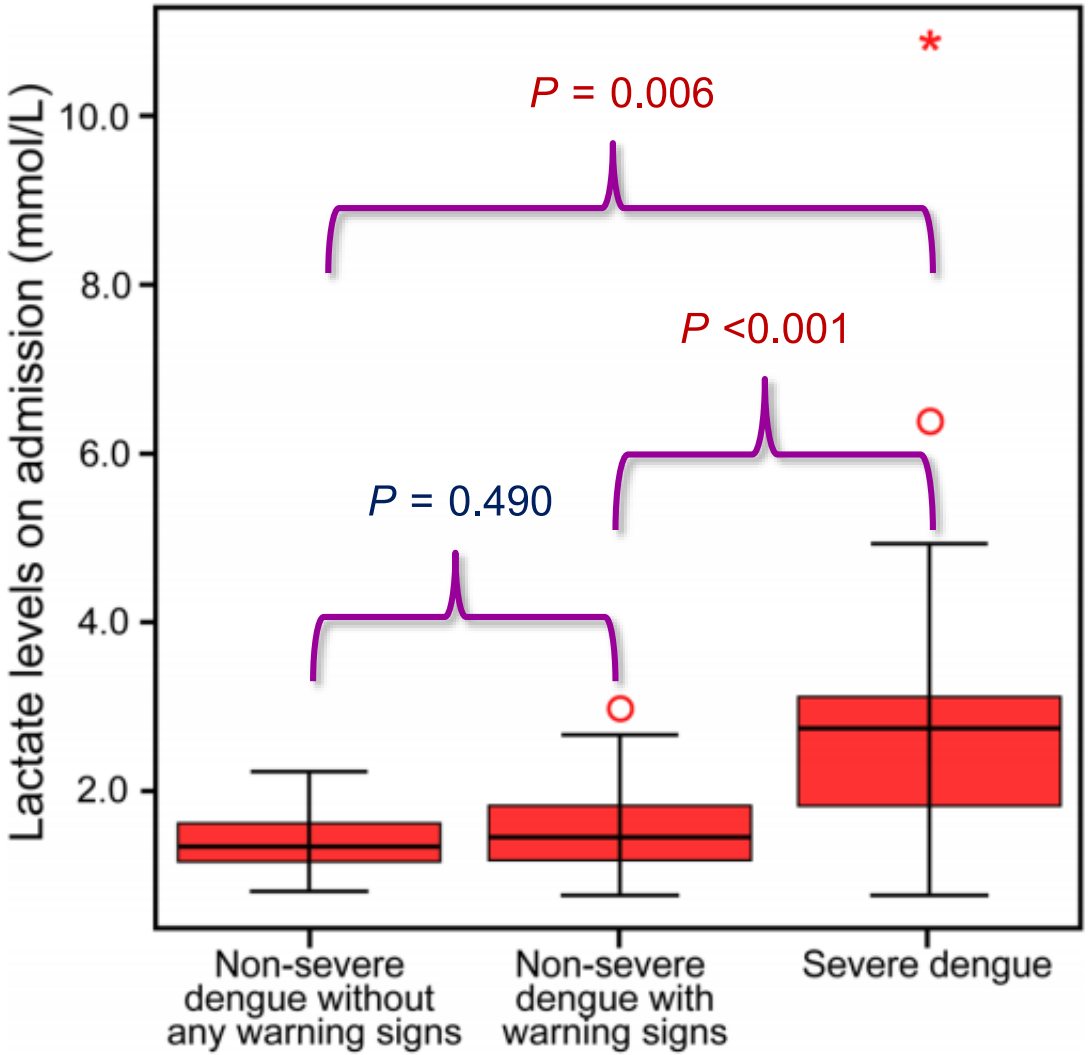
Lab. factors for Predicting Dengue Severity in Adults

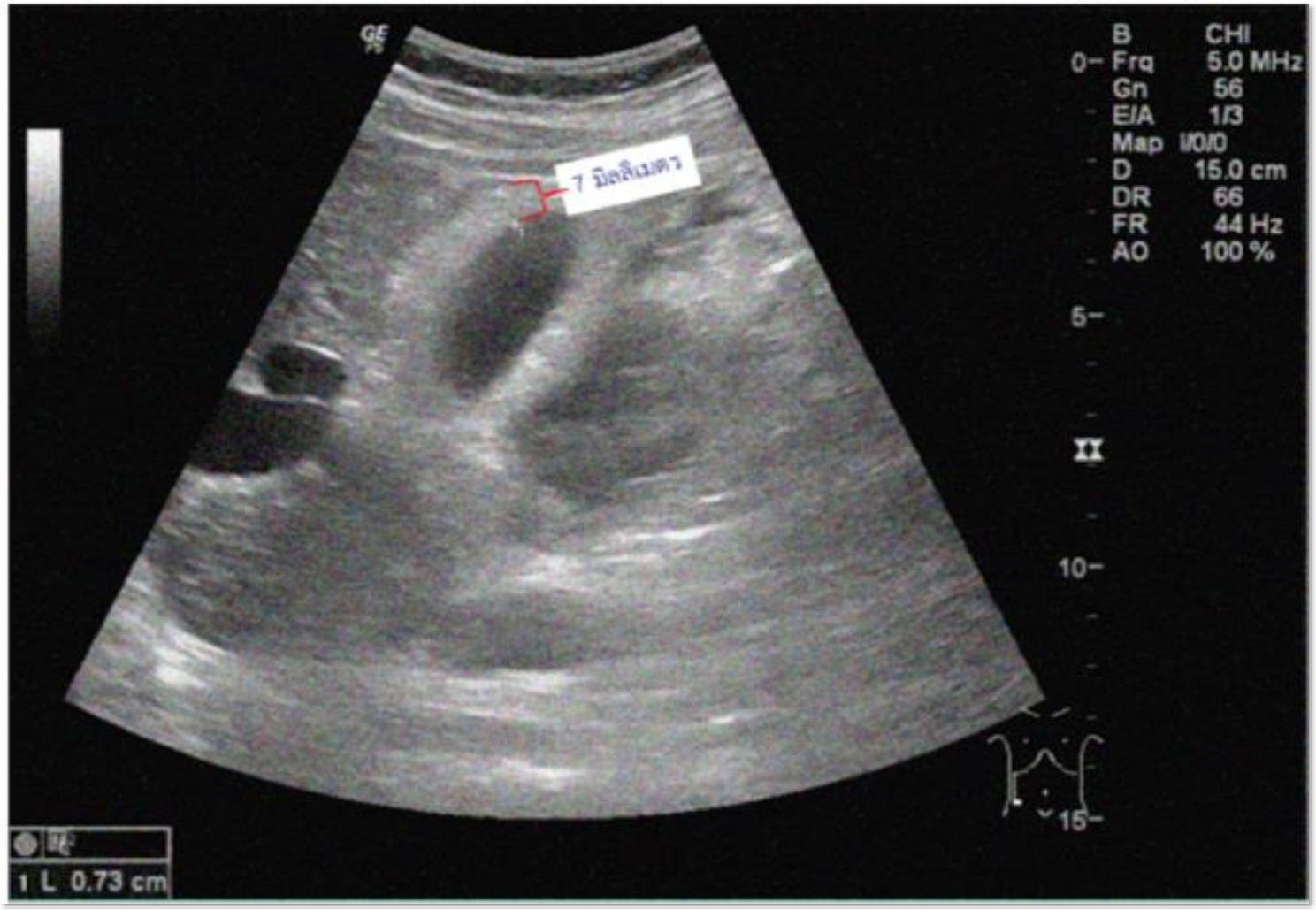
Character	Lee MS et al	Malavige GN et al	Pozo-Aguilar JO et al	Thanachartwet V et al	Malhi TH et al
Country	Taiwan	Brazil	Mexico	Thailand	Malaysia
Year	2002	2002-2005	2009	2012-2014	2008-2014
Severity	DHF	DHF	Severe dengue	Severe dengue	DHF
Lab. factors					
Dengue infection	Secondary [OR 2.1]	Secondary [OR 5.0]	Secondary [OR 5.7]	-	Secondary [OR 2.7]
Blood test	-	-	-	Serum lactate ≥2 mmol/L [OR 7.3]	
Ultrasound	GBW thickening [OR 6.1]	-	-	-	GBW thickening [OR 1.7]

Lactate Levels at Admission according to Dengue Severity



Thanachartwet V *et al.* BMC Infect Dis. 2015;15:420. doi: 10.1186/s12879-015-1150-2.

Gall Bladder Wall Thickening in Adults with DSS



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*

Risk of severe dengue

- Female (OR = 1.13, 95% CI = 1.01–1.26)
- Dengue virus serotype 2 was associated with severe disease in children.
- Secondary infections (OR 2.26, 95% CI = 1.65–3.09)
- Pre-existing comorbidities:
  - ✓ DM (OR = 4.38, 95% CI = 2.58–7.43)
  - ✓ HT (OR = 2.19, 95% CI = 1.36–3.53)
  - ✓ Renal disease (OR = 4.67, 95% CI = 2.21–9.88)
  - ✓ CVS disease (OR = 2·79, 95% CI = 1.04–7.50)

Sangkaew S, *et al.* Lancet Infect Dis 2021;21(7):1014-1026. doi: 10.1016/S1473-3099(20)30601-0.

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Clinical features during the febrile phase associated with progression to severe disease

- Vomiting
  (OR = 2.25, 95% CI = 1.87–2.71)
- Abdominal pain and tenderness
  (OR = 1.92, 95% CI = 1.35–2.74)
- Spontaneous or mucosal bleeding
  (OR = 1.57, 95% CI = 1.13–2.19)
- Presence of clinical fluid accumulation
  (OR = 4.61, 95% CI = 2.29–9.26)

Sangkaew S, *et al.* Lancet Infect Dis 2021;21(7):1014-1026. doi: 10.1016/S1473-3099(20)30601-0.

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During the first 4 days of illness

- Lower PLT count (MD –0.34, 95% CI –0.54 to –0.15)
- Lower serum ALB (MD–0.5, 95% CI –0.86 to –0.15)
- Higher AST/ALT
  - AST (MD 1.06, 95% CI = 0.54 to 1.57)
  - ALT (MD 0.73, 95% CI = 0.36 to 1.09)

Sangkaew S, *et al.* Lancet Infect Dis 2021;21(7):1014-1026. doi: 10.1016/S1473-3099(20)30601-0.

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Meta-analysis : Risk Factors for Death in Dengue

Variables	OR	95%CI
DM	2.5	1.5-4.2
HT	2.4	1.4-4.1
Shock	308.1	42.6-2230.4

Guo C *et al.* Front Cell Infect Microbiol 2017;7:317. doi: 10.3389/fcimb.2017.00317.

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Comparisons Dengue Severity Classification between Dengue Patients with Type 2 DM

	DM2 with HbA1C <7%		DM2 with HbA1C ≥7%		Controls
	No comorbid (n = 10)	Comorbid (n = 7)	No comorbid (n = 47)	Comorbid (n = 23)	(n=621)
Age	58 (42-78)*	62 (53-78)*	61 (39-78)*	65 (41-77)*	46 (18-84)
DHF I-II	3 (30)	2 (26)	22 (47)*	14 (61)*	180 (29)
DSS	0	0	2 (4)*	2 (9)*	5 (0.8)
Severe dengue	0	0	8 (17)*	8 (35)*	7 (1.1)
Fatality	0	0	2 (4.3)	2 (8.7)	4 (0.6)

Comorbidities : HTN, CKD, ESRD, CVA, IHD

Lee IK *et al.* J Microbiol Immunol Infect 2018. pii: S1684-1182(18)30006-9.

แนวทางการดูแลรักษาผู้ป่วยโรคไข้เลือดออก (ฉบับย่อ)

Short guideline for dengue case management

- ผู้ป่วย**กลุ่มที่มีความเสี่ยงสูง**ต่อการเกิดโรคไข้เลือดออกที่รุนแรงและมีภาวะแทรกซ้อน ประกอบด้วย
  - เด็กอายุน้อยกว่า 1 ปี สตรีตั้งครรภ์ ผู้สูงอายุ ผู้ป่วยโรคอ้วน
  - ผู้ที่มีโรคประจำตัวเรื้อรัง เช่น โรคเบาหวาน โรคความดันเลือดสูง โรคหัวใจ โรคตับ โรคเลือด และโรคไต
  - ผู้ที่กินยาต้านการแข็งตัวของเลือด (anticoagulants) /ยาต้านเกล็ดเลือด (antiplatelets)/NSAIDs
  - ผู้ป่วยที่มีระดับความรู้สึกตัวลดลง ผู้ป่วยที่มีภาวะเลือดออกผิดปกติ และผู้ป่วยที่มีภาวะช็อก

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Stepwise Approach for Management of Dengue in Adults

- Diagnosis of dengue
- Risk factors for severe disease
- Evaluation of dengue severity
- Evaluation of disease phase
- Management

Pathogenesis in Dengue Severity

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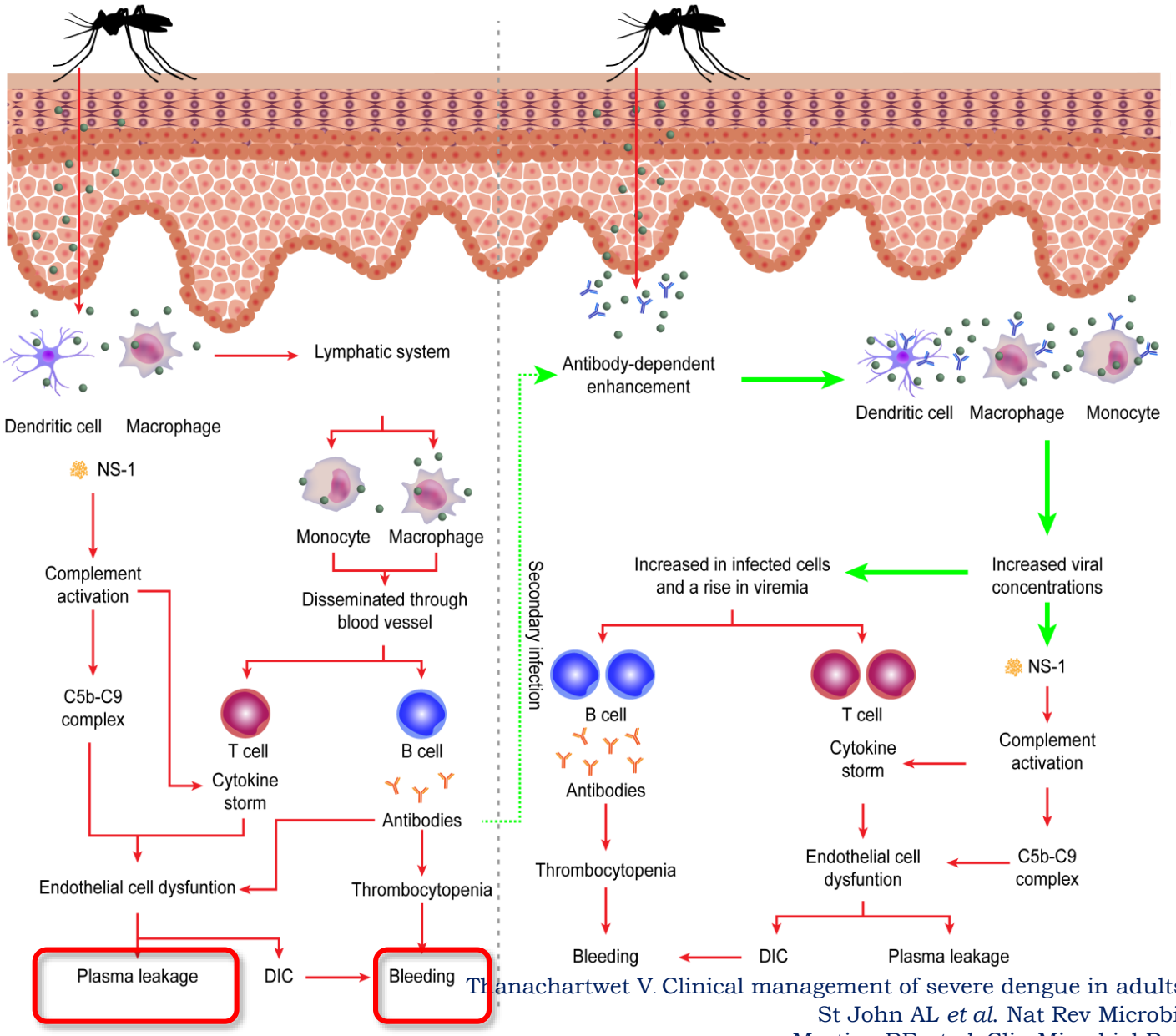
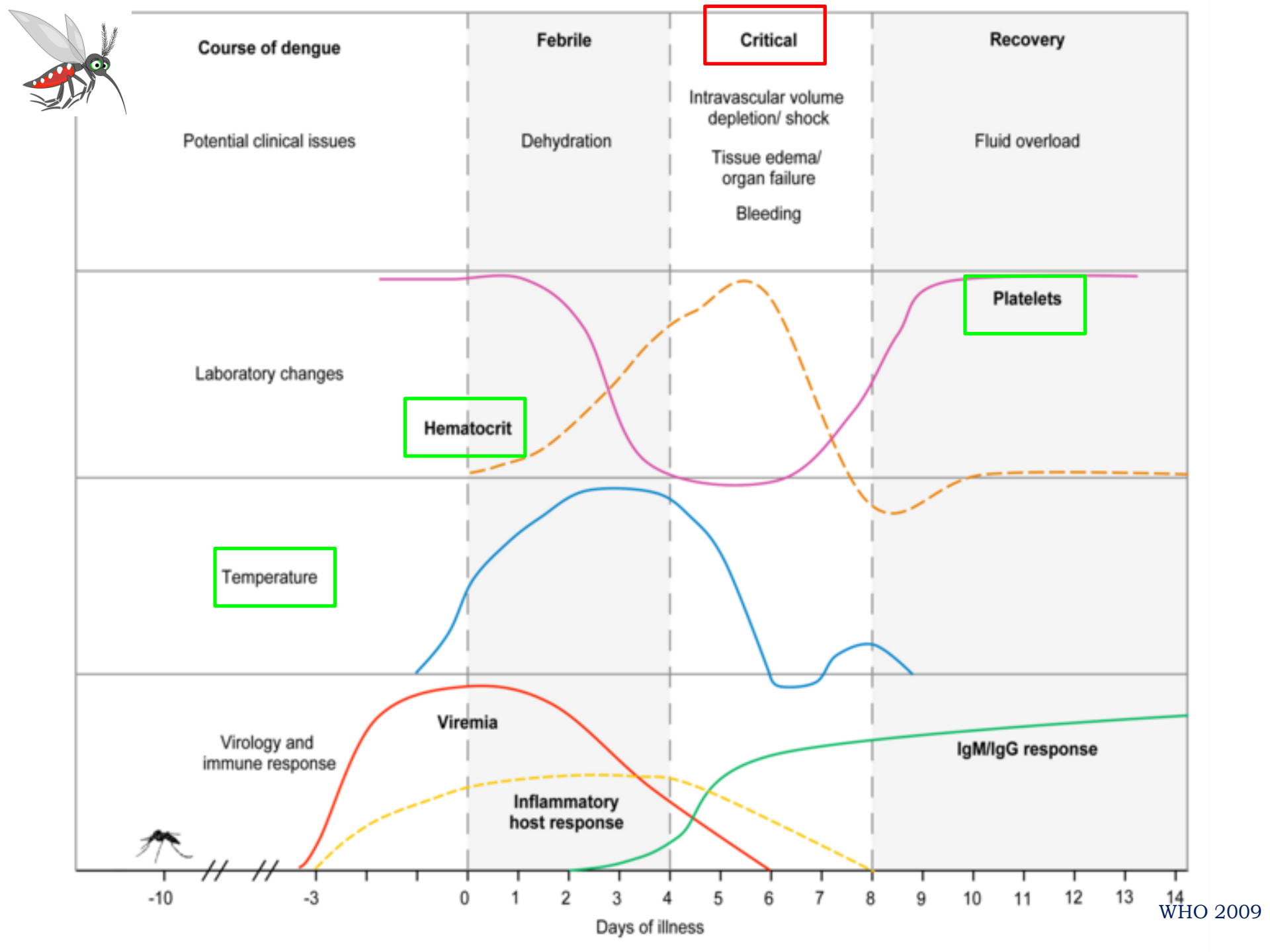


Thanachartwet V. Clinical management of severe dengue in adults; 2017. pp 47-56.
St John AL *et al.* Nat Rev Microbiol 2013;11:420-6.
Martina BE *et al.* Clin Microbiol Rev 2009;22:564-81.


Course of dengue
Febrile
Critical
Recovery
Potential clinical issues
Dehydration
Intravascular volume depletion/ shock
Tissue edema/ organ failure
Bleeding
Fluid overload
Laboratory changes
Platelets
Hematocrit
Temperature
Virology and immune response
Viremia
Inflammatory host response
IgM/IgG response
-10
-3
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Days of illness

WHO 2009

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Stepwise Approach for Management of Dengue in Adults

- Diagnosis of dengue
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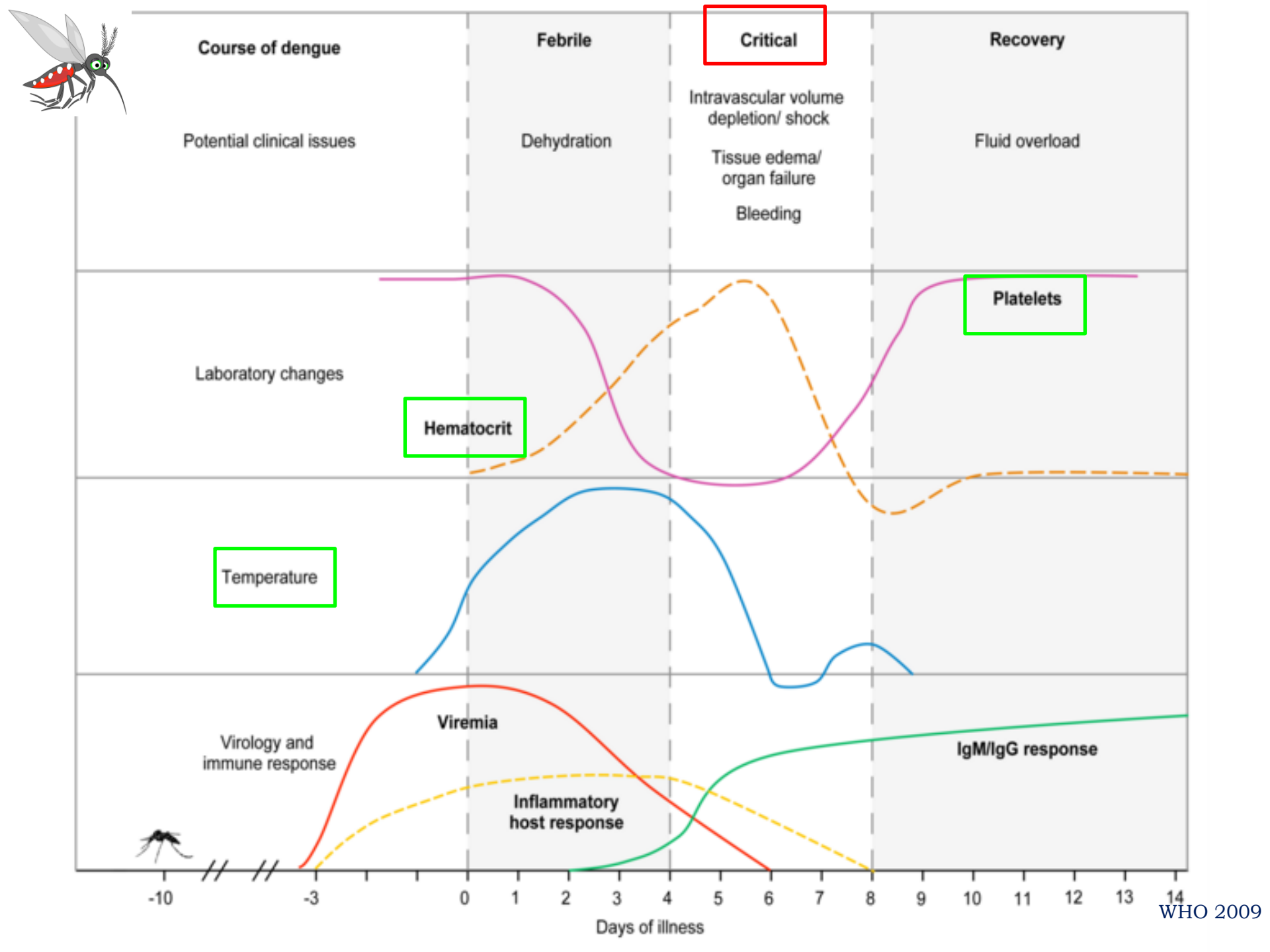
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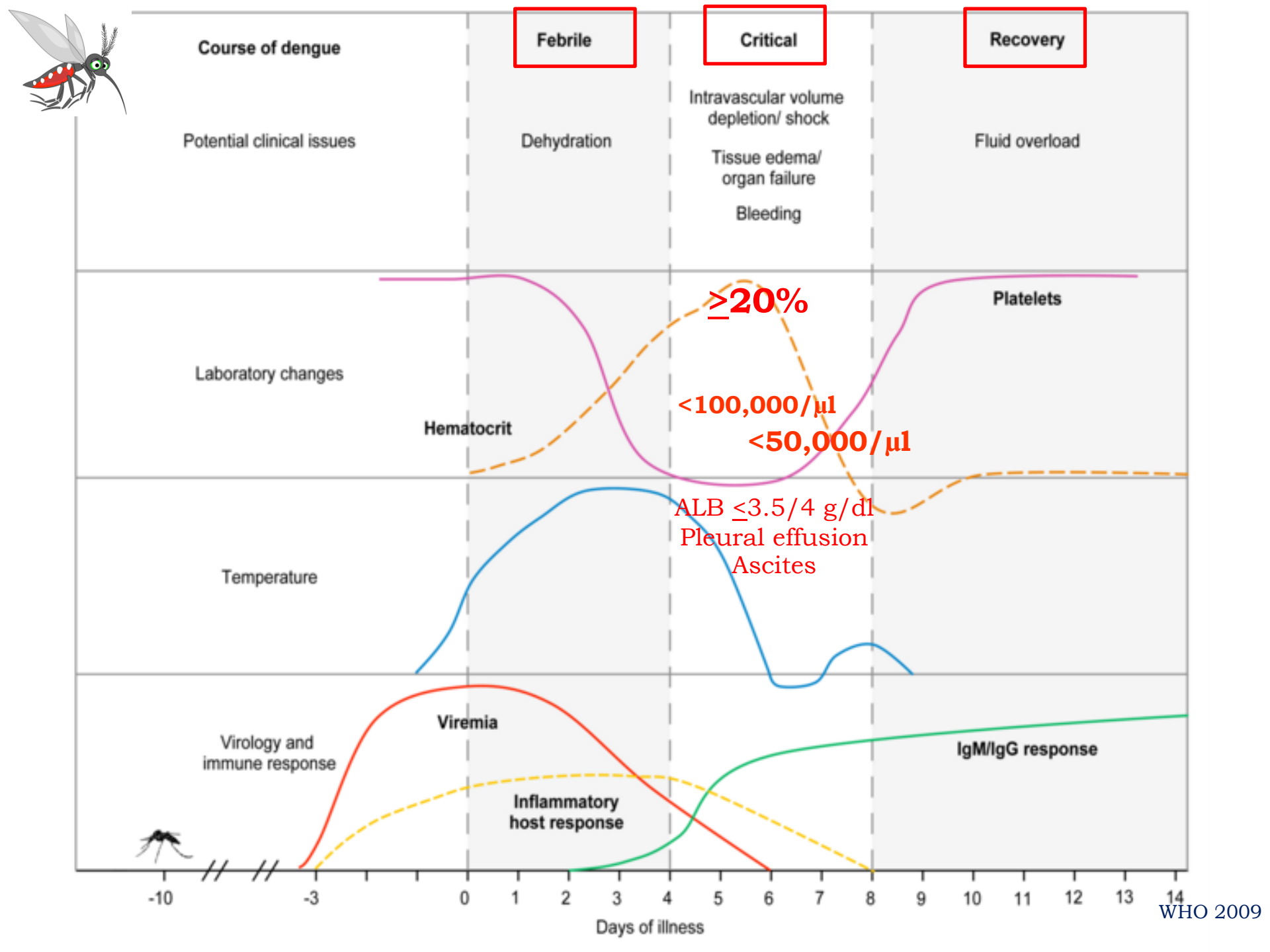
Days of illness

WHO 2009


Course of dengue
Febrile
Critical
Recovery
Potential clinical issues
Dehydration
Intravascular volume depletion/ shock
Tissue edema/ organ failure
Bleeding
Fluid overload
Laboratory changes
≥20%
Platelets
Hematocrit
<100,000/µl
<50,000/µl
ALB ≤3.5/4 g/dl
Pleural effusion
Ascites
Temperature
Virology and immune response
Viremia
IgM/IgG response
Inflammatory host response
-10
-3
0
1
2
3
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5
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7
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14
Days of illness

WHO 2009

Diagnosis of DHF

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Patients present with acute febrile illness 2-7 days with :

Clinical symptoms and signs

1. Abnormal bleeding

- Cutaneous bleeding : positive tourniquet test, petechiae or ecchymosis
- Mucosal bleeding : gum bleeding, epistaxis, GI bleeding or abnormal uterine bleeding (heavy or frequent menstrual bleeding)

2. Hepatomegaly ± tenderness, abdominal pain or vomiting

3. Dengue shock syndrome

- Circulatory failure : rapid and weak pulse, cold clammy skin, PP <20 mmHg
- Hypotension with tissue hypoperfusion : dizziness, fainting, syncope, decrease UO, restlessness, altered sensorium, CRT >2 sec

Lab. Investigations

1. Evidence of plasma leakage : HCT ≥20%, pleural effusion, ascites and/or serum ALB (<3.5 g/dl in normal weight or <4.0 g/dl in obesity)
2. PLT count ≤100,000 /mm^3

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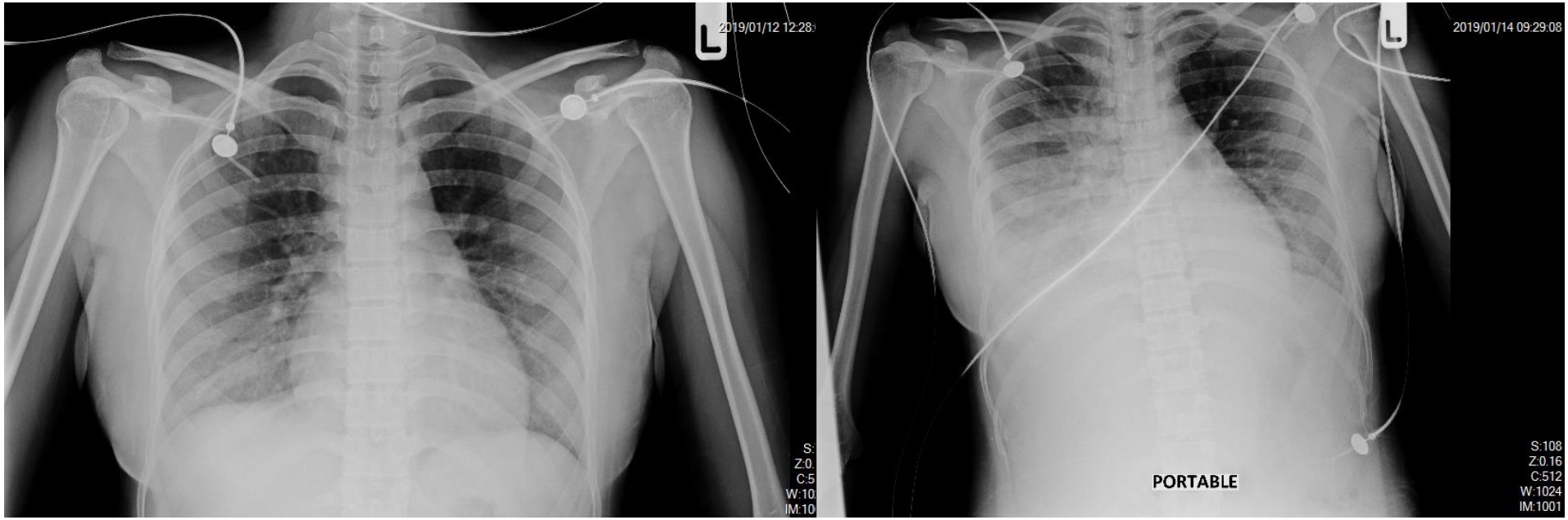
Plasma Leakage : Pleural Effusion



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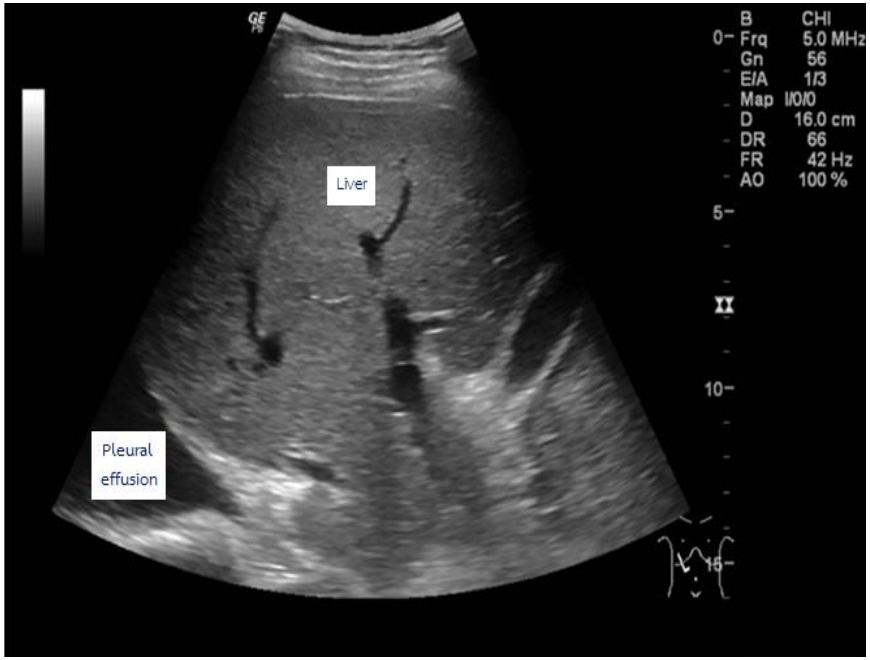
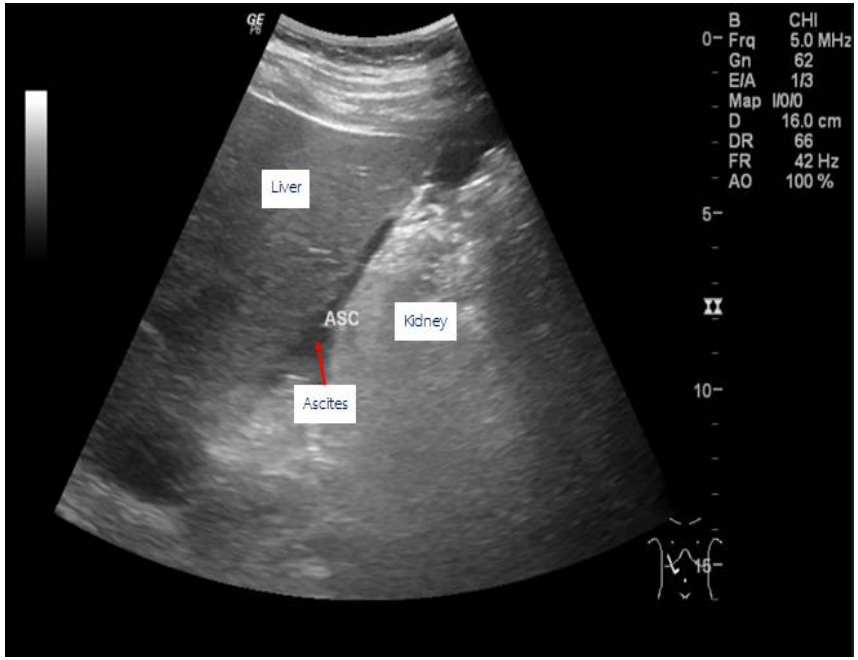
Plasma Leakage : Pleural Effusion/Ascites





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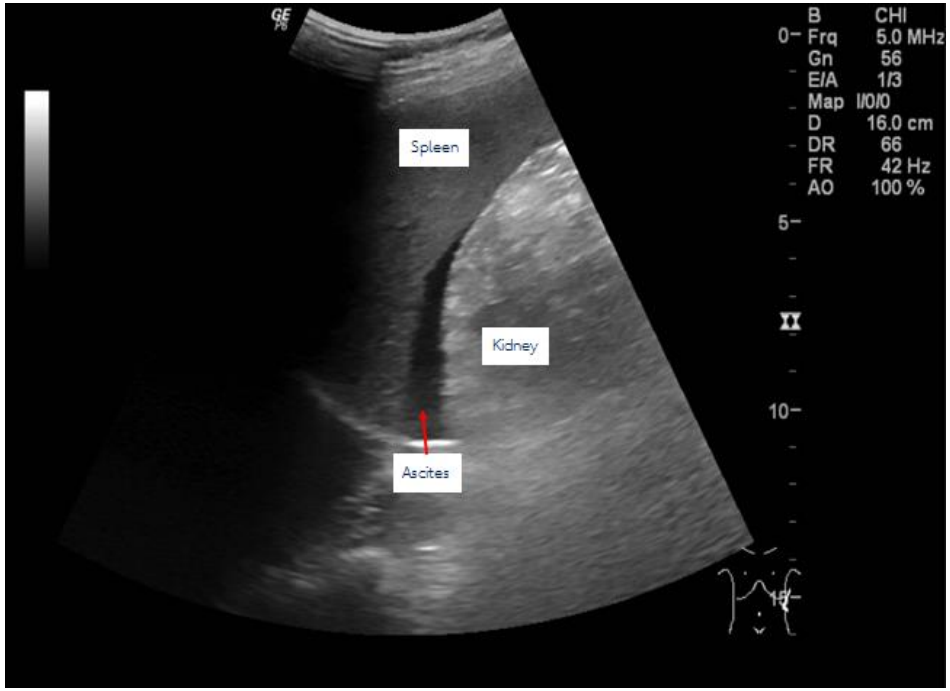
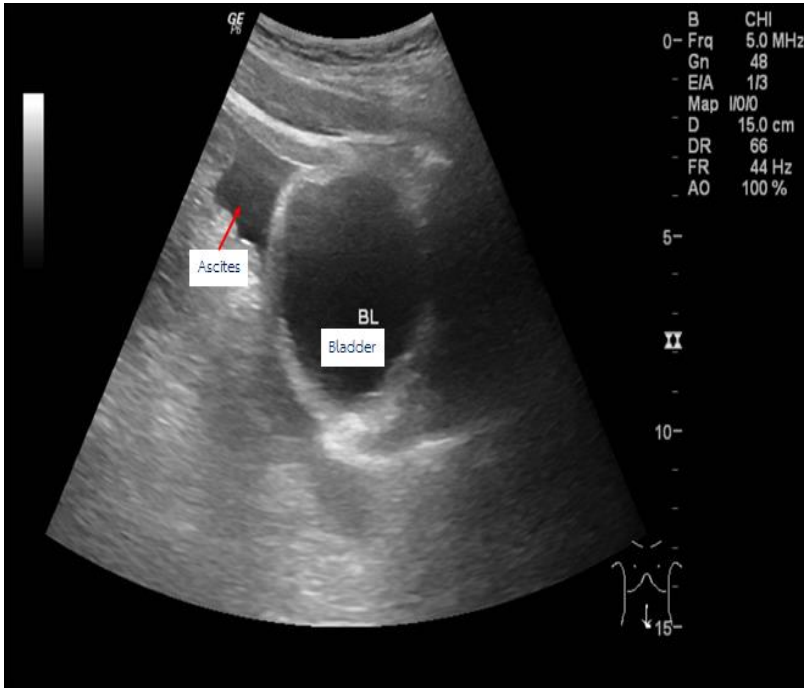
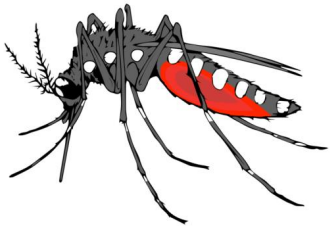
Plasma Leakage : Ascites





PLOS ONE



RESEARCH ARTICLE

Predictors of plasma leakage among dengue patients in Thailand: A plasma-leak score analysis

Sutopa Talukdar[1], Vipa Thanachartwet[1]*, Varunee Desakorn[1], Supat Chamnanchanunt[1], Duangjai Sahassananda[2], Mukda Vangveeravong[3], Siripen Kalayanarooj[3], Anan Wattanathum[4]

1 Faculty of Tropical Medicine, Department of Clinical Tropical Medicine, Mahidol University, Bangkok, Thailand, **2** Faculty of Tropical Medicine, Information Technology Unit, Mahidol University, Bangkok, Thailand, **3** Department of Medical Services, Queen Sirikit National Institute of Child Health, Ministry of Public Health, Bangkok, Thailand, **4** Department of Medicine, Pulmonary and Critical Care Division, Phramongkutklao Hospital, Bangkok, Thailand

* vipa.tha@mahidol.edu

Characteristic	Multivariate logistic regression analysis	
	OR (95%CI)	P-value
BMI ≥25 kg/m^2	1.784 (1.040-3.057)	0.035
PLT <100,000	2.151 (1.269-3.647)	0.004
AST/ALT ≥100 U/L	2.189 (1.231-3.891)	0.008

WHO, 2011

Talukdar S *et al.* PLoS One. 2021 Jul 29;16(7):e0255358. doi: 10.1371/journal.pone.0255358.

https://www.dms.go.th/backend//Content/Content_FIle/Bandner_(Small)/Attach/25640302103903AM_CPG%20Adult%20Dengue.pdf

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Stepwise Approach for Management of Dengue in Adults

- Diagnosis of dengue
- Risk factors for severe disease
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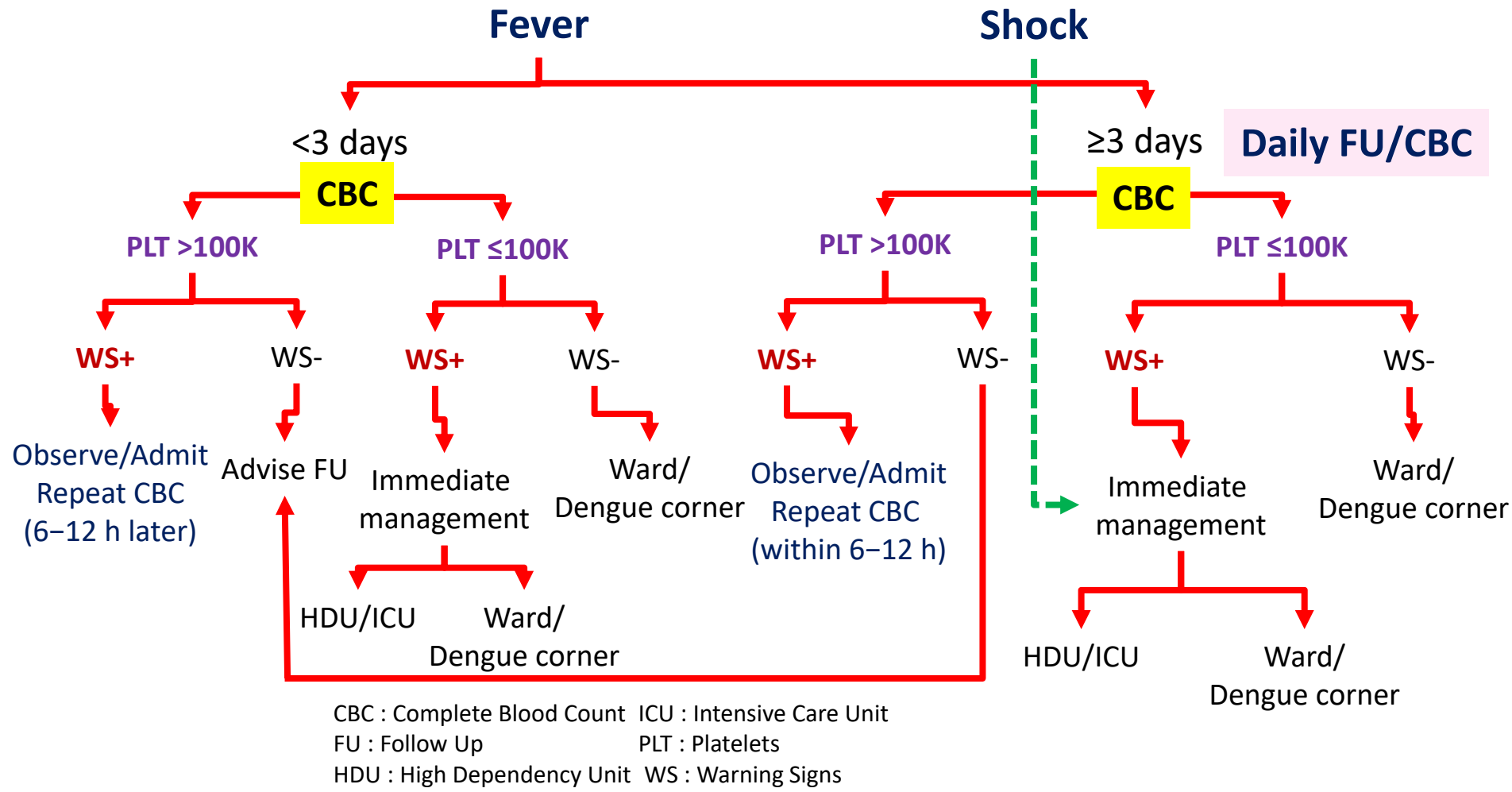
- Management (Febrile phase)

OPD triage



CBC : Complete Blood Count ICU : Intensive Care Unit
FU : Follow Up PLT : Platelets
HDU : High Dependency Unit WS : Warning Signs

อาการ/อาการแสดงที่เป็นสัญญาณเตือน (Warning symptoms and signs)

- ไข้ลดลงแต่อาการไม่ดีขึ้น ยังคงมีอาการอ่อนเพลีย ไม่มีแรง กระสับกระส่าย หรือซึมลง
- ปวดท้องหรืออาเจียนมากกว่า 3 ครั้งต่อวัน
- หน้ามืด จะเป็นลม เวียนศีรษะ หรือมีมือและเท้าเย็น
- ปัสสาวะลดลงหรือไม่มีปัสสาวะใน 4–6 ชั่วโมงที่ผ่านมา
- มีภาวะเลือดออกผิดปกติ โดยเฉพาะอย่างยิ่ง ภาวะเลือดออกในบริเวณเยื่อเมือกต่าง ๆ เช่น เลือดกำเดาไหล ถ่ายอุจจาระสีดำ อาเจียนเป็นเลือดสดหรือเป็นสีดำ และประจำเดือนมานอกรอบหรือมามากผิดปกติ เป็นต้น หรือมีภาวะ intravascular hemolysis เกิดขึ้น โดยสังเกตจากปัสสาวะมีสีน้ำตาลเข้ม มีสีดำ หรือมีสีโค้ก

เกณฑ์การรับผู้ป่วยที่มีการติดเชื้อไวรัสเดงกีหรือผู้ป่วยที่สงสัย จะเป็นไข้เลือดออกเดงกีไว้เป็นผู้ป่วยในโรงพยาบาล

- รับประทานอาหารและดื่มน้ำไม่ได้ อาเจียนมาก ปวดท้อง อ่อนเพลีย ไม่มีแรง หน้ามืด หรือเป็นลม
- มีภาวะเลือดออกผิดปกติมาก โดยเฉพาะอย่างยิ่ง ผู้หญิงที่มีประจำเดือนมามากกว่าปกติหรือมีประจำเดือนมานอกรอบ และผู้ป่วยที่มีปัสสาวะสีน้ำตาลเข้ม มีสีดำ หรือมีสีโค้ก
- มีภาวะเดงกีช็อก pulse pressure แคบหรือมีความดันเลือดต่ำ
- มีค่าฮีมาโทคริตมากกว่าร้อยละ 45 ในผู้หญิง (ผู้ใหญ่) หรือมากกว่าร้อยละ 50 ในผู้ชาย (ผู้ใหญ่) หรือเพิ่มขึ้นตั้งแต่ร้อยละ 20 ขึ้นไป เมื่อเทียบกับค่าฮีมาโทคริตเดิม
- มีปริมาณเกล็ดเลือด $\leq$100,000 /mm^3 และเริ่มมีการรั่วของพลาสมา
- มีค่า AST หรือ ALT $\geq$500 U/l
- มีการทำงานบกพร่องของไต หัวใจ หรือระบบประสาท เช่น ปัสสาวะลดลง หัวใจเต้นผิดจังหวะ หรือระดับความรู้สึกตัวลดลง
- ผู้ป่วยต่อไปนี้เป็นผู้ป่วยที่มีความเสี่ยงสูง ให้พิจารณารับเป็นผู้ป่วยในตามความเหมาะสม ได้แก่ เด็กอายุน้อยกว่า 1 ปี สตรีตั้งครรภ์ ผู้สูงอายุ ผู้ป่วยโรคอ้วน ผู้ที่มีโรคประจำตัวเรื้อรัง เช่น โรคเบาหวาน โรคความดันเลือดสูง โรคหัวใจ โรคตับ โรคเลือด และโรคไต เป็นต้น รวมทั้งผู้ที่กินยาต้านการแข็งตัวของเลือด (anticoagulants) /ยาต้านเกล็ดเลือด (antiplatelets)
- ผู้ป่วยที่ไม่สามารถมาติดตามการรักษาแบบผู้ป่วยนอกได้

Short guideline for dengue case management 2023

Management in Febrile Phase

- **Control fever:**

✓ Place tepid sponging at least 15 minutes for reducing fever
  - Cold water immersion : heat convection 0.1°C/min
  - Place tepid sponging 15 min : reduce body temp 1.5°C

✓ If the patient is shivering, stop tepid sponging and using a light sheet to cover body rather than a heavy blanket.
  - Shivering is a regulatory mechanism to increase heat in body.
  - Cover body with a light sheet would help heat evaporation better than using a heavy blanket.

Courtesy by General Thanom Supaporn, MD.
Short guideline for dengue case management 2023

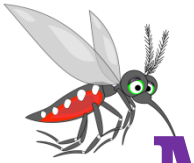
Management of in Febrile Phase

- **Control fever:**

✓ Take acetaminophen only if fever is still over 38.5°C

✓ Recommended doses of acetaminophen should be given at least 4 hours apart, when taken as an overdose can cause hepatitis.

✓ Avoid taking aspirin, NSAIDs and steroid due to increase the risk of severe bleeding, acute hepatitis and acute kidney injury



Management of in Febrile Phase

- **Diet and fluids:**
  - ✓ Advice to give soft, balanced and nutritious diet such as ice cream, milk or fruit juice
  - ✓ Avoid eating black or red-color foods/drinks as these may interfere with the interpretation of vomiting blood
  - ✓ Avoid drinking plain water which may cause electrolyte imbalance particularly low serum sodium level
  - ✓ Oral electrolyte solution (ORS) is recommended if the patient refuses to take oral food.

ข้อบ่งชี้ในการให้สารน้ำทดแทนทางหลอดเลือดดำ

- ผู้ป่วยที่มีอาการอาเจียนมากกว่า 3 ครั้งต่อวัน
- ผู้ป่วยที่มีภาวะขาดน้ำในระดับปานกลางหรือรุนแรง
- ผู้ป่วยที่อยู่ในระยะวิกฤตและมีการรั่วของพลาสมา โดยพบว่ามีค่าฮีมาโทคริตเพิ่มขึ้น ≥10%* หรือผู้ป่วยที่อยู่ในระยะวิกฤตที่ไม่สามารถรับประทานอาหารหรือดื่มน้ำเกลือแร่ได้
- ผู้ป่วยที่มีภาวะเดงกีช็อก

หมายเหตุ *ผู้ป่วยที่มีภาวะเลือดออกอาจไม่พบภาวะเลือดข้นขึ้นได้

Comparisons the Effects of Oral and IV Fluid Replacement in Adults with Non-shock DHF In Taiwan

- A observational study in adult patients (>18 years) with non-shock DHF admitted to a medical centre in southern Taiwan
- Comparing the effects of oral hydration (n=19) and IV fluid replacement (n=30)
- No significant difference was found in demographics, clinical manifestations and HCT between the two groups.
- No significant difference was found in daily PP, HCT and PLT between the two groups for 7 days in hospital.
- Patients with IV fluid replacement :
  - ✓ Had a significantly longer hospital stay compared to those with oral hydration (7.4±2.7 days vs. 5.3±2.2 days, P=0.007)
  - ✓ Prone to develop pleural effusion and/or pulmonary edema

Lee IK *et al.* Trans R Soc Trop Med Hyg 2010;104(8):541-5. doi: 10.1016/j.trstmh.2010.05.003.

How to Choose Type of IV Fluid in Non-shock Dengue (Adults)?

1. Isotonic crystalloid :

- 5% dextrose in normal saline
- 0.9 sodium chloride

2. Balanced crystalloid :

- Acetated Ringer's with/without 5% dextrose
- Lactated Ringer's with/without 5% dextrose

3. Colloid :

- 5% human albumin
- 10% Dextran-40 in NSS

Note: Patients with BS >200 mg/dl should avoid providing IV fluid containing 5% dextrose.

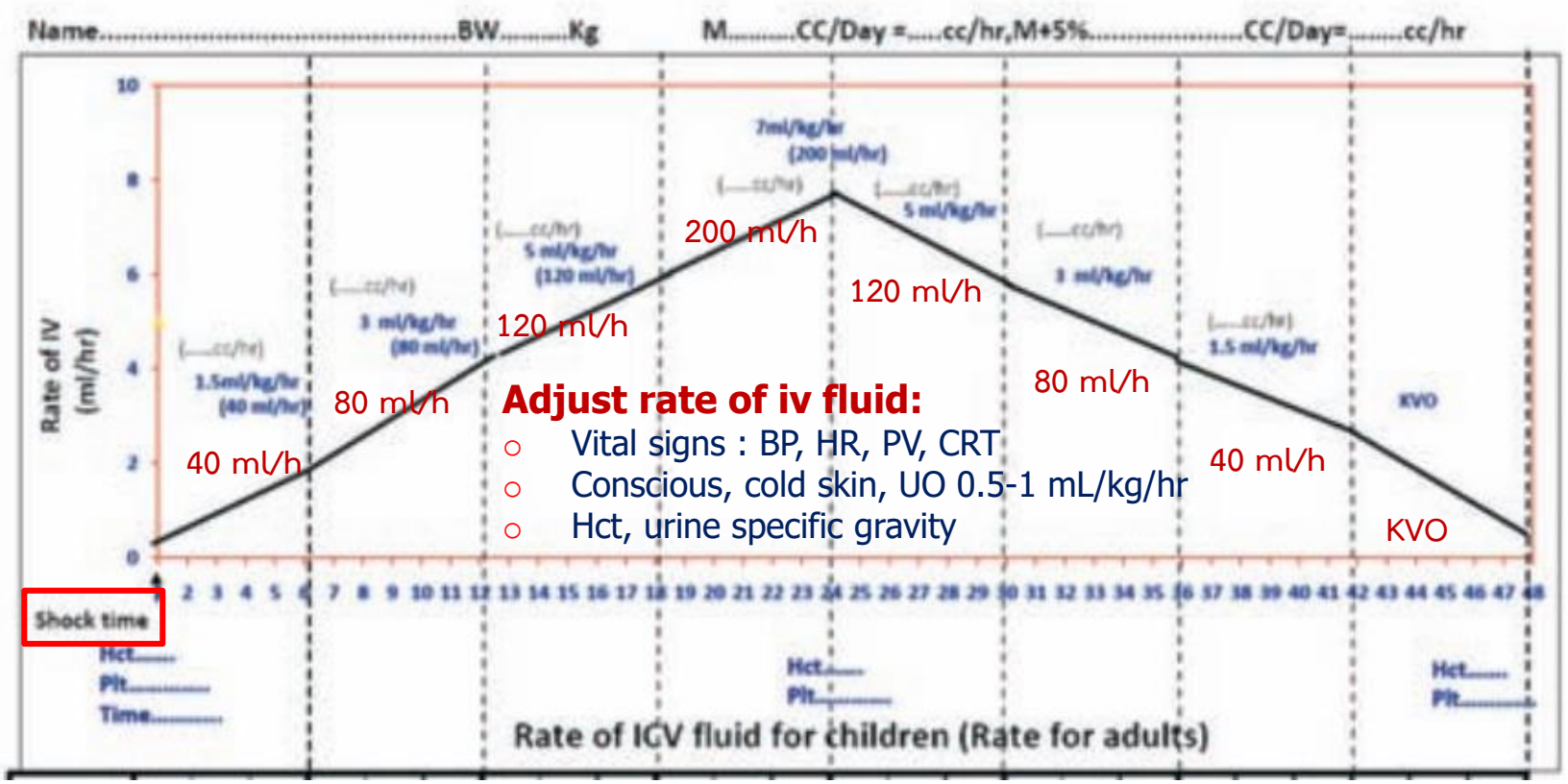
Rates of IV Fluid Infusion in Non-shock Dengue (Adults)

Degree of HCT rising:

- If HCT rising <20%, starting IV fluid less than maintenance rate (40-60 ml/h)
- If HCT rising ≥20%, starting IV fluid at maintenance rate (80–100 ml/h)
- If HCT rising >25%, starting IV fluid at more than maintenance rate (100–120 ml/h)

Note: Doses of IV fluid indicating above include oral fluid intake.

Rate of infusion in Non-shock DHF



Kalayanarooj S. and Nimmannitya S. In: Guidelines for Dengue and Dengue Haemorrhagic Fever Management. Bangkok Medical Publisher, Bangkok 2003.
WHO 2011. https://apps.who.int/iris/handle/10665/204894f

การติดตามผู้ป่วยโรคไข้เลือดออกในระยะไข้

- **อาการและอาการแสดง**
  - ระดับความรู้สึกตัว การรับประทานอาหาร ปวดท้อง อาเจียน และภาวะเลือดออกผิดปกติ
- **สัญญาณชีพ**
  - อุณหภูมิร่างกาย ค่าความดันเลือด อัตราหัวใจเต้น อัตราการหายใจ ควรตรวจติดตามทุก 4 ชั่วโมง
- **ค่าฮีมาโทคริต**
  - ควรตรวจติดตามทุก 12–24 ชั่วโมง อาจทำการตรวจซ้ำให้ถี่ขึ้นในผู้ป่วยที่มีภาวะเลือดออกผิดปกติ
- **ปริมาณปัสสาวะ**
  - ควรประเมินปริมาณปัสสาวะทุก 4–8 ชั่วโมงในผู้ป่วย
  - โดยทั่วไป ควรมีปริมาณปัสสาวะออก 0.5–1 ml/kg/h แต่ผู้ป่วยเด็กทารก ผู้ป่วยโรคอ้วน และสตรีตั้งครรภ์ ควรมีปริมาณปัสสาวะออก 0.5 ml/kg/h

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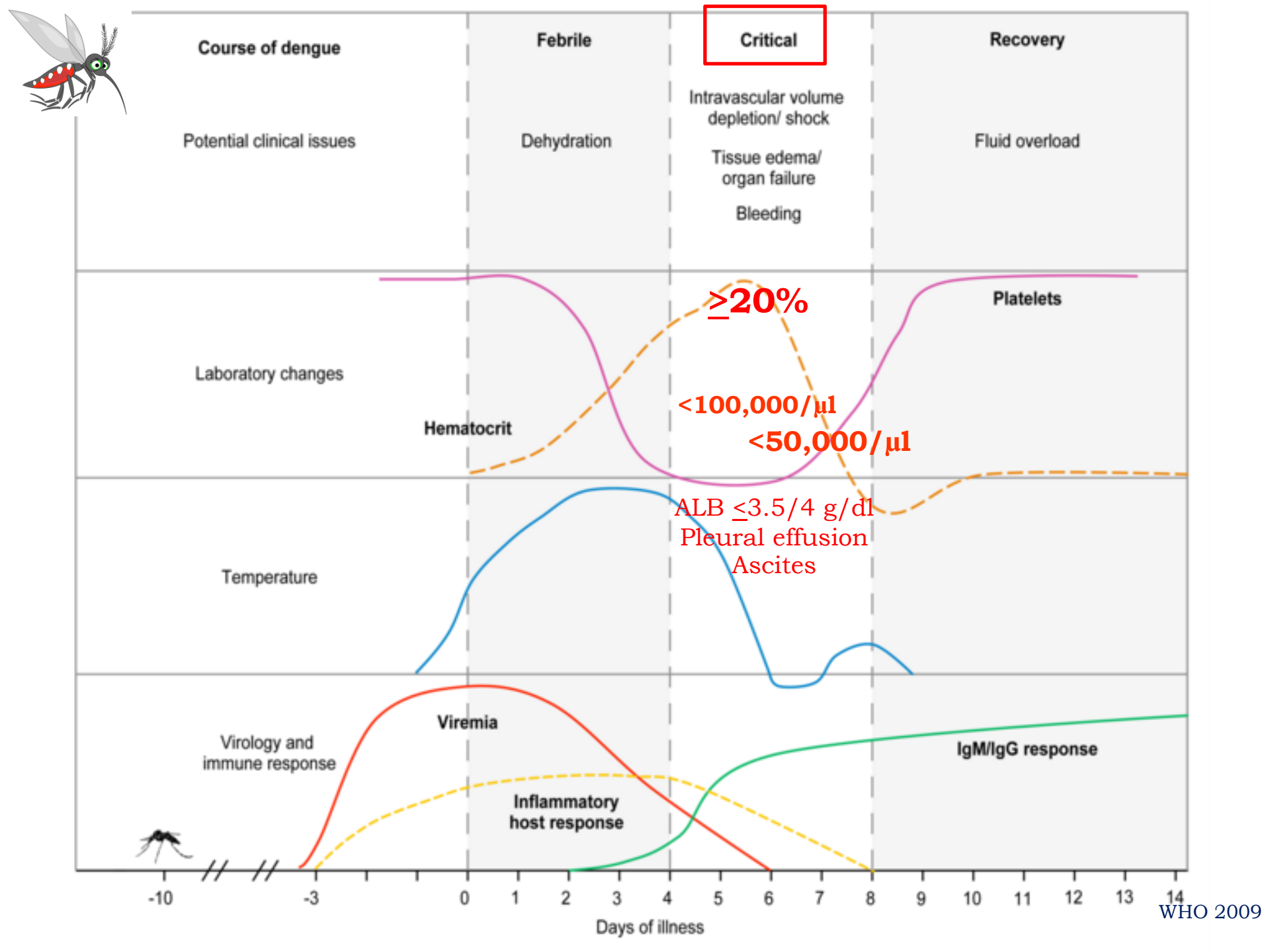
Stepwise Approach for Management of Dengue in Adults

- Diagnosis of dengue
- Risk factors for severe disease
- Evaluation of dengue severity
- Evaluation of disease phase
- Management (Critical phase)

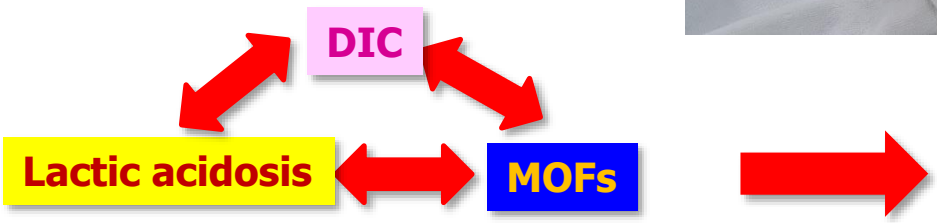

Course of dengue
Febrile
Critical
Recovery
Potential clinical issues
Dehydration
Intravascular volume depletion/ shock
Tissue edema/ organ failure
Bleeding
Fluid overload
Laboratory changes
≥20%
Platelets
Hematocrit
<100,000/µl
<50,000/µl
ALB ≤3.5/4 g/dl
Pleural effusion
Ascites
Temperature
Virology and immune response
Viremia
IgM/IgG response
Inflammatory host response
-10
-3
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Days of illness

WHO 2009

Keypoint for Management of Dengue Patients in Critical Phase : Early Dx of DSS

Adults with Multi-organs Failure in DSS

Prolonged shock : Vicious cycle
(lactic acidosis, multi-organ failure, DIC)



CFR >90%

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Dengue Shock Syndrome

- **Circulatory failure** :
  - ✓ Rapid and weak pulse
  - ✓ Cold clammy skin particularly cold extremities
  - ✓ PP <20 mmHg (25% of adults with DSS)
- **Hypotension with tissue hypoperfusion** :
  - ✓ Dizziness, fainting, syncope, decrease urine volume, restlessness, altered mental status
  - ✓ Capillary refill time >2 second

แนวทางการวินิจฉัยและรักษาโรคไข้เลือดออกเดงกี ฉบับเฉลิมพระเกียรติ สำหรับแพทย์. กรุงเทพฯ : กระทรวงสาธารณสุข ; 2561. หน้า 22-92.
https://www.dms.go.th/backend//Content/Content_FIle/Bandner_(Small)/Attach/25640302103903AM_CPG%20Adult%20Dengue.pdf

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How to Choose Type of IV Fluid in Dengue Shock Syndrome?

1. Isotonic crystalloid :

- 5% dextrose in normal saline
- 0.9 sodium chloride

2. Balanced crystalloid :

- Acetated Ringer's with/without 5% dextrose
- Lactated Ringer's with/without 5% dextrose

3. Colloid :

- 5% human albumin
- 10% Dextran-40 in NSS

Note: Patients with BS >200 mg/dl should avoid providing IV fluid containing 5% dextrose.

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Choice of IV fluid in DSS?

Double-blind RCT : Colloid (Dextran 70 [12 pts]/3% gelatin [13 pts])
: Crystalloid (Ringer's lactate [13 pts]/0.9%NaCl [12pts])

Parameter	Fluid type	*n*	Baseline value (95% CI)	Comparison of baseline values (*P* value)*	Change at peak dose (95% CI)	Effect of fluid type over time (*P* value)†
Hematocrit (%)	Crystalloid	25	49.6 (47.4–51.8)	.53	−6.1‡ (−4.5–−7.7)	.01
	Colloid	25	47.5 (45.3–49.7)		−9.7‡ (−7.4–−11.9)	
Pulse rate (beats/min)	Crystalloid	25	120 (114–126)	.34	−12§ (−6.2–−17.8)	.37
	Colloid	25	124 (119–128)		−15.8‡ (−9.2–−22.5)	
Systolic blood pressure (mm Hg)	Crystalloid	25	98.8 (94–103.5)	.03	+5.0 (9.7–0.31)	.005
	Colloid	25	88.6 (79.5–97.7)		+20.4‡ (12.3–24.5)	
Diastolic blood pressure (mm Hg)	Crystalloid	25	81.0 (76.1–86.0)	.04	−4.2 (−9.4–+1.0)	.07
	Colloid	25	73.4 (66.0–80.8)		+11 (−2.5–24.5)	
Pulse pressure (mm Hg)	Crystalloid	25	17.8 (16.3–19.3)	.15	+9.4‡ (6.9–12.0)	.02
	Colloid	25	15.4 (12.3–18.5)		+14.6‡ (0.7–2.0)	
Cardiac index (L/min · m^2)	Crystalloid	25	2.27 (2.11–2.44)	.47	+0.64‡ (0.47–0.80)	.02
	Colloid	25	2.18 (1.95–2.41)		+1.0‡ (0.73–1.3)	

Children Dengue

Dung NM *et al.* Clin Infect Dis 1999;29:787-94.

Choice of IV fluid in DSS?

Children Dengue

Double-blind RCT: Colloid (Dextran 70 [55 pts]/3% gelatin [56 pts])
: Crystalloid (Ringer's lactate [55 pts]/0.9%NaCl [56 pts])

PP recovery time

Decrease HCT

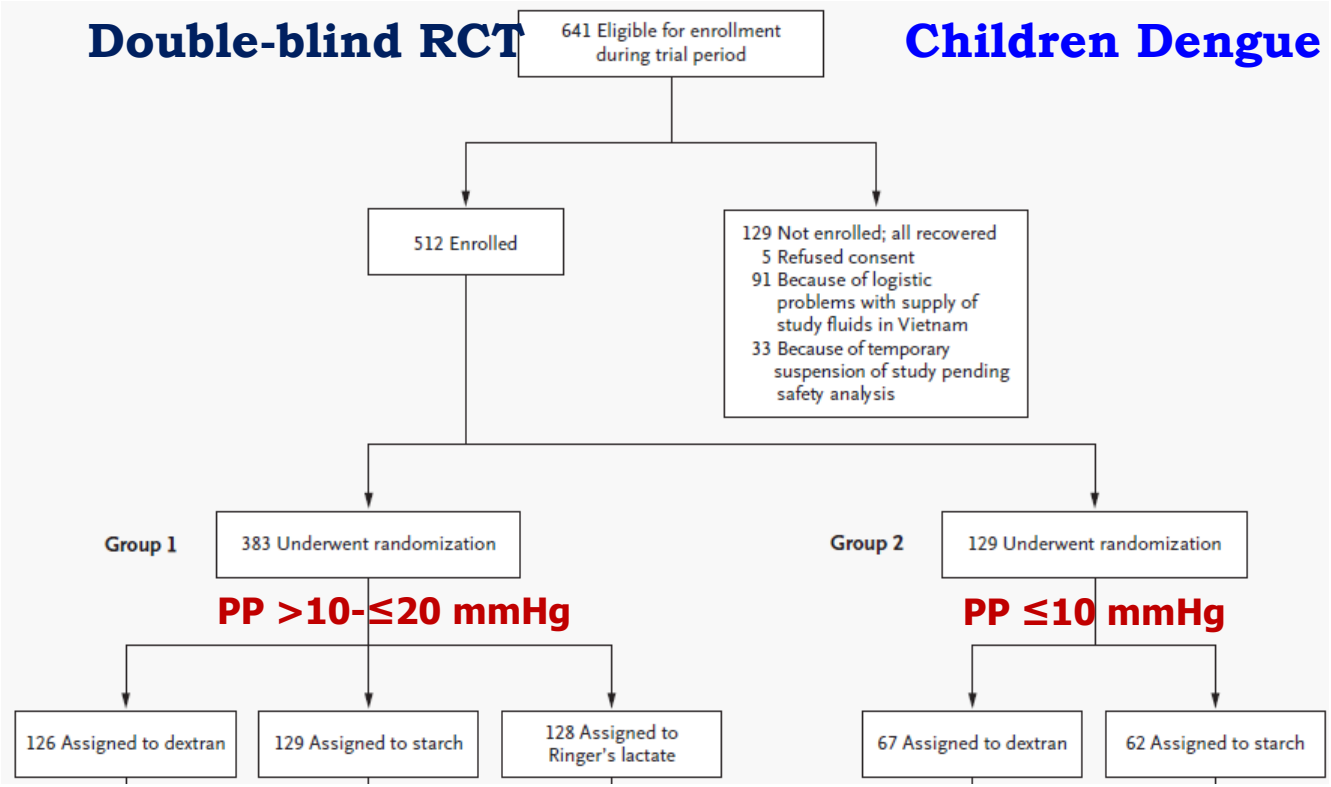
Decrease PR

Outcome variable	Solution administered: All patients (*n* = 222)	Dextran 70 (*n* = 55)	Gelatin (*n* = 56)	Lactate Ringer's (*n* = 55)	"Normal" saline (*n* = 56)	*P*
Primary						
PPRT, h median (range)	0.75 (0.25–7)	0.50 (0.25–3)	0.50 (0.25–)	0.75 (0.25–7)	0.75 (0.25–3)	.030[a]
PPRT >1 h, no. (%) of patients	21 (9.5)	3 (5.5)	3 (5.4)	11 (20)	4 (7.1)	.022[a]
"Reshock" rate, no. (%) of patients	63 (28.4)	16 (29.1)	15 (26.8)	16 (29.1)	16 (28.6)	.992
Time to first episode of "reshock" (*n* = 63)						
Mean h ± SD	11.7 ± 5.5	15 ± 6.8	11.4 ± 4	10 ± 4.1	10.3 ± 5.6	.068
Range	1.5–23	2.5–23	3–17	3–16	1.5–23	
Secondary						
Decrease in hematocrit at 1 h, %						
Mean ± SD	8.4 ± 3.8	11.5 ± 3.3	9.7 ± 3.0	5.7 ± 2.8	6.5 ± 2.9	<.001[a]
Range	−2 to 19	2 to 19	0 to 16	−2 to 13	0 to 17	
Decrease in pulse at 1 h, beats/min						
Mean ± SD	15.1 ± 10.1	14.9 ± 9.9	18.5 ± 11.3	13.2 ± 9.2	13.5 ± 8.9	.023[a]
Range	20–44	−20 to 36	0–44	−10 to 36	0–40	
Total volume of iv fluid infused, mL/kg						
Mean ± SD	134.1 ± 20.6	134.3 ± 22.1	135 ± 23.5	134.2 ± 19.9	132.9 ± 16.6	.954
Range	89–212	89–189	93–212	103–182	106–172	
Requirement for dextran after first hour, no. (%) of patients	69 (31.1)	17 (30.9)	15 (26.8)	20 (36.4)	17 (30.4)	.749
Volume of dextran after first hour, mL/kg (*n* = 69)[b]						
Mean ± SD	28.3 ± 12.7	22.1 ± 6.1	30.7 ± 11.6	33.5 ± 14.3	26.3 ± 14.3	.035[a]
Range	10–69	10–37.5	14.5–57	15–64	15–69	
Required frusemide, no. (%) of patients	35 (15.7)	5 (9.1)	10 (17.9)	8 (14.5)	12 (21.4)	.328

NOTE. PPRT, pulse pressure recovery time.

Ngo NT *et al.* Clin Infect Dis. 2001;32(2):204-13.

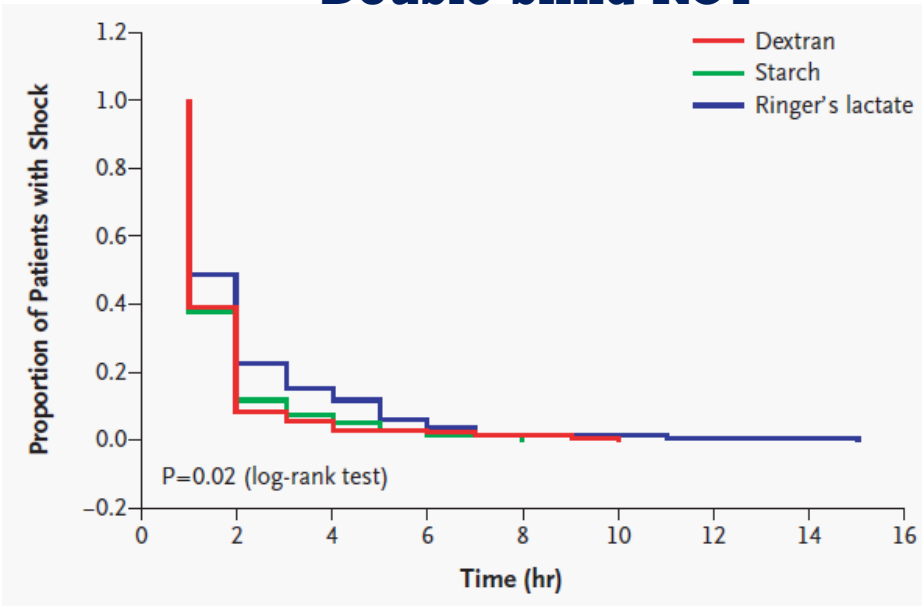
Choice of IV fluid in DSS?



Will BA *et al*. N Engl J Med 2005;353:877-89.

Kaplan-Meier Curves form Fluid Resuscitation to Initial Cardiovascular Stability

Double-blind RCT

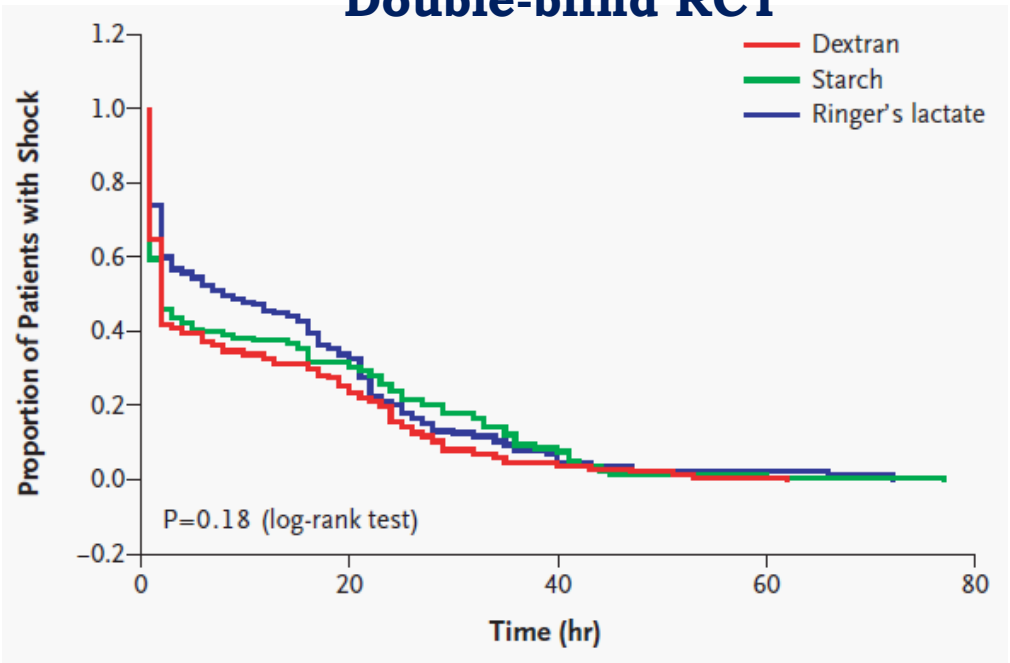


Patients who received RLS took longer time to achieve initial cardiovascular stability.

Will BA *et al.* N Engl J Med 2005;353:877-89.

Kaplan-Meier Curves form Fluid Resuscitation to Sustained Cardiovascular Stability

Double-blind RCT



Severe allergic type reactions : 6% Dextran 70 (P <0.001)

Will BA *et al.* N Engl J Med 2005;353:877-89.

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Clinical Characteristics of Dengue Shock Syndrome in Vietnamese Children: A 10-Year Prospective Study in a Single Hospital

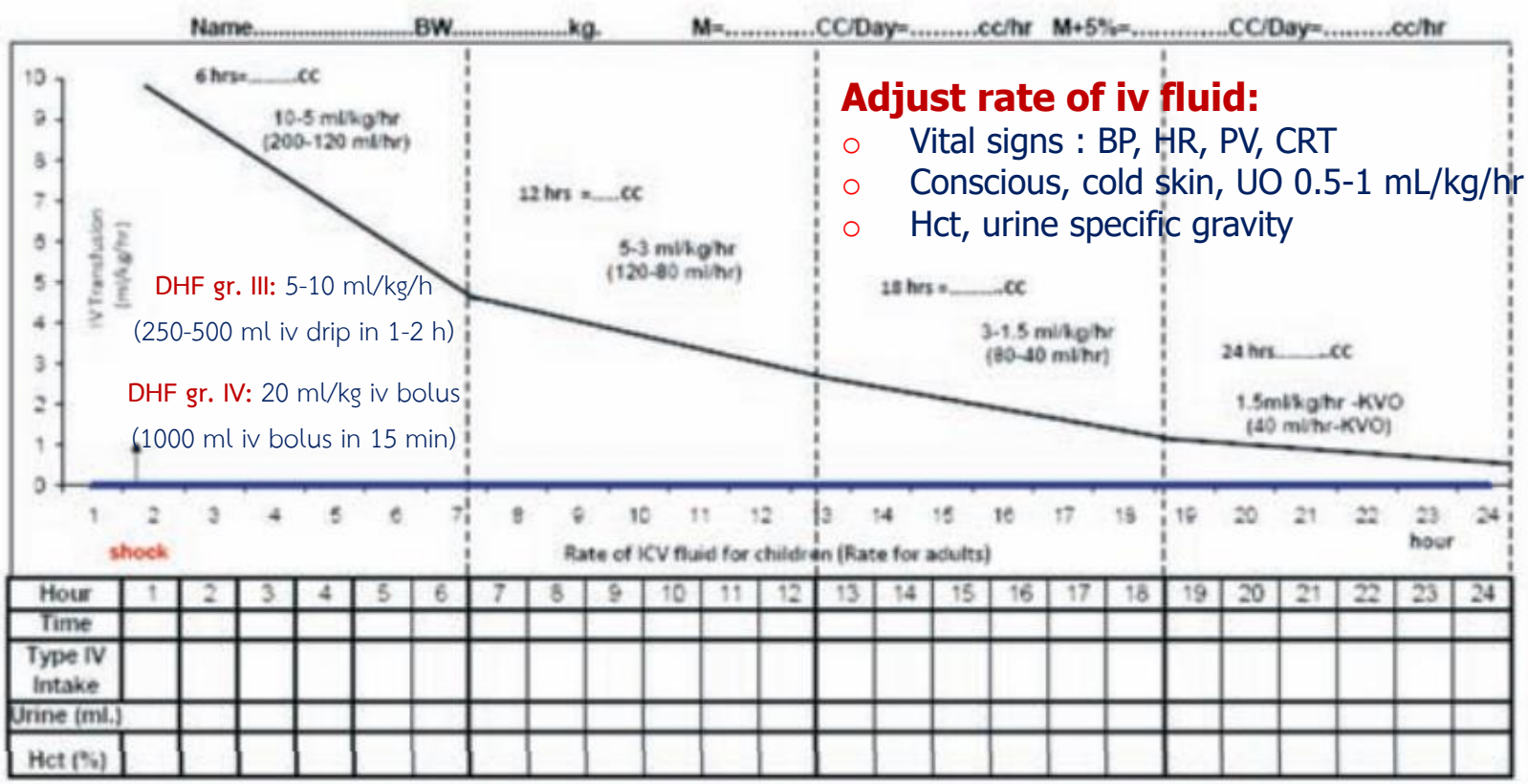
Phung Khanh Lam,[1] Dong Thi Hoai Tam,[2] Tran Vinh Diet,[3] Cao Thi Tam,[3] Nguyen Thi Hanh Tien,[1] Nguyen Tan Thanh Kieu,[1] Cameron Simmons,[1,4] Jeremy Farrar,[1,4] Nguyen Thi Ngoc Nga,[3] Phan Tu Qui,[1,3] Nguyen Minh Dung,[3] Marcel Wolbers,[1,4] and Bridget Wills[1,4]

[1]Oxford University Clinical Research Unit, Hospital for Tropical Diseases, [2]University of Medicine and Pharmacy of Ho Chi Minh City, and [3]Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam; and [4]Centre for Tropical Medicine, Centre for Clinical Vaccinology and Tropical Medicine, University of Oxford, United Kingdom

Lam PK *et al.* Clin Infect Dis. 2013;57(11):1577-86.

Considering the observational study only, most children recovered well with standard crystalloid resuscitation, although 547 of 1211 (45%) patients also received colloid therapy, 244 (45%) of them within the first 2 hours.

Rate of infusion in DSS



DHF gr. III: 5-10 ml/kg/h
(250-500 ml iv drip in 1-2 h)

DHF gr. IV: 20 ml/kg iv bolus
(1000 ml iv bolus in 15 min)

Adjust rate of iv fluid:

- Vital signs : BP, HR, PV, CRT
- Conscious, cold skin, UO 0.5-1 mL/kg/hr
- Hct, urine specific gravity

Hour	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Time																								
Type IV Intake																								
Urine (ml.)																								
Hct (%)																								

Kalayanarooj S. and Nimmannitya S. In: Guidelines for Dengue and Dengue Haemorrhagic Fever Management. Bangkok Medical Publisher, Bangkok 2003.

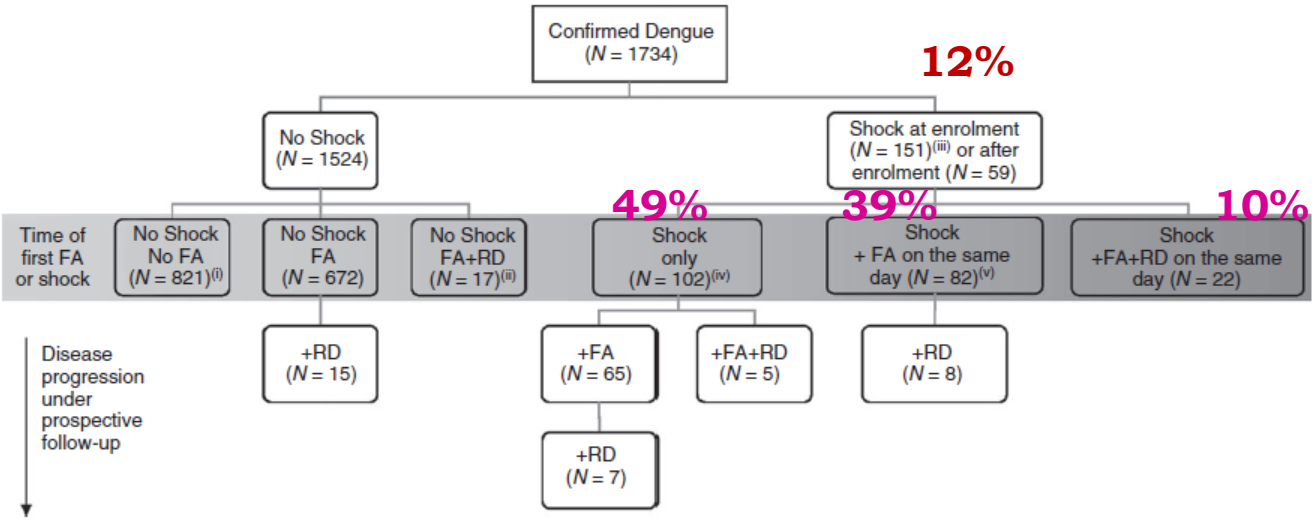
WHO 2011. https://apps.who.int/iris/handle/10665/204894f

WHO 2009. https://apps.who.int/iris/handle/10665/44188

การติดตามผู้ป่วยโรคไข้เลือดออกในระยะวิกฤต

- **อาการและอาการแสดง**
  - ระดับความรู้สึกตัว การรับประทานอาหาร ปวดท้อง อาเจียน และภาวะเลือดออกผิดปกติ
- **สัญญาณชีพ**
  - อุณหภูมิร่างกาย ควรตรวจติดตามทุก 4–6 ชั่วโมง
  - ค่าความดันเลือด อัตราหัวใจเต้น pulse volume ค่า capillary refill time และอัตราการหายใจ ร่วมกับความเย็นของมือและเท้า ควรตรวจติดตามทุก 2–4 ชั่วโมงในผู้ป่วยที่ไม่มีภาวะเดงกีช็อก และควรตรวจติดตามทุก 15 นาทีในผู้ป่วยที่มีภาวะเดงกีช็อก จนกระทั่งอาการคงที่ จึงตรวจติดตามทุก 1 ชั่วโมง
- **ค่าฮีมาโทคริต**
  - ควรตรวจติดตามทุก 4–6 ชั่วโมง อาจทำการตรวจซ้ำให้ถี่ขึ้นในผู้ป่วยที่มีภาวะเลือดออกผิดปกติ
- **ปริมาณปัสสาวะ**
  - ควรประเมินปริมาณปัสสาวะทุก 4–8 ชั่วโมงในผู้ป่วยที่ไม่มีภาวะเดงกีช็อก
  - ควรประเมินปริมาณปัสสาวะทุก 2–4 ชั่วโมงในผู้ป่วยที่มีภาวะเดงกีช็อก
  - โดยทั่วไป ควรมีปริมาณปัสสาวะออก 0.5–1 ml/kg/h แต่ผู้ป่วยเด็กทารก ผู้ป่วยโรคอ้วน และสตรีตั้งครรภ์ ควรมีปริมาณปัสสาวะออก 0.5 ml/kg/h

Dose and Duration of IV fluid in DSS?



Children and Adults with Dengue

Study Area : Asia and Latin America

Rosenberger KD *et al.* TMIH 2016;21:445-53.

Multivariable Cox Regression Analysis for Risk Factors of Respiratory Distress and Fluid Accumulation in DSS

Predictor	Shock		Respiratory distress with fluid accumulation	
	AHR (*P*-value)	95%CI	AHR (*P*-value)	95%CI
Demographics/anthropometry/referral history				
Age group				
≥ 15 years	Reference		Reference	
< 15 years	1.92 (0.106)	0.87–4.25	**3.85 (0.001)**	1.69–8.77
Sex				
Male	Reference			
Female	**2.05 (0.031)**	1.07–3.95		
BMI				
Underweight	**2.62 (0.012)**	1.24–5.54		
Normal	Reference			
Overweight	1.94 (0.145)	0.80–4.70		
Inpatient referral				
No			Reference	
Yes			1.81 (0.064)	0.97–3.39
IV fluid management				
Fluid administration prior to enrolment/referral				
No fluid	Reference			
Fluid administered	**2.60 (0.033)**	1.08–6.27		
Amount of IV fluids (10 ml/kg) in previous 24 h period	1.11 (0.059)	1.00–1.23	**1.18 (< 0.001)**	1.10–1.28
Number of days with IV fluid therapy (until previous day)			**1.66 (0.004)**	1.17–2.34
Fluid bolus administered in previous 24 h period				
No			Reference	
Yes			**2.90 (0.005)**	1.37–6.12

Age <15 yrs

Referral pts

Greater & Longer

Fluid bolus

Rosenberger KD *et al.* TMIH 2016;21:445-53.

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Multivariable Cox Regression Analysis for Risk Factors of Respiratory Distress and Fluid Accumulation in DSS

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Normal	Reference			
Overweight	1.94 (0.145)	0.80–4.70		
Fluid bolus administered in previous 24 h period				
No			Reference	
Yes			**2.90 (0.005)**	1.37–6.12

Rapid (<30min) and large fluid bolus (>15 ml/kg) should be avoided, unless the patient is hypotensive.

Dondorp AM *et al.* In: Dondorp AM, Dünser MW, Schultz MJ, editors. Sepsis Management in Resource-limited Settings [Internet]. Cham (CH): Springer; 2019.

Madanayake *et al. BMC Infectious Diseases* (2021) 21:286
https://doi.org/10.1186/s12879-021-05971-6

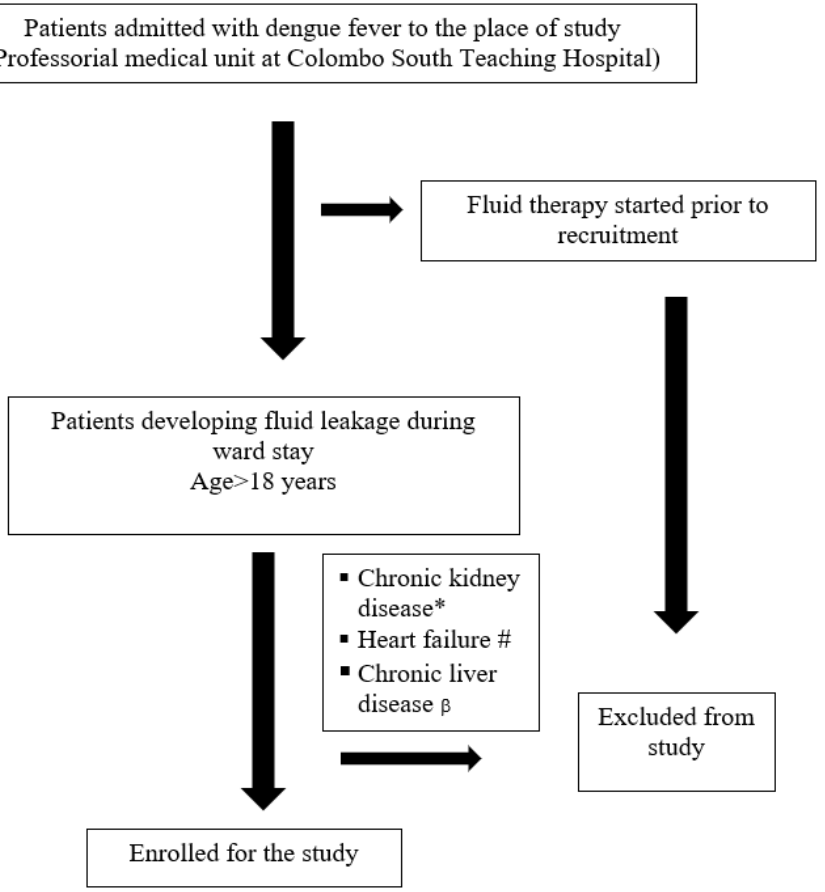
BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Fluid requirement in adult dengue haemorrhagic fever patients during the critical phase of the illness: an observational study

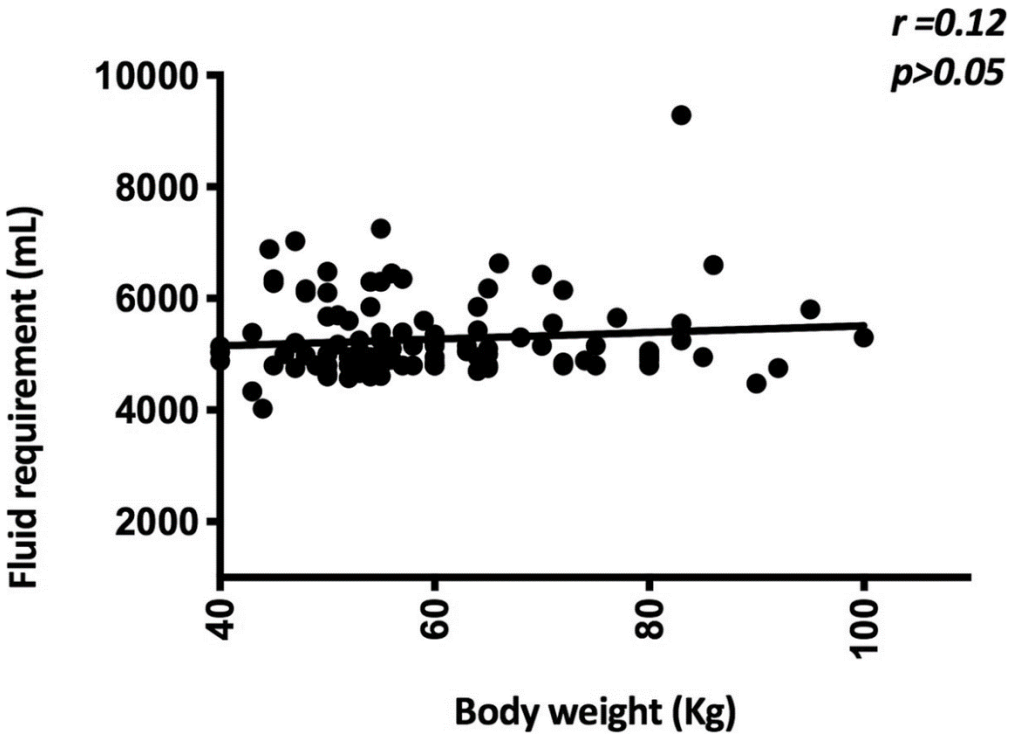
PMW Madanayake[1†], AEU Jayawardena[2], S L Wijekoon[2], N Perera[1,2*] and JKP Wanigasuriya[1,2†]

- An observational follow-up study was conducted in Sri Lanka from Jan–Jul 2017
- University Medical Unit of Colombo South Teaching Hospital, Sri Lanka
- 115 DHF patients with aged >18 years
- Aims of this study :
  - to identify the fluid requirements of DHF patients
  - to identify whether features of fluid overload are present in patients who exceeded the fluid quota



Madanayake P *et al*. BMC Infect Dis. 2021;21(1):286. doi: 10.1186/s12879-021-05971-6.

Fluid Requirement of the Study Population Based On the Body Weight



- Fluid requirement of the patients were plotted against the body weight of the patients.
- Fluid requirement was not seen to correlate with the body weight of the patient or the BMI of the patient.
- Patients with body weight of >50 kg required the same amount of fluid as patients with body weight 50 kg.

Madanayake P *et al*. BMC Infect Dis. 2021;21(1):286. doi: 10.1186/s12879-021-05971-6.

Administered Fluid and Severity of DHF

Parameter	≤M + 5% deficit n = 35	M + 5%–7.5% deficit *n* = 56	≥M + 7.5% deficit *n* = 24	P value
Fluid administered during 0–48 h of the critical phase (ml), mean (SD)[a]				
0–12	1197.4 (62.3)	1439.9 (349.3)	1596.7 (359.1)	< 0.0001
13–24	1180.4 (80.4)	1327.9 (238.6)	1831.1 (570.5)	< 0.0001
25–36	1170.1 (97.6)	1305.1 (245.6)	1391.9 (341.7)	< 0.0001
37–48	1141.3 (113.8)	1208.7 (186.4)	1238.5 (246.5)	0.01
Category of DHF, n (%)				
Grade I and II	35 (100)	46 (82.1)	7 (29.2)	
Grade III	0	10 (17.9)	15 (62.5)	< 0.0001
Grade IV	0	0	2 (8.3)	

4,689 ml

5,282 ml

6,058 ml

[a]Analysed by kruskal-Wallis test

Madanayake P *et al*. BMC Infect Dis. 2021;21(1):286. doi: 10.1186/s12879-021-05971-6.

Presence of Fluid Overload in the Study Population

Patients were examined at the end of the critical phase (48 h later) by the research team for evidence of fluid overload.

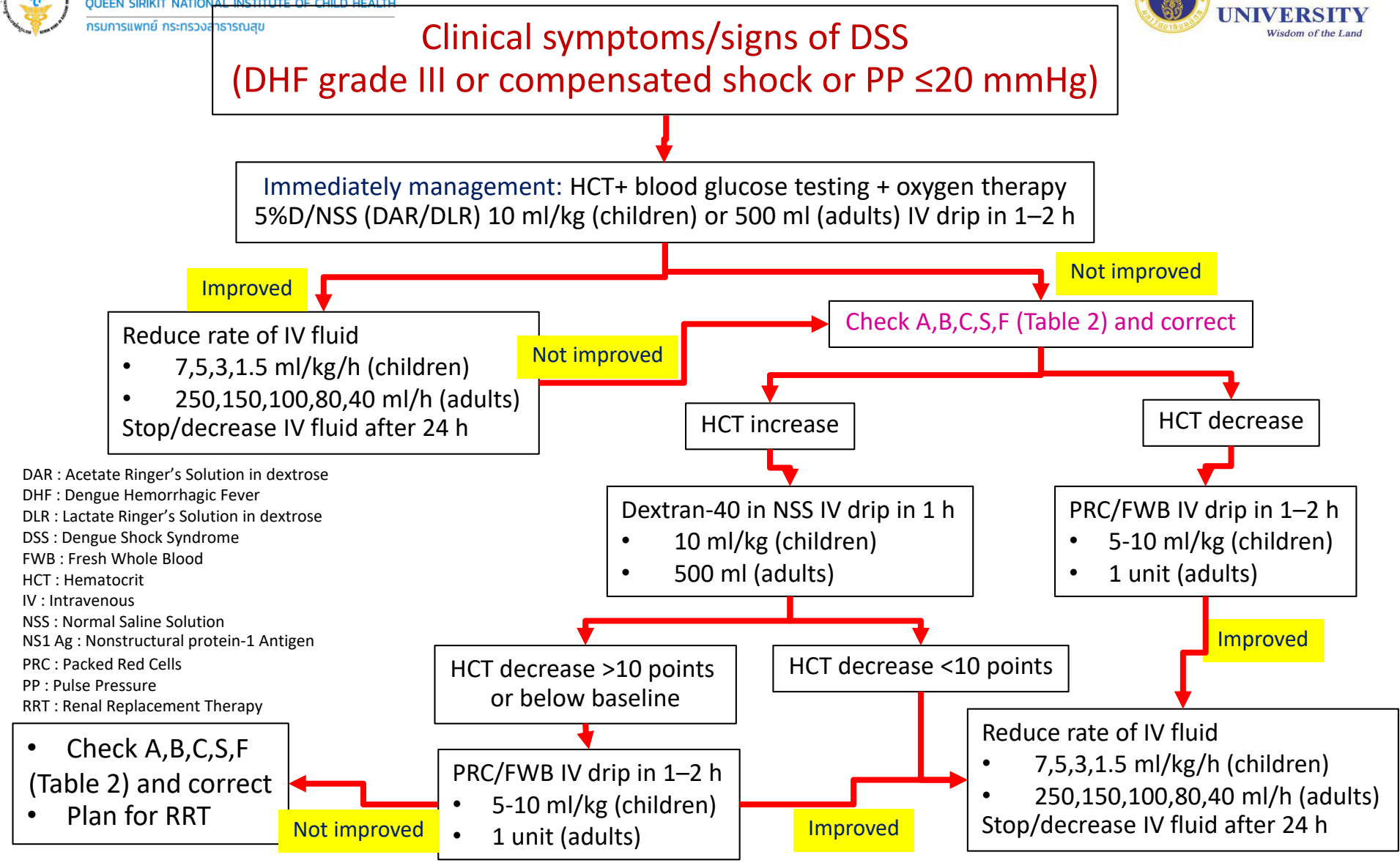
	4,689 ml	5,282 ml	6,058 ml	
Fluid overload	**≤M + 5%** ***n*** **= 35**	**M+ 5% - M+ 7.5%** ***n*** **= 56**	**≥M+ 7.5%** ***n*** **= 24**	***P*** **value**
None	35 (100)	54 (96.4)	12 (50)	< 0.0001
Mild	0	2 (3.6)	6 (25)	
Moderate-severe	0	0	6 (25)	

- Mild fluid overload evidence by facial puffiness.
- Moderate to severe fluid overload evidence by SOB due to moderate to severe ascites and/or large pleural effusion with receiving diuretic therapy for relieve symptoms of fluid overload.

- Reasons for administering excess fluid included evidence of shock (96%) and rising HCT (4%).
- Patients requiring fluid ≥ M + 7.5% (≈6 L) needed saline boluses, dextran and blood transfusion more frequently than patients who received fluid <7.5% deficit.

Fluid requirement in DSS during critical phase (48 h) ≈ 6 L

Madanayake P *et al*. BMC Infect Dis. 2021;21(1):286. doi: 10.1186/s12879-021-05971-6.



DAR : Acetate Ringer's Solution in dextrose
DHF : Dengue Hemorrhagic Fever
DLR : Lactate Ringer's Solution in dextrose
DSS : Dengue Shock Syndrome
FWB : Fresh Whole Blood
HCT : Hematocrit
IV : Intravenous
NSS : Normal Saline Solution
NS1 Ag : Nonstructural protein-1 Antigen
PRC : Packed Red Cells
PP : Pulse Pressure
RRT : Renal Replacement Therapy

DHF grade IV or decompensated shock or BP/PR can not be measured)

- Immediately management: HCT+ blood glucose testing + oxygen therapy

NSS/AR/LR IV free flow or 10 ml/kg (children) or 500-1000 ml (adults) IV bolus

- Check A,B,C,S,F (Table 2) and correct

Improved

Not improved

- Repeat IV fluid bolus
- NaHCO3 1-2 mEq/kg (children) or 50-100 ml (adults)

Change IV fluid to 5%D/NSS 10 ml/kg (children) or 500 ml (adults) IV drip in 1–2 h

Not improved

Check HCT

Improved

HCT increase

HCT decrease

AR : Acetate Ringer's Solution
BP : Blood pressure
DHF : Dengue Hemorrhagic Fever
LR : Lactate Ringer's Solution
FWB : Fresh Whole Blood
HCT : Hematocrit
IV : Intravenous
NSS : Normal Saline Solution
PR : Pulse Rate
PRC : Packed Red Cells
RRT : Renal Replacement Therapy

Reduce rate of IV fluid
- 7,5,3,1.5 ml/kg/h (children)
- 250,150,100,80,40 ml/h (adults)

Stop/decrease IV fluid after 24 h

Dextran-40 in NSS IV drip in 1 h
- 10 ml/kg (children)
- 500 ml (adults)

PRC/FWB IV drip in 1–2 h
- 5-10 ml/kg (children)
- 1 unit (adults)

Improved

HCT decrease >10 points or below baseline

HCT decrease <10 points

- Check A,B,C,S,F (Table 2) and correct
- Plan for RRT

Not improved

PRC/FWB IV drip in 1–2 h
- 5-10 ml/kg (children)
- 1 unit (adults)

Improved

Reduce rate of IV fluid
- 7,5,3,1.5 ml/kg/h (children)
- 250,150,100,80,40 ml/h (adults)

Stop/decrease IV fluid after 24 h

Abbreviations	Laboratory investigations	Notes
A–Acidosis	Blood gas (capillary or venous)	– Metabolic acidosis indicates prolonged shock with organ impairment such as acute liver failure and acute kidney injury. – AST, ALT, ALB, BUN, Cr, Electrolytes – 7.5%NaHCO3 IV ○ 1–2 mEq/kg (children) ○ 50–100 ml (adults)
B–Bleeding	Hematocrit	– If hematocrit decrease, lower than baseline, or not rising ≥20% when develop shock which indicate bleeding or intravascular hemolysis. – Cross match for PRC transfusion
C–Calcium	Serum calcium or ionized calcium	– Hypocalcemia is common in DHF patients, but asymptomatic. – Calcium supplement is indicated in complicated cases. – 10% calcium gluconate IV dilute and push slowly >5 min or IV drip in 10–20 min ○ 1 ml/kg (children) ○ 10 ml (adults)
S–Blood sugar	Blood sugar	– Patients with impaired liver function may have hypoglycemia. – Diabetes patients may have hyperglycemia. – Random blood glucose or glucostix test
F–Fluid overload	Physical examination Chest radiography, Ultrasound	– Furosemide IV ○ 1 mg/kg/dose (children) ○ 40 mg (adults)

ข้อบ่งชี้ในการให้ 10% Dextran-40 in NSS

- ผู้ป่วยที่มีค่าฮีมาโทคริตเพิ่มขึ้นเมื่อได้รับ isotonic crystalloid ในปริมาณมาก และยังมี unstable vital signs การได้รับ isotonic crystalloid ในปริมาณมาก หมายถึง การได้รับ isotonic crystalloid ด้วยอัตราเร็ว 200–240 ml/h ในช่วง 6 ชั่วโมงแรกหลังจากที่มีอาการช็อก หรือการได้รับ isotonic crystalloid ในอัตราเร็ว 100–120 ml/h ในช่วงหลังจากที่มีอาการช็อกนานกว่า 6 ชั่วโมง
- ผู้ป่วยที่มีอาการแน่นท้อง แน่นหน้าอก หรือหายใจลำบาก และยังมีค่าฮีมาโทคริตเพิ่มขึ้น
- ผู้ป่วยที่ยังคงมีค่าฮีมาโทคริตเพิ่มขึ้นเรื่อย ๆ ประมาณร้อยละ 25–30 จากเดิมหลังจากได้รับ isotonic crystalloid ตามข้อแนะนำ

Note

-5% albumin can be used in patients DSS or prolonged shock who having AKI.
-However, patients who receiving 5% albumin may develop more plasma leakage than those with Dextran 40 as oncotic pressure of 5% albumin is similar to plasma.

การให้ 10% Dextran-40 in NSS

- ✓ **ควรทำการตรวจค่าฮีมาโทคริตก่อนและหลังการให้ dextran 40**
- ✓ **อัตราเร็วของ dextran 40 ควรให้ 10 ml/kg/h (เด็ก) และ 500 ml (ผู้ใหญ่) ใน 1 ชั่วโมง**
- ✓ **ทำการแปลผลค่าฮีมาโทคริต เพื่อวางแผนการให้สารน้ำต่อไป ดังนี้**

- ผู้ป่วยที่มีค่าฮีมาโทคริตลดลงไม่เกิน 10 จุดและไม่ต่ำกว่าค่า baseline เดิมของผู้ป่วย ให้เปลี่ยนชนิดของสารน้ำทดแทนทางหลอดเลือดดำเป็น isotonic crystalloid
- ผู้ป่วยที่มีค่าฮีมาโทคริตลดลงมากกว่า 10 จุดหรือลดต่ำกว่าค่า baseline เดิมของผู้ป่วย ให้นึกถึงภาวะเลือดออกผิดปกติหรือภาวะ intravascular hemolysis ในกรณีนี้ ควรให้เลือดทดแทน

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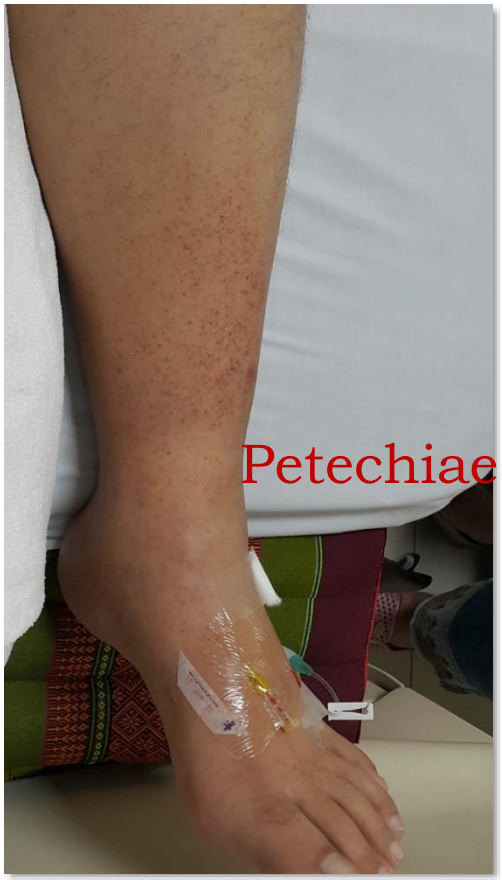
Hematological Complications in Dengue

- **Abnormal bleeding**
  - ✓ **Not severe** : petechiae, ecchymosis, gum bleeding, epistaxis, heavy and frequent menstrual bleeding
  - ✓ **Severe** : GI bleeding
- **Lab. investigations**
  - ✓ Low platelet
  - ✓ Abnormal coagulogram

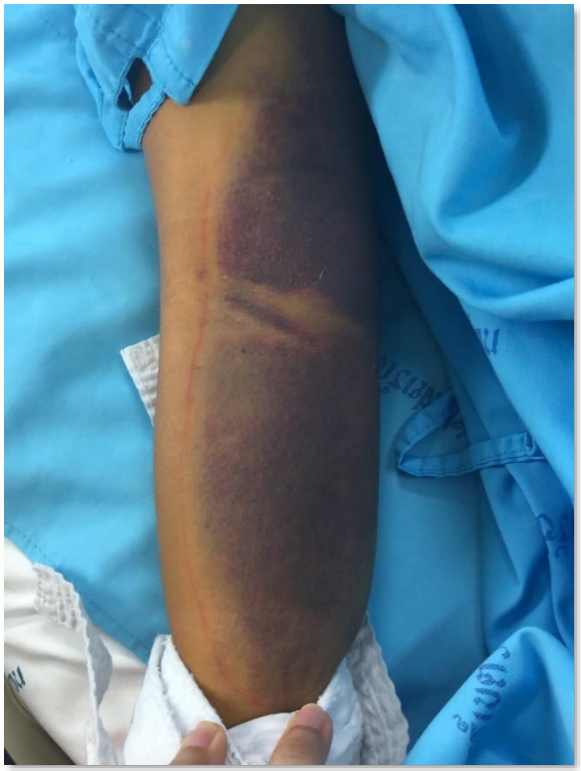
- DHF: Prolonged APTT & TT > PT
- DSS (prolonged shock): Prolonged APTT & TT & PT

วิภา ธนาชาติเวทย์. การดูแลรักษาเดงกีรุนแรงทางคลินิกในผู้ใหญ่; ๒๕๖๐. หน้า ๑๖๑-๑๗๕.

Cutaneous Bleeding in Dengue

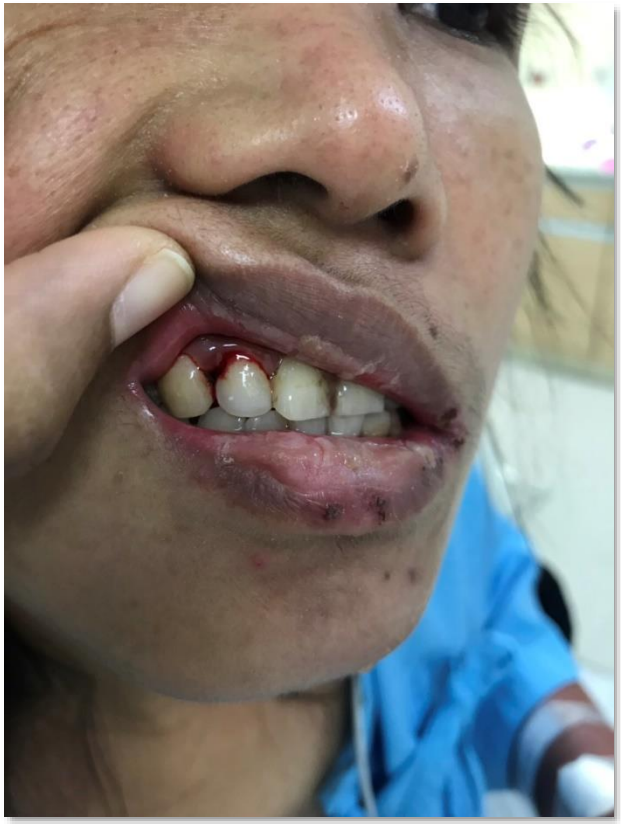


Ecchymosis



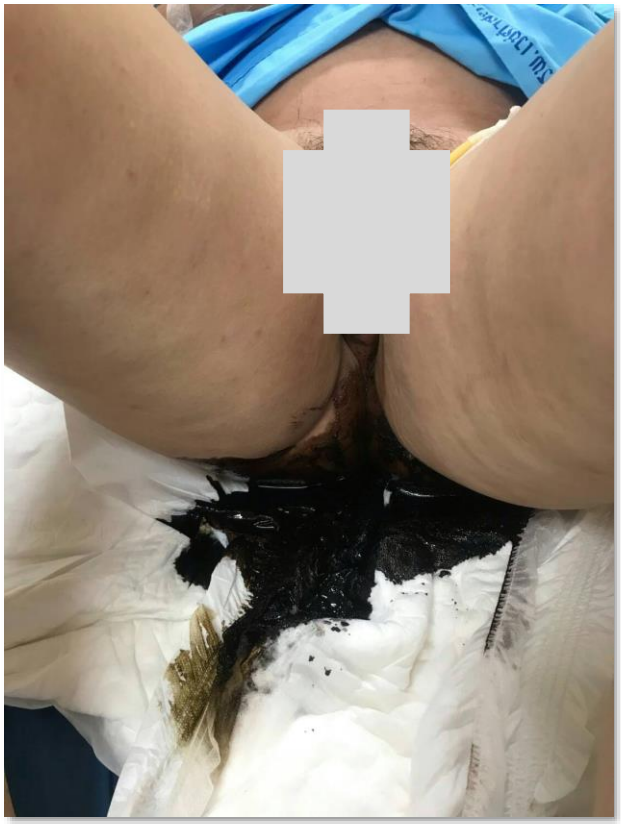
Mucosal Bleeding in Dengue

Gum Bleeding



Epistaxis

GI bleeding



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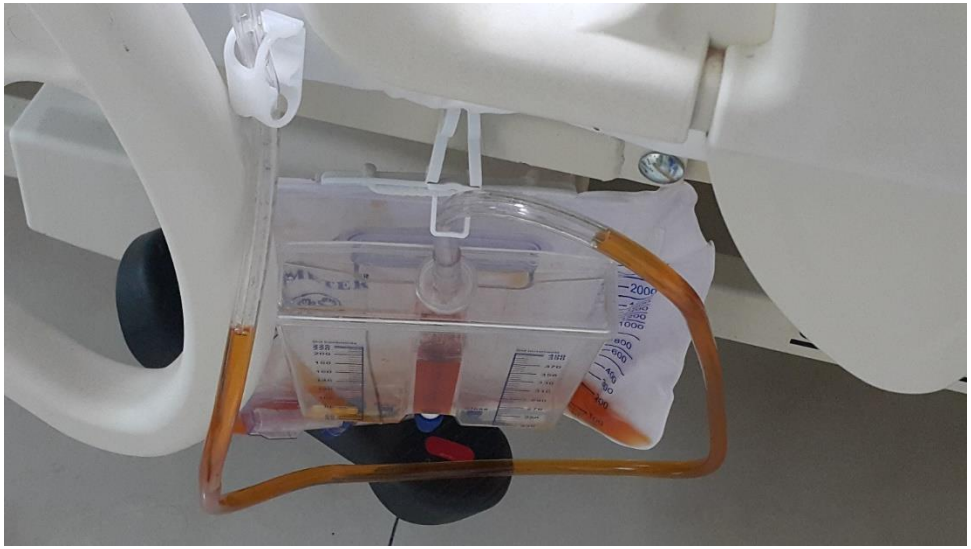
Hematuria and Intravascular Hemolysis in Dengue



Hematuria

Hemoglobinuria

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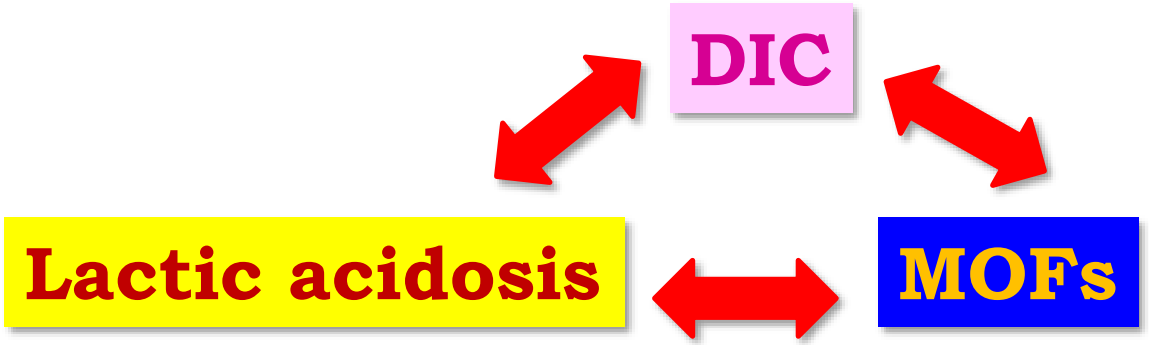
GI Bleeding/Lung hemorrhage/Exit site Bleeding

Management of Bleeding in Dengue

- **Bleeding in dengue :** Low PLT, APTT prolong, PT prolong (liver failure)
- **PRC or LPRC >>>** PLT or FFP
- **Prolonged shock :** Vicious cycle

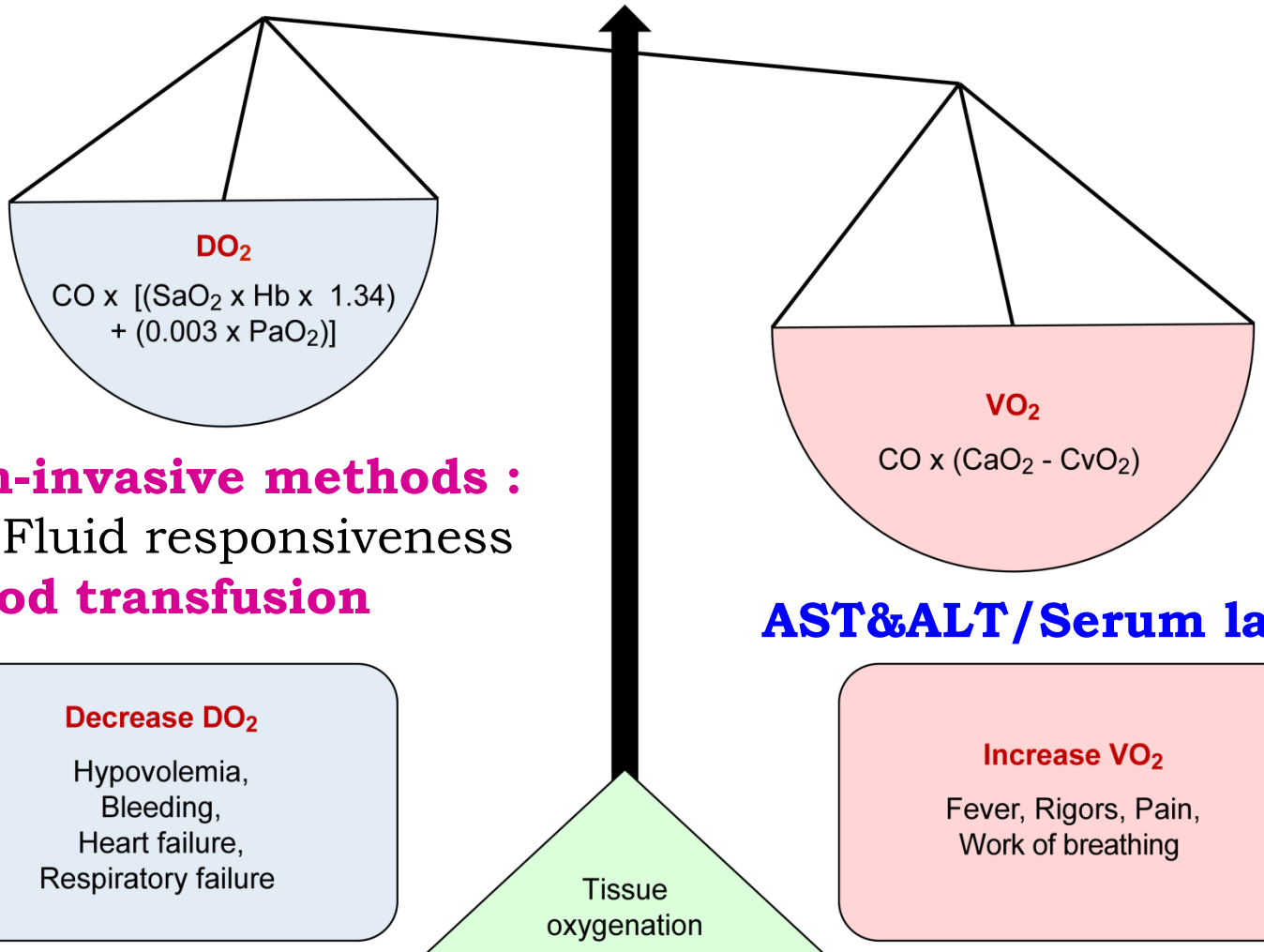


WHO, 2009; WHO 2012

ข้อบ่งชี้ในการให้เลือดทดแทน

- ผู้ป่วยเด็กที่มีเลือดออกมากกว่าร้อยละ 10 ของปริมาณเลือดทั้งหมด (6–8 ml/kg) หรือผู้ป่วยผู้ใหญ่ที่มีเลือดออก ≥300 ml
- ผู้ป่วยโรคธาลัสซีเมีย พาหะของโรคธาลัสซีเมีย หรือโรคพร่องเอนไซม์ G6PD ที่มีภาวะซีด เนื่องจากมีภาวะ intravascular hemolysis
- ผู้ป่วยภาวะเดงกีช็อกที่ยังคงมี unstable vital signs หลังได้รับสารน้ำทดแทนทางหลอดเลือดดำในปริมาณมาก หรือไม่สามารถลดอัตราเร็วของสารน้ำลงได้ และมีค่าฮีมาโทคริตลดลงจากเดิม เท่าเดิม หรือต่ำกว่าค่า baseline เดิมของผู้ป่วย
- ผู้ป่วยที่มีค่าฮีมาโทคริตลดลงมากกว่า 10 จุด หรือมีค่าฮีมาโทคริตลดต่ำกว่าค่า baseline เดิมของผู้ป่วย หลังจากได้รับ dextran 40 ในปริมาณ 10 ml/kg/h (เด็ก) หรือ 500 ml (ผู้ใหญ่) ในเวลา 1 ชั่วโมง

Balance O_2 Delivery & O_2 Consumption in DSS



Non-invasive methods :

✓ Fluid responsiveness

Blood transfusion

AST&ALT/Serum lactate

Decrease DO_2

Hypovolemia,
Bleeding,
Heart failure,
Respiratory failure

Increase VO_2

Fever, Rigors, Pain,
Work of breathing

วิภา ธนาชาติเวทย์. การดูแลรักษาเด็กวิกฤตทางคลินิกในผู้ใหญ่; ๒๕๖๐. หน้า ๑๓๙-๑๕๙.
Molnar Z *et al*. Curr Opin Anesthesiol. 2017;30:171-7.

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Backward Stepwise Regression Model to Predict Lactate in Dengue Patients

R^2 0.473, adjusted R^2 0.462, $F_{3,148}$ 44.22, P-value <0.001

Explanatory variable	Coefficient b	P-value
Constant	1.872	<0.001
Alanine aminotransferase (ALT)	0.001	<0.001
Serum creatinine (Cr)	0.620	0.006
Cardiac index (CI)	-0.256	0.012

Lactate = 1.872 + 0.001 **ALT** + 0.620 **Cr** – 0.256 **CI**

Thanachartwet V *et al.* BMC Infect Dis. 2015;15:420. doi: 10.1186/s12879-015-1150-2.

Prophylactic PLT/FFP Transfusion in Dengue???

QUESTION: PLT prophylaxis?

1. PLT ≤ 50,000
2. PLT ≤ 20,000
3. PLT ≤ 10,000

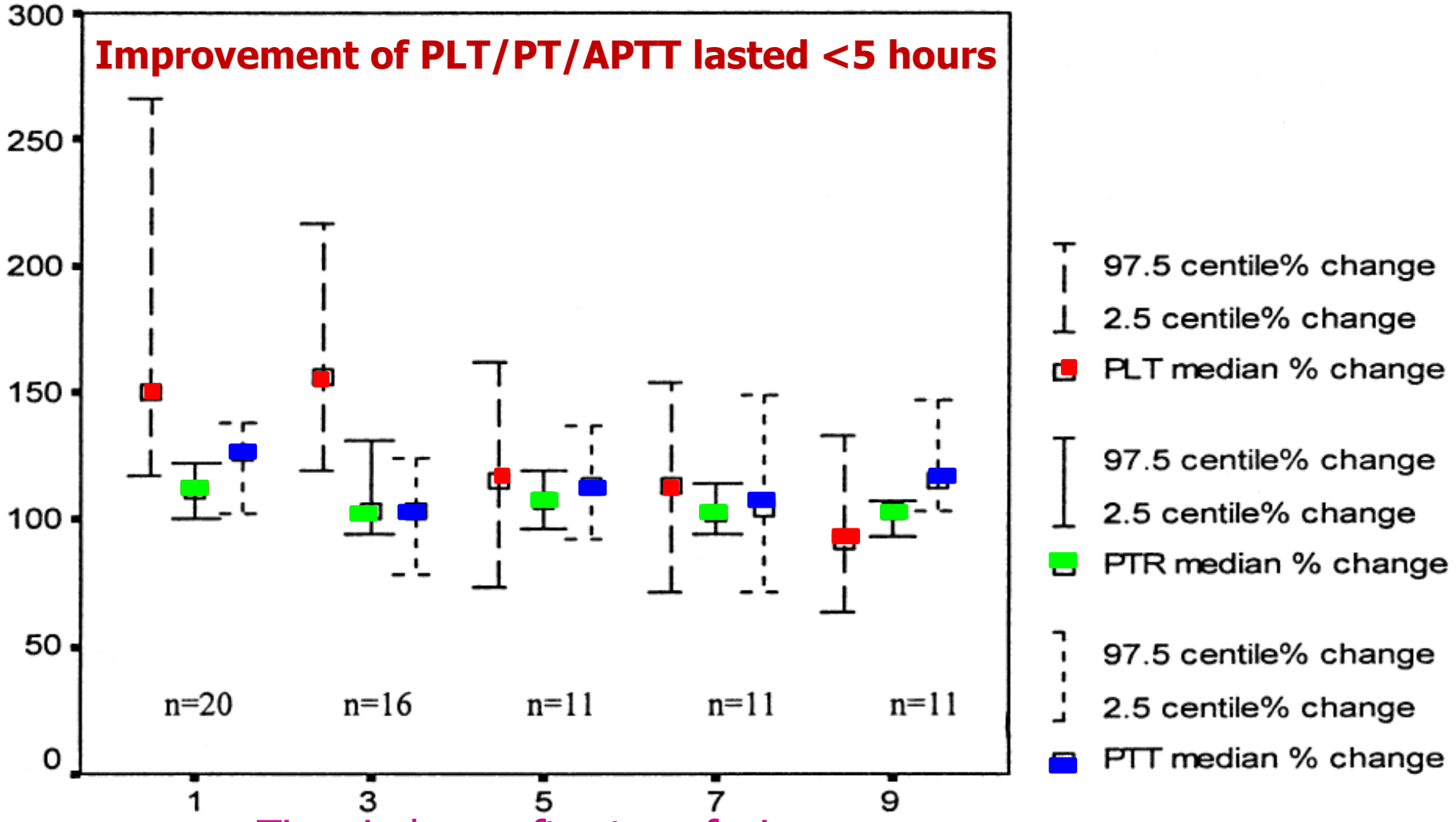
Received PLT/FFP

No any PLT/FFP

Clinical parameter*	Period groups 1990-1996 (n = 53)	Period groups 1997-2000 (n = 53)	P value	Treatment groups† Group 1 (n = 60)	Treatment groups† Group 2 (n = 46)	P value
Age (y)	6.0 (0.1-11.7)	6.0 (0.1-12.0)	.795	6.0 (0.1-11.0)	6.0 (0.3-12.0)	.243
Male:Female ratio	1:0.9	1:1	.846	1:0.8	1:1.2	.448
Duration of shock (h)	4.0 (0.1-11.0)	6.0 (3.0-12.7)	.805	4.0 (0.1-11.4)	4.0 (0.1-9.8)	.918
Percentage increase in hematocrit	53.0 (15.5-96.7)	42.0 (11.0-100.0)	.539	53.0 (15.8-94.8)	42.0 (9.5-100.0)	.239
Lowest platelet count ($\times 10^9$/L)	22.0 (8.3-117.8)	21.0 (5.0-70.6)	.172	20.5 (5.0-75.7)	22.0 (8.1-120.6)	.127
Highest Prothrombin time ratio	1.2 (1.0-2.8)	1.2 (1.0-2.0)	.194	1.2 (1.0-2.7)	1.1 (1.0-1.5)	.207
Highest Partial Thromboplastin time (sec)	72.1 (35.4-124.7)	75.7 (45.0-202.0)	.395	77.7 (43.8-158.8)	71.3 (35.0-202.0)	.347
Total volume of FFP transfused (mL/kg)	20 (0.0-68.4)	0.0 (0.0-40.0)	.000	20.0 (0.0-66.2)	0 (0.0-0.0)	.000
Total platelets transfused (U/kg)	0.1 (0.0-0.9)	0.0 (0.0-0.6)	.000	0.2 (0.0-0.9)	0 (0.0-0.0)	.000
Total fluid balance (mL/kg)	119.5 (23.4-276.2)	110.0 (10.4-205.4)	.574	121.0 (4.7-273.2)	107.0 (53.5-185.3)	.045
Days of thrombocytopenia	5.0 (0.3-12.7)	5.0 (3.0-9.3)	.135	5.0 (2.0-9.0)	4.0 (0.4-13.8)	.395
Days of hospitalization	7.0 (4.0-19.6)	6.0 (3.0-12.7)	.023	7.0 (4.0-17.0)	5.0 (3.0-17.3)	.000
‡Incidence (%) of bleeding (95% CI)	56.6 (43.3-69.0)	49.1 (36.1-62.1)	.559	60.0 (47.4-71.4)	43.5 (30.2-57.8)	.136
Incidence (%) of pulmonary edema (95% CI)	22.6 (13.5-35.5)	17.0 (9.2-29.2)	.626	30.0 (19.9-42.5)	6.5 (9.2-29.2)	.006

Lum LC *et al*. J Pediatr 2003;143(5):682-4

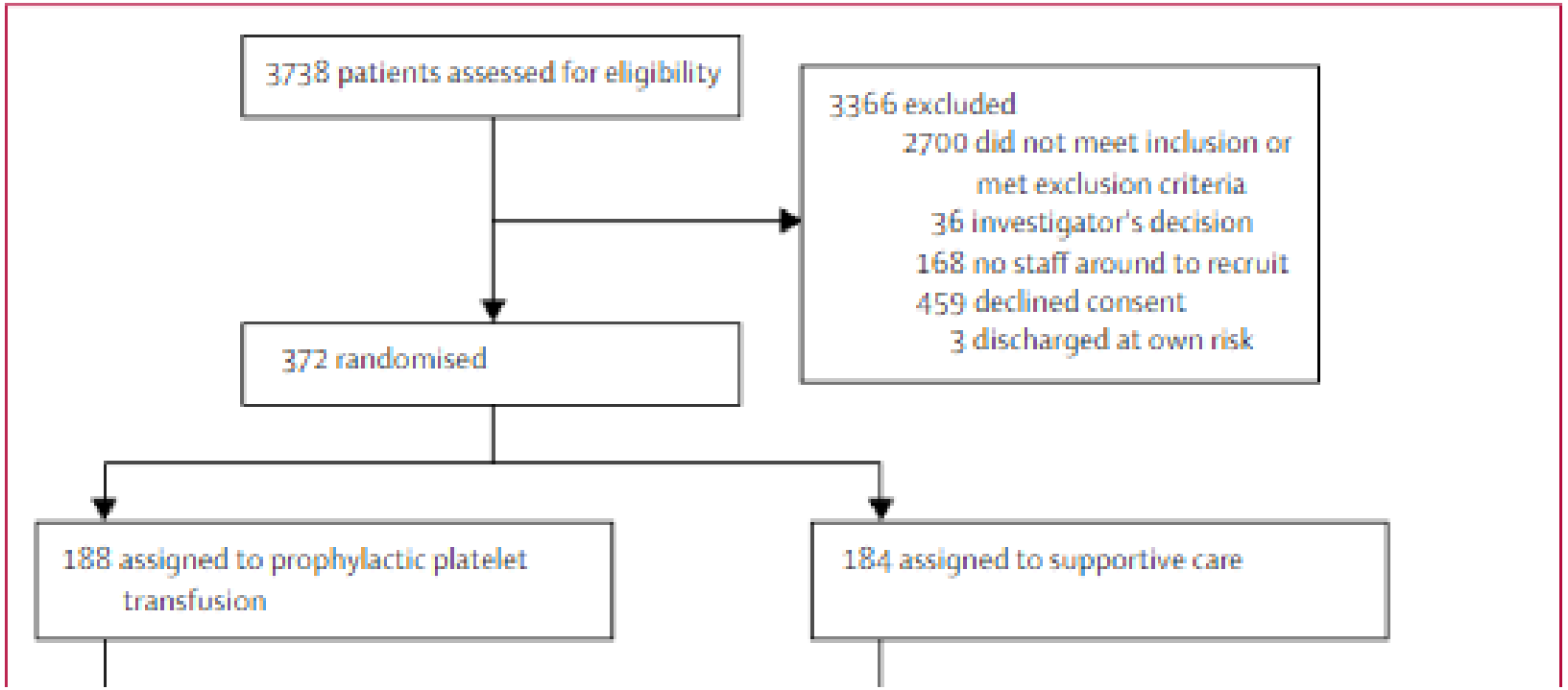
Percentage Change in PLT, PT and APTT after Transfusion of PLT conc. and FFP



Lum LC *et al*. J Pediatr 2003;143(5):682-4

Prophylactic platelet transfusion plus supportive care versus supportive care alone in adults with dengue and thrombocytopenia: a multicentre, open-label, randomised, superiority trial

David C Lye, Sophia Archuleta, Sharifah F Syed-Omar, Jenny G Low, Helen M Oh, Yuan Wei, Dale Fisher, Sasheela S L Ponnampalavanar, Limin Wijaya, Linda K Lee, Eng-Eong Ooi, Adeeba Kamarulzaman, Lucy C Lum, Paul A Tambyah, Yee-Sin Leo



188 assigned to prophylactic Platelet transfusion

184 assigned to supportive care

Lye DC *et al*. Lancet. 2017;389(10079):1611-1618. doi: 10.1016/S0140-6736(17)30269-6.

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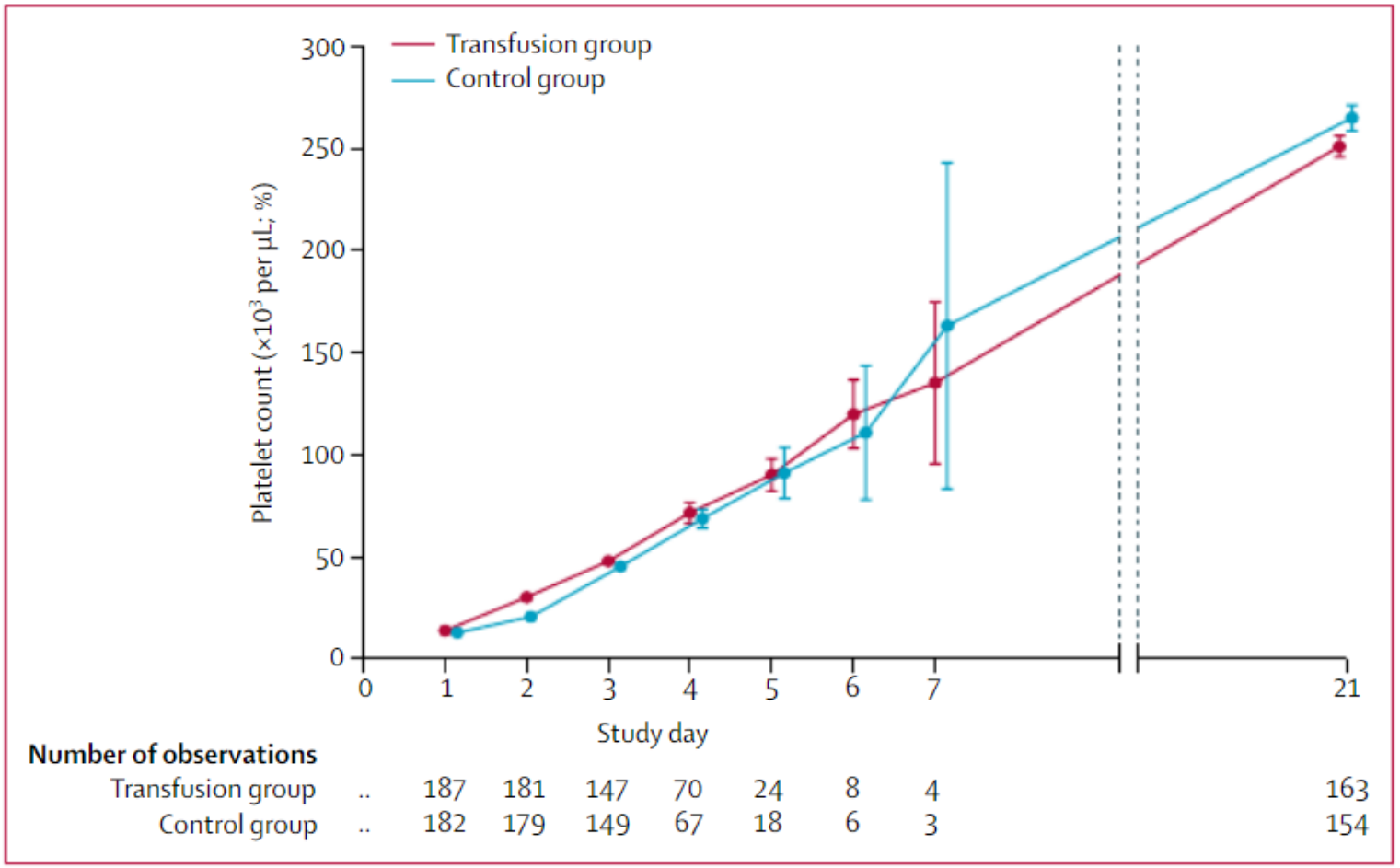
Mean Daily Platelet Count



Lye DC *et al.* Lancet. 2017;389(10079):1611-1618. doi: 10.1016/S0140-6736(17)30269-6.

Adverse Events

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Adverse events		**Transfused patients (n=188)**	**Controls (n=181)**
Cardiac disorders	Chest pain Fluid overload	1 (0·53%) 1 (0·53%)	0 0
Immune system disorders	Urticaria Anaphylactic reaction	3 (1·60%) 1 (0·53%)	0 0
Infections and infestations	Infectious pleural effusion Abscess	0 0	1 (0·55%) 1 (0·55%)
Injury, poisoning and procedural complications	Fall Transfusion-related acute lung injury	0 1 (0·53%)	1 (0·55%) 0
Metabolism and nutrition disorders	Hypokalaemia	1 (0·53%)	0
Respiratory, thoracic and mediastinal disorders	Epistaxis	2 (1·06%)	0
Skin and subcutaneous tissue disorders	Pruritus Maculopapular rash	1 (0·53%) 1 (0·53%)	0 0
Vascular disorders	Haematoma	1 (0·53%)	0

Lye DC *et al.* Lancet. 2017;389(10079):1611-1618. doi: 10.1016/S0140-6736(17)30269-6.

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Potential Harm of Prophylactic Platelet Transfusion in Adult Dengue Patients

Variable	Non-transfused (n = 302)	Transfused (n = 486)	*P*
*Clinical outcomes**			
Volume of platelet given (mL)	NA	234 (100–618)	NA
Volume of fluid received (ml) per day	1400 (342–2878)	1530 (500–3000)	<0.01
Received blood transfusion	1	5	0.41
Time to clinical bleeding, days	1 (1–3)	1 (1–3)	0.77
Platelet increment next day, x 10^3 platelets/mm^3	5 (-6-31)	8 (-6-43)	< 0.0001
Time for platelet count ≥50 x 10^3 platelets/mm^3, days	2 (0–4)	3 (1–5)	< 0.0001
Clinical bleeding, without petechiae	55 (18.2%)	114 (23.5%)	0.08
Internal bleeding	4 (1.3%)	17 (3.4%)	0.07
Mucosal bleeding	28 (9.3%)	89 (18.3%)	0.001
Median length of hospital stay, days	5 (5–7)	6 (4–8)	< 0.0001
Liver failure	0	2	0.53
Renal failure	0	1	1
ICU admission	2 (0.66%)	6 (1.23%)	0.44
Death	0 (0%)	1 (0.2%)	0.43

Lee Th *et al.* PLoS Negl Trop Dis. 2016;10(3):e0004576. doi: 10.1371/journal.pntd.0004576

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Stepwise Approach for Management of Dengue in Adults

- Diagnosis of dengue
- Risk factors for severe disease
- Evaluation of dengue severity
- Evaluation of disease phase
- Management (Organ impairment)

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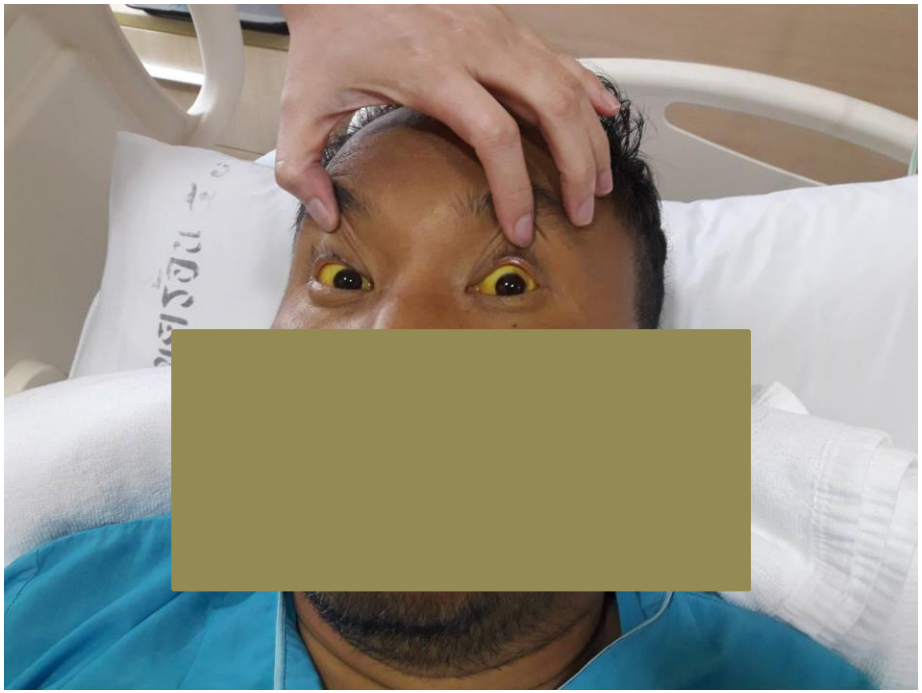
Adults with Acute Liver Failure in DSS



Liver Complications in Dengue

- **Hepatitis** : 32-93% (AST/ALT ≈ 2:1)
  - ✓ **Acute hepatitis** : 4-15%
    - ○ AST/ALT >1000 U/L
    - ○ Abnormal bleeding, acute kidney injury, acalculus cholecystitis, and encephalopathy ร่วมด้วย
  - ✓ **Fulminant hepatic failure** : 0.2-5%
    - ○ Case fatality rate 35%
- **Hypoalbuminemia** : 13-66%
- **Hyperbilirubinemia** : 7-17%

วิภา ธนาชาติเวทย์. การดูแลรักษาเดงกีรุนแรงทางคลินิกในผู้ใหญ่; ๒๕๖๐. หน้า ๑๗๗-๑๙๓.
Penafiel A *et al.* J intensive Care Med. 2006:21:369-71.
Kumaraaena RS *et al.* Hepatol Int. 2010;4:533-4.

Liver Complications in Dengue (Management)

- **Supportive treatment**
- **Avoid hepatotoxic drugs**
- **N-acetylcysteine i.v.**
  - 5 patients with hepatic encephalopathy grade I-II
    - complete recovery
  - 3 patients with hepatic encephalopathy grade III-IV
    - Death
- **Molecular adsorbent re-circulating system**
  - Recovery time of liver was similar to supportive treatment.

วิภา ธนาชาติเวทย์. การดูแลรักษาเดงกีรุนแรงทางคลินิกในผู้ใหญ่; ๒๕๖๐. หน้า ๑๗๗-๑๙๓.
Penafiel A *et al.* J intensive Care Med. 2006:21:369-71.
Kumaraaena RS *et al.* Hepatol Int. 2010;4:533-4.

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Cardiac Complications in Dengue

Clinical manifestations

- Cardiac dysrhythmia : 29-63%
- Functional myocardial impairment : 40%
- Myocarditis : 15%

Pathogenesis

- Direct DENV infection and/or immune response
- Myocardial edema : plasma leakage
- Coronary hypoperfusion : volume depletion
- Electrolyte abnormalities : hypocalcemia, hypokalemia

วิภา ธนาชาติเวทย์. การดูแลรักษาเดงกีรุนแรงทางคลินิกในผู้ใหญ่; ๒๕๖๐. หน้า ๑๖๑-๑๗๕.

PLOS ONE

RESEARCH ARTICLE

Dynamic Measurement of Hemodynamic Parameters and Cardiac Preload in Adults with Dengue: A Prospective Observational Study

Vipa Thanachartwet[1]*, Anan Wattanathum[2], Duangjai Sahassananda[3], Petch Wacharasint[4], Supat Chamnanchanunt[1], Ei Khine Kyaw[1], Akanitt Jittmittraphap[5], Mali Naksomphun[6], Manoon Surabotsophon[7], Varunee Desakorn[1]

1 Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand, **2** Pulmonary and Critical Care Division, Department of Medicine, Phramongkutklao Hospital, Bangkok 10400, Thailand, **3** Information Technology Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand, **4** Critical Care Division, Department of Anesthesiology, Phramongkutklao Hospital, Bangkok 10400, Thailand, **5** Department of Microbiology and Immunology, Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand, **6** Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand, **7** Pulmonary and Critical Care Division, Department of Medicine, Ramkhamhaeng Hospital, Bangkok 10240, Thailand

* vipa.tha@mahidol.edu

Thanachartwet V *et al.* PLoS One. 2016;11(5):e0156135. doi: 10.1371/journal.pone.0156135.

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250 adults with suspected dengue admitted to the Hospital for Tropical Diseases, Mahidol University, Bangkok in Thailand

- 38 patients had underlying medical illness.
- 31 patients had mixed infection.
- 14 patients had negative results for dengue RT-PCR, micro-neutralization and anti-dengue virus IgM/IgG antibodies.
- 5 patients were <15 years of age.

162 hospitalized adults with confirmed dengue viral infection were recruited to the study

- 145 (89.5%) patients did not develop dengue shock during hospitalization.
- 17 (10.5%) patients developed dengue shock during hospitalization.

Thanachartwet V *et al.* PLoS One. 2016;11(5):e0156135. doi: 10.1371/journal.pone.0156135.

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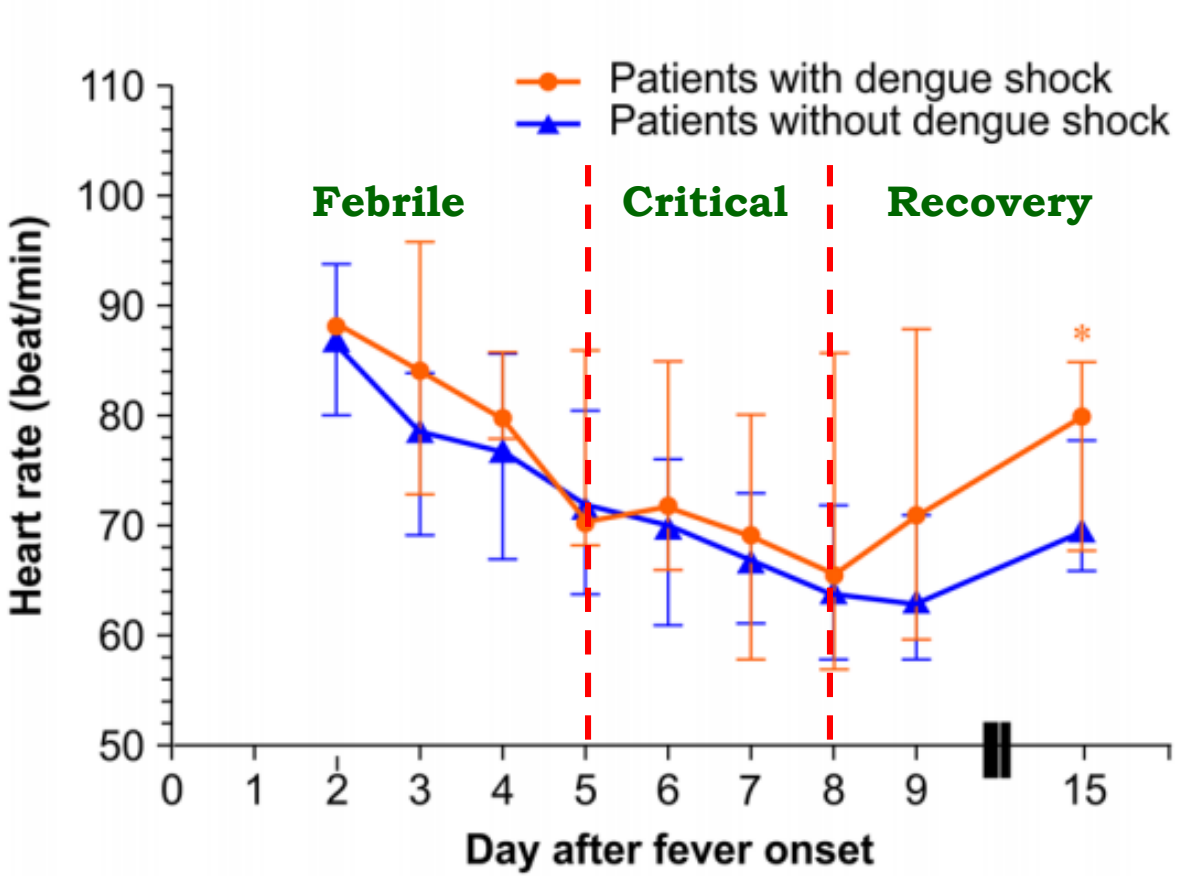
C



HR (beats/min)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 15
Dengue with shock (n)	2	4	7	13	15	15	12	9	15
Dengue without shock (n)	26	50	94	122	130	110	68	34	137
P-value	NA	0.311	0.141	0.533	0.207	0.648	0.540	0.126	0.041

Thanachartwet V *et al.* PLoS One. 2016;11(5):e0156135. doi: 10.1371/journal.pone.0156135.

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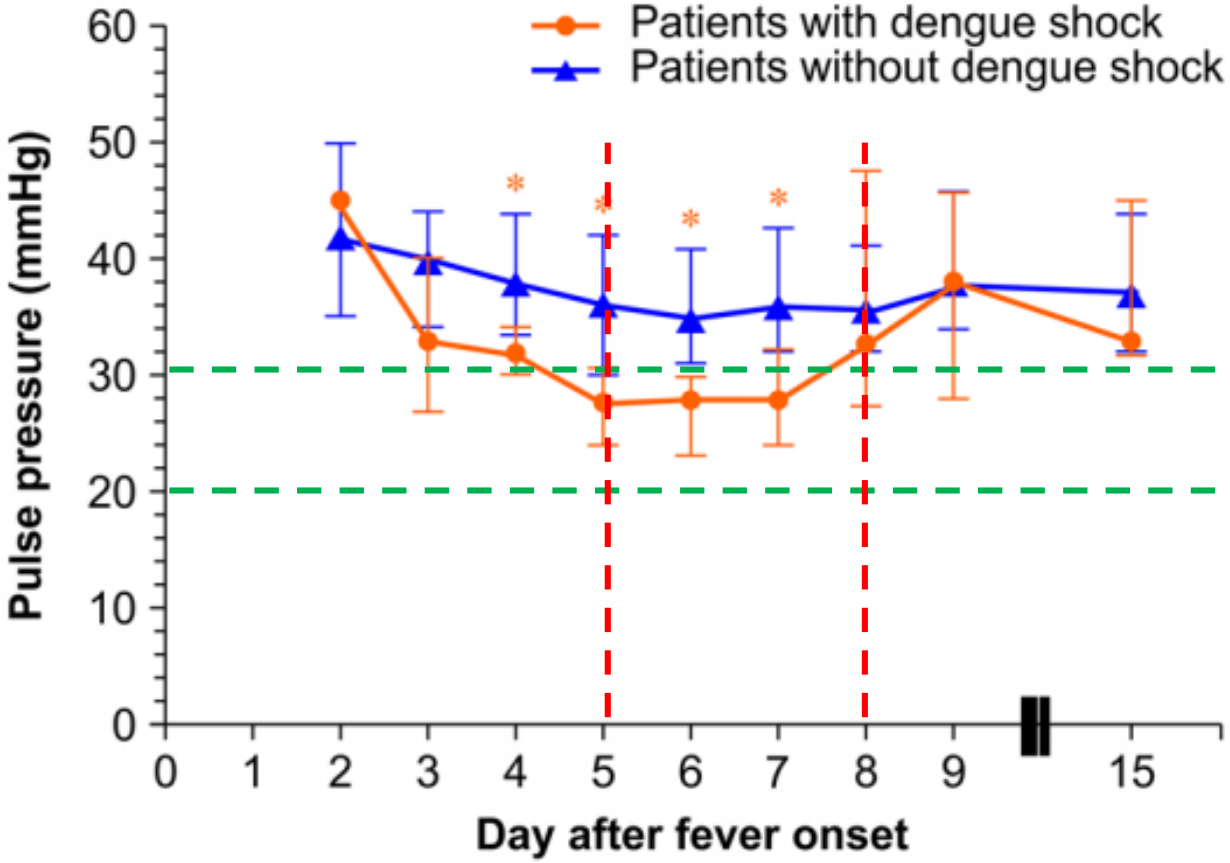
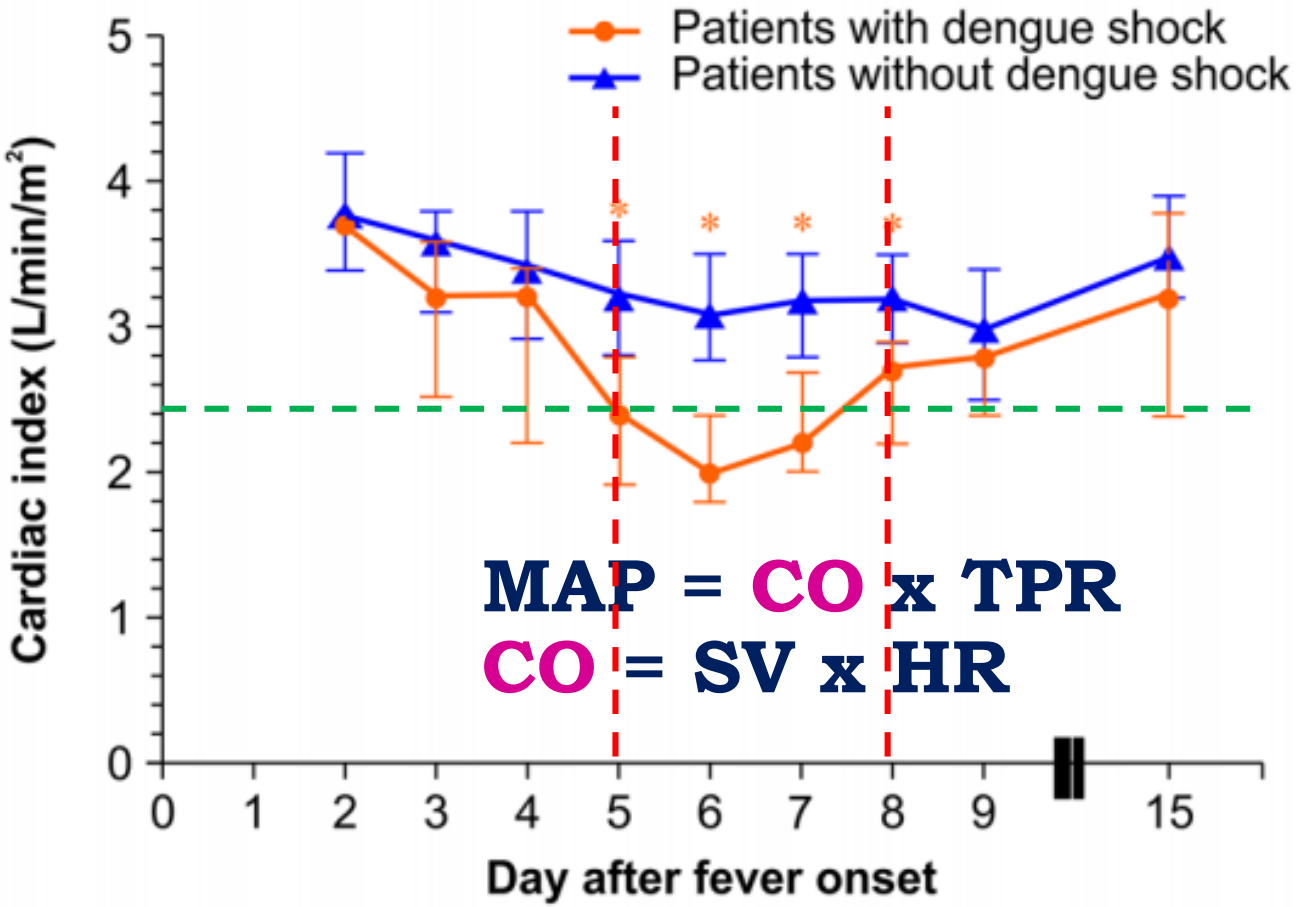
B



PP (mmHg)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 15
Dengue with shock (n)	2	4	7	13	15	15	12	9	15
Dengue without shock (n)	26	50	94	122	130	110	68	34	136
P-value	NA	0.166	0.031	<0.001	<0.001	<0.001	0.467	0.649	0.486

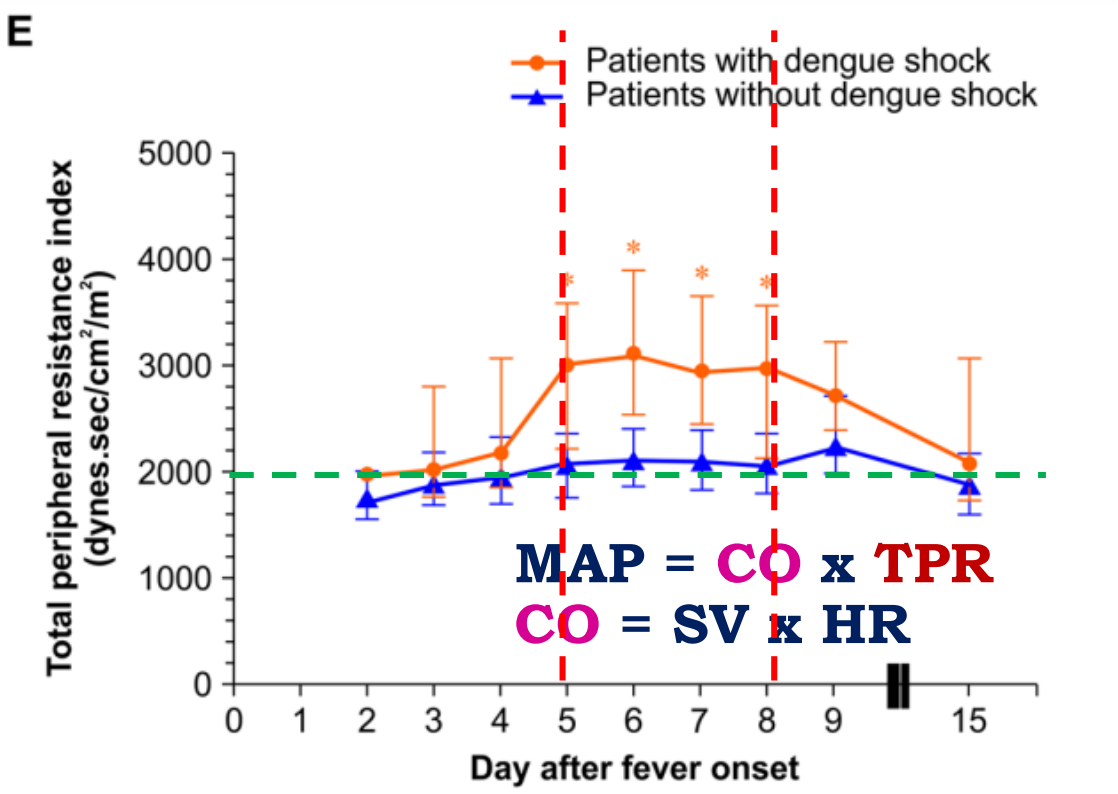
Thanachartwet V *et al.* PLoS One. 2016;11(5):e0156135. doi: 10.1371/journal.pone.0156135.

D



CI (L/min/m²)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 15
Dengue with shock (n)	2	4	7	13	15	15	12	9	15
Dengue without shock (n)	26	50	94	122	130	110	68	34	137
P-value	NA	0.252	0.103	<0.001	<0.001	<0.001	0.001	0.066	0.116

Thanachartwet V *et al.* PLoS One. 2016;11(5):e0156135. doi: 10.1371/journal.pone.0156135.



TPRI (dynes·sec/cm⁵/m²)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 15
Dengue with shock (n)	2	4	7	13	15	15	12	9	15
Dengue without shock (n)	26	50	94	122	130	110	68	34	136
P-value	NA	0.472	0.124	0.001	<0.001	<0.001	0.009	0.066	0.151

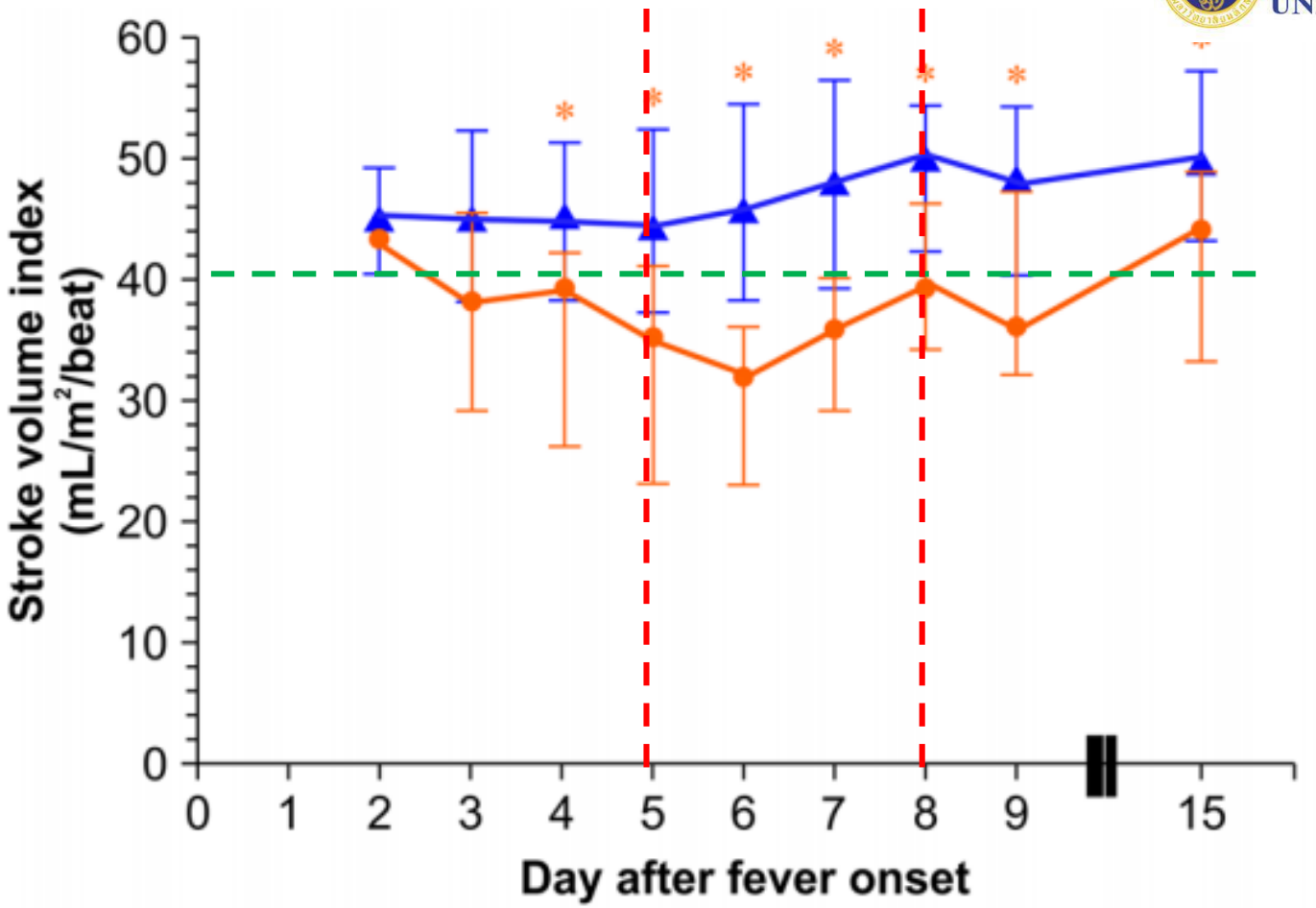
Compensated shock

- Rapid and weak pulse
- Cold clammy skin) particularly cold extremities
- CRT >2 sec
- PP <20 mmHg (25% in adults)

Decompensated shock

- BP drop : hypotension
- Organs failure

Thanachartwet V *et al.* PLoS One. 2016;11(5):e0156135. doi: 10.1371/journal.pone.0156135.



SVI (mL/m²/beat)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 15
Dengue with shock (n)	2	4	7	13	15	15	12	9	15
Dengue without shock (n)	26	50	94	122	130	110	68	34	137
P-value	NA	0.128	0.018	<0.001	<0.001	<0.001	0.003	0.024	0.005

Thanachartwet V *et al.* PLoS One. 2016;11(5):e0156135. doi: 10.1371/journal.pone.0156135.

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Clinical/Lab & Outcomes

Characteristic	All dengue (n = 162)	DSS (n=17)	No DSS (n = 145)	*P-value*
Skin bleeding	92 (57%)	13 (76%)	79 (54%)	0.141
Mucosal bleeding	78 (48%)	14 (82%)	64 (44%)	0.006
AKI	16 (10%)	6 (36%)	10 (7%)	0.002
Elevated Trop T	2 (1%)	2 (12%)	0	0.010
NT-proBNP ≥500	23 (14%)	6 (35%)	17 (12%)	0.018
Death	2 (1%)	2 (12%)	0	0.010

DSS : AST/ALT >1,000 IU/L [6 patients, 35%]
: Impaired consciousness [4 patients, 24%]
: Hypovolemic shock [9 patients, 53%]
: Cardiogenic shock [8 patients, 47%]

India : 62% of pts with DSS had LVEF <40%

Vietnam : severe dengue pts had combine systolic and diastolic dysfunction.

Thanachartwet V *et al.* PLoS One. 2016;11(5):e0156135. doi: 10.1371/journal.pone.0156135.
Wali JP *et al.* Int J Cardiol. 1998; 64(1):31–6.
Yacoub S *et al.* Crit Care Med. 2012; 40(2):477–83

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Neurological Complications in Dengue

- Neurological complications in dengue : 14-26%
- **Central nervous system involvement** (80%) : headache, dizziness, vomiting, restlessness, drowsiness, seizure and unconsciousness
  - **Encephalopathy** : metabolic abnormalities
    - ✓DSS coincide : 78-100%
    - ✓CSF findings : normal WBC/protein/sugar
  - **Encephalitis** : DENV invasion
    - ✓Focal neurological signs
    - ✓CSF findings : increase WBC, DENV detection

วิภา ธนาชาติเวทย์. การดูแลรักษาเดงกีรุนแรงทางคลินิกในผู้ใหญ่; ๒๕๖๐. หน้า ๑๗๗-๑๙๓.

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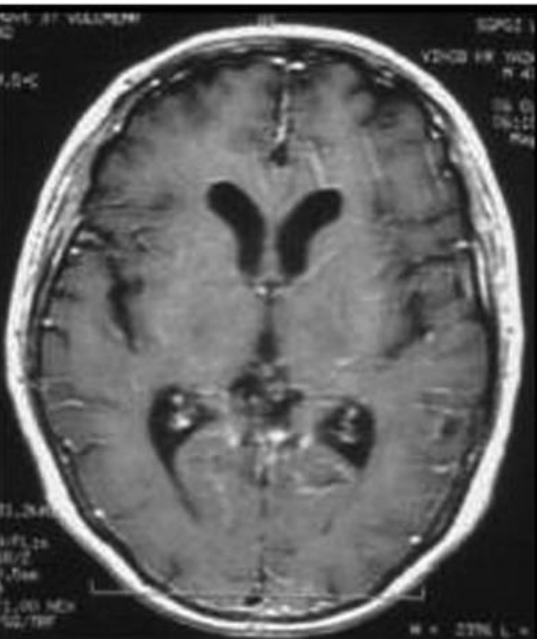
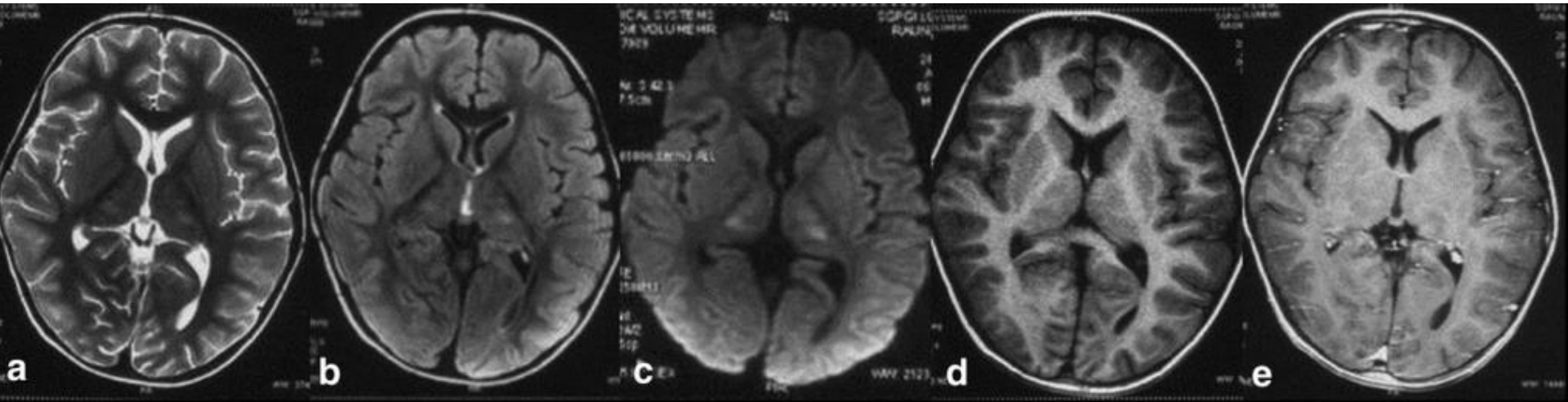
MRI in Dengue Patients



- **No abnormalities :** 22-54%
- **Abnormalities :** 45-78%
  - Cerebral edema
  - Signal changes in thalamus, basal ganglia and white matter, meningeal enhancement
  - CNS bleeding

Bhoi SK *et al.* J Neurol Sci. 2014;342(1-2):36-41. doi: 10.1016/j.jns.2014.04.018.
วิภา ธนาชาติเวทย์. การดูแลรักษาเดงกีรุนแรงทางคลินิกในผู้ใหญ่; ๒๕๖๐. หน้า ๑๗๗-๑๙๓.



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Kidney Complications in Dengue

- **Proteinuria :** 22-43%
- **Hematuria :** 13%
- **Acute kidney injury :** 10-14%
  - ✓ Case fatality rate : 9-29%
  - ✓ Risk factors for development of AKI in dengue :
    - ○ Diabetes mellitus
    - ○ DSS, MOFs
    - ○ Patients receiving NSAIDs or Selective Cox-inhibitors
    - ○ Patients receiving diuretics, ACEIs or ARBs as an anti-HT drug
    - ○ Patients having bacterial co-infection

วิภา ธนาชาติเวทย์. การดูแลรักษาเดงกีรุนแรงทางคลินิกในผู้ใหญ่; ๒๕๖๐. หน้า ๑๗๗-๑๙๓.

Bacterial Co-infection in Dengue

Clinical manifestations

- **Concurrent bacteremia** (positive blood culture sampled from patients < 72 hr after hospitalization) : 0.2-1.0% (CFR 29%)
- **Bacterial co-infection :** 0.3-4%

Clinical and Lab. suspected bacterial co-infection in dengue :

- Prolonged fever
- Tachycardia
- Leukocytosis or bandemia
- MOFs particularly AKI
- Longer hospitalization

วิภา ธนาชาติเวทย์. การดูแลรักษาเดงกีรุนแรงทางคลินิกในผู้ใหญ่; ๒๕๖๐. หน้า ๑๖๑-๑๗๕.
Trunfio M *et al.* Infection. 2017;45:1-10.

Symptoms and Signs of Recovery after Fever has Gone Away

- **A**–Appetite
- **B**–Bradycardia
- **C**–Convalescence rash or itching
- **D**–Diuresis

Short guideline for dengue case management 2023

Mahidol University
Faculty of Tropical Medicine

Stepwise Approach for Management of Dengue in Adults

- Diagnosis of dengue
- Risk factors for severe disease
- Evaluation of dengue severity
- Evaluation of disease phase
- Management (Comorbidities)

แนวทางการดูแลรักษาผู้ป่วยโรคไข้เลือดออก (ฉบับย่อ)

Short guideline for dengue case management

- ผู้ป่วย**กลุ่มที่มีความเสี่ยงสูง**ต่อการเกิดโรคไข้เลือดออกที่รุนแรงและมีภาวะแทรกซ้อน ประกอบด้วย
  - เด็กอายุน้อยกว่า 1 ปี สตรีตั้งครรภ์ ผู้สูงอายุ ผู้ป่วยโรคอ้วน
  - ผู้ที่มีโรคประจำตัวเรื้อรัง เช่น โรคเบาหวาน โรคความดันเลือดสูง โรคหัวใจ โรคตับ โรคเลือด และโรคไต
  - ผู้ที่กินยาต้านการแข็งตัวของเลือด (anticoagulants) /ยาต้านเกล็ดเลือด (antiplatelets)/NSAIDs
  - ผู้ป่วยที่มีระดับความรู้สึกตัวลดลง ผู้ป่วยที่มีภาวะเลือดออกผิดปกติ และผู้ป่วยที่มีภาวะช็อก

Diabetes Care in Hospital

- Perform HbA1c test on all patients with DM or hyperglycemia (BS >140 mg/dl), if not performed in the previous 3 months. **(B)**
- Insulin therapy should be initiated for treatment of persistent hyperglycemia (BS ≥180 mg/dl on two occasions). **(A)**
  - A target glucose range of 140-180 mg/dl for most critically ill and noncritically ill patients is recommended **(A)**
  - A target glucose range of 100-180 mg/dl for noncritically ill patients is recommended by experts.
- Continue home therapy with oral glucose-lowering drugs may be appropriate in certain circumstances of noncritical care setting.
  - Sodium-glucose cotransporter 2 (SGLT2) inhibitors should be discontinued due to the risk of euglycemic DKA in patients with infection.
- Blood glucose monitoring
- Consult with a specialized diabetes when possible **(C)**

ElSayed NA, *et al.* Diabetes Care. 2023;46(Suppl 1):S267-S278.

Antihypertensive Drugs in Dengue

- Risk factors for development of AKI in dengue :
  - Diabetes mellitus
  - DSS, MOFs
  - Patients receiving NSAIDs or Selective Cox-inhibitors
  - Patients receiving diuretics, ACEIs or ARBs as an anti-HT drug
  - Patients having bacterial co-infection
- Cardiac complications in dengue :
  - Cardiac dysrhythmia : 29-63%
  - Functional myocardial impairment : 40%
  - Myocarditis : 15%

Thanachartwet V. Clinical management of severe dengue in adults; 2017. pp 161-175.
Thanachartwet V. Clinical management of severe dengue in adults; 2017. pp 177-193.

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Antiplatelets and Anticoagulants in Dengue

Risk of bleeding

- Age >75 years
- Diabetes, Hypertension
- Prior bleeding within the previous 3 months
- PLT count <100,000/mm^3
- Liver disease (INR >1.5)
- CKD (eGFR <30 $ml/min/m^2$)
- Combined use of an anticoagulant and an antiplatelet medication (ASA, NSAIDs etc.)
- Dual antiplatelet therapy

Decousus H, *et al.* Chest 2011;139:69. Huhtakangas J, *et al.* Stroke 2011;42(9):2431
Boulanger M, *et al.* Neurology 2016;87(9):870. Ehelepola NDB, *et al.* Am J Trop Med Hyg. 2020;102(1):17-19.
Chia PY, et al. J Infect. 2021;82(2):270-275.

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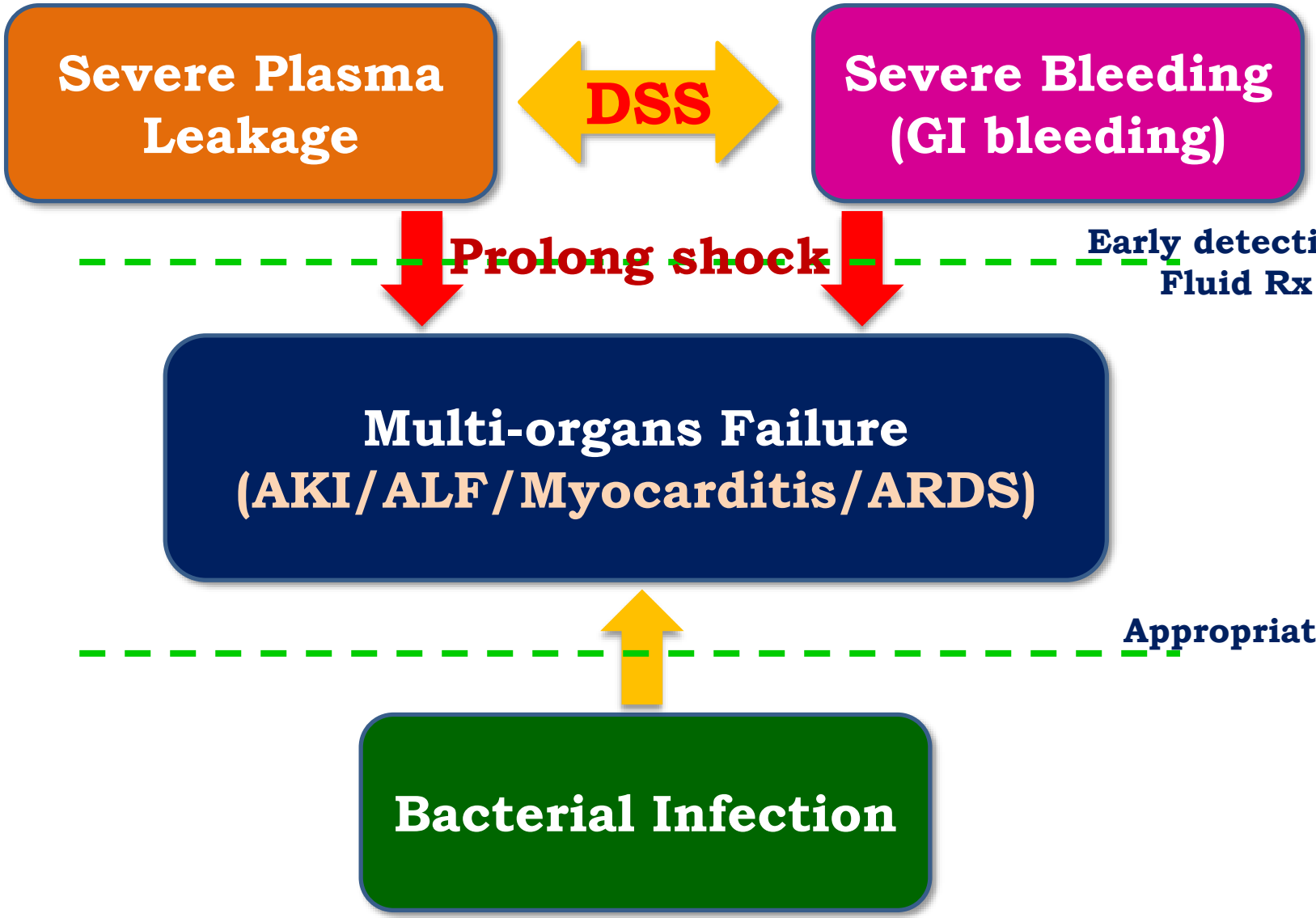
Hints : Management of Dengue



mine the mass of objects it orbited. When Cassini began threading the gap between Saturn and its rings during its last passes, the team could pick out the gravitational pull of the rings—and hence their mass. "The central value is consistently 0.4 Mimas's mass," Iess said. If theories that link mass to age are correct, he added, "This is a clear indication that the rings did not form together with Saturn."

That conclusion is buttressed by another line of evidence presented at the meeting. A constant rain of sooty micrometeorites falls into Saturn from the edge of the solar system, which would be expected to darken the pristine water ice in the rings over time. How quickly they would darken depends on the bombardment rate, which has been uncertain.

INFECTIOUS DISEASE

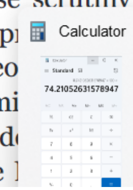
Safety concerns derail dengue vaccination program

Other vaccine candidates likely to face increased scrutiny

By **Dennis Normile**

The effort to deploy a pioneering vaccine against dengue, a mosquito-borne disease that affects tens of millions of people each year, is in disarray following Sanofi Pasteur's November announcement that the vaccine's use should be dramatically cur-

Health Sciences in Bethesda, Maryland, who was among those who warned of possible dangers early on. Its problems will certainly increase scrutiny of other vaccines now in develop[...] In-Kyu Yoon, director of the Seo[...] Global Dengue & Aedes-Transmi[...]ses Consortium. "I think both d[...] and country ministries will be l[...]ore carefully at the issues



Up-and-coming dengue vaccines

Manufacturers for the two dengue vaccines following Sanofi Pasteur's are collecting more data to evaluate safety; results are expected by the end of 2018.

VACCINE	MANUFACTURER	VACCINE TYPE	MECHANISM	STATUS
Dengvaxia	Sanofi Pasteur	Live attenuated	Yellow fever vaccine backbone with key genes from four dengue viruses	In use
DENVax	Takeda	Live attenuated	Dengue serotype 2 backbone with key genes from other three dengue viruses	Initial results late 2018
TV003/ TV005	National Institute of Allergy and Infectious Diseases and Butantan Institute	Live attenuated	Wild-type strains with genetic mutations	Initial results late 2018

https://www.science.org/doi/epdf/10.1126/science.358.6370.1514

Efficacy of a Tetravalent Dengue Vaccine (TAK-003) in Healthy Children and Adolescents

- Phase 3, double-blind, randomized, placebo-controlled trial
- Healthy children and adolescents at 26 sites in Asia and Latin America (dengue endemic area): Brazil (4 sites), Colombia (4 sites), the Dominican Republic (2 sites), Nicaragua (1 sites), Panama (4 sites), the Philippines (4 sites), Sri Lanka (4 sites), and Thailand (3 sites)
- Healthy children and adolescents 4 to 16 years of age were randomly assigned in a 2:1 ratio to receive two doses of vaccine or placebo between September 2016 and March 2017.
- Vaccine and placebo were administered subcutaneously into the upper arm.
- One 0.5-ml dose of TAK-003 contained approximately 3.6, 4.0, 4.6, and 5.1 $\log_{10}$ plaque-forming units of TDV-1, TDV-2, TDV-3, and TDV-4, respectively.
- The placebo was a 0.5-ml injection of saline.

Efficacy of a Tetravalent Dengue Vaccine (TAK-003) in Healthy Children and Adolescents

- **During active surveillance**, participants presenting with febrile illness or clinically suspected dengue have blood samples taken in the acute phase (i.e., as soon as possible and preferably within 5 days after fever onset) and convalescent phase (i.e., 7 to 14 days after the acute-phase specimen is obtained).
- Testing includes RT-PCR, ELISA for dengue NS1, IgM, and IgG; and HCT, PLT count, AST, ALT.
- RT-PCR and NS1 ELISA are performed only on the acute-phase specimen.
- **Efficacy analyses:** virologically confirmed dengue is defined as febrile illness or illness clinically suspected to be dengue by the investigator in association with a positive serotype-specific RT-PCR result.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

1 year

Efficacy of a Tetravalent Dengue Vaccine in Healthy Children and Adolescents

Shibadas Biswal, M.D., Humberto Reynales, M.D., Ph.D., Xavier Saez-Llorens, M.D., Pio Lopez, M.D., Charissa Borja-Tabora, M.D., Pope Kosalaraksa, M.D., Chukiat Sirivichayakul, M.D., Veerachai Watanaveeradej, M.D., Luis Rivera, M.D., Felix Espinoza, M.D., LakKumar Fernando, M.D., Reynaldo Dietze, M.D., Kleber Luz, M.D., Rivaldo Venâncio da Cunha, M.D., José Jimeno, M.D.

Biswal S, *et al*. N Engl J Med 2019; 381:2009-2019.

The Journal of Infectious Diseases

MAJOR ARTICLE

2 year

Efficacy of a Dengue Vaccine Candidate (TAK-003) in Healthy Children and Adolescents 2 Years after Vaccination

Eduardo López-Medina,[1,a] Shibadas Biswal,[2,a] Xavier Saez-Llorens,[3] Charissa Borja-Tabora,[4] Lulu Bravo,[5] Chukiat Sirivichayakul,[6] Luis Martinez Vargas,[7] Maria Theresa Alera,[8] Hector Velásquez,[9] Humberto Reynales,[10] Luis Rivera,[11] Veerachai Watanaveeradej,[12] Edith Johana Rodriguez-Arenales,[13] Delia Yu,[14] Felix Espinoza,[15] Reynaldo Dietze,[16] LakKumar Fernando,[17] Pujitha Wickramasinghe,[18] Edson Duarte Moreira Jr,[19] Asvini D. Fernando,[20] Dulanie Gunasekera,[21] Kleber Luz,[22] Rivaldo Venâncio da Cunha,[23] Vianney Tricou,[24] Martina Rauscher,[24] Mengya Liu,[2] Inge LeFevre,[24] Derek Wallace,[2] Pope Kosalaraksa,[25,b] Astrid Borkowski,[24,b]; for the TIDES Study Group

López-Medina E, *et al*. J Infect Dis. 2022;225(9):1521-1532. doi: 10.1093/infdis/jiaa761.

Efficacy of a tetravalent dengue vaccine in healthy children aged 4–16 years: a randomised, placebo-controlled, phase 3 trial

1.5 year

Shibadas Biswal*, Charissa Borja-Tabora*, Luis Martinez Vargas, Hector Velásquez, Maria Theresa Alera, Victor Sierra, Edith Johana Rodriguez-Arenales, Delia Yu, V Pujitha Wickramasinghe, Edson Duarte Moreira Jr, Asvini D Fernando, Dulanie Gunasekera, Pope Kosalaraksa, Felix Espinoza, Eduardo López-Medina, Lulu Bravo, Suely Tuboi, Yanee Hutagalung, Pedro Garbes, Ian Escudero, Martina Rauscher, Svetlana Bizjajeva, Inge LeFevre, Astrid Borkowski, Xavier Saez-Llorens*, Derek Wallace*, for the TIDES study group†

Tricou V, *et al*. Lancet. 2020;395(10234):1434-1443. doi: 10.1016/S0140-6736(20)30556-0.

Summary

Background A substantial unmet need remains for safe and effective vaccines against dengue virus disease, particularly for individuals who are dengue-naive and those younger than 9 years. We aimed to assess the efficacy, safety, and immunogenicity of a live attenuated tetravalent dengue vaccine (TAK-003) in healthy children aged 4–16 years.

Lancet 2020; 395: 1423-33
Published Online March 17, 2020

Clinical Infectious Diseases

MAJOR ARTICLE

3 year

Three-year Efficacy and Safety of Takeda's Dengue Vaccine Candidate (TAK-003)

Luis Rivera,[1,a] Shibadas Biswal,[2,a] Xavier Sáez-Llorens,[3] Humberto Reynales,[4] Eduardo López-Medina,[5] Charissa Borja-Tabora,[6] Lulu Bravo,[7] Chukiat Sirivichayakul,[8] Pope Kosalaraksa,[9] Luis Martinez Vargas,[10] Delia Yu,[11] Veerachai Watanaveeradej,[12] Felix Espinoza,[13] Reynaldo Dietze,[14] LakKumar Fernando,[15] Pujitha Wickramasinghe,[16] Edson Duarte Moreira Jr,[17] Asvini D. Fernando,[18] Dulanie Gunasekera,[19] Kleber Luz,[20] Rivaldo Venâncio da Cunha,[21] Martina Rauscher,[22] Olaf Zent,[22] Mengya Liu,[2] Elaine Hoffman,[2] Inge LeFevre,[22] Vianney Tricou,[22] Derek Wallace,[2] Maria Theresa Alera,[23,b] and Astrid Borkowski[22,b]; for the TIDES study group

Rivera L, *et al*. Clin Infect Dis. 2022;75(1):107-117. doi: 10.1093/cid/ciab864.

Long-term efficacy and safety of a tetravalent dengue vaccine (TAK-003): 4·5-year results from a phase 3, randomised, double-blind, placebo-controlled trial

4.5 year

Vianney Tricou*, Delia Yu*, Humberto Reynales, Shibadas Biswal, Xavier Saez-Llorens, Chukiat Sirivichayakul, Pio Lopez, Charissa Borja-Tabora, Lulu Bravo, Pope Kosalaraksa, Luis Martinez Vargas, Maria Theresa Alera, Luis Rivera, Veerachai Watanaveeradej, Reynaldo Dietze, LakKumar Fernando, V Pujitha Wickramasinghe, Edson Duarte Moreira Jr, Asvini D Fernando, Dulanie Gunasekera, Kleber Luz, Ana Lucia Oliveira, Suely Tuboi, Ian Escudero, Yanee Hutagalung, Eric Lloyd, Martina Rauscher, Olaf Zent, Nicolas Folschweiller, Inge LeFevre, Felix Espinoza†, Derek Wallace†

Tricou V, *et al*. Lancet Glob Health. 2024;12(2):e257-e270. doi: 10.1016/S2214-109X(23)00522-3.

Summary

Background About half of the world's population lives in dengue-endemic areas. We aimed to evaluate the long-term efficacy and safety of two doses of the tetravalent dengue vaccine TAK-003 in preventing symptomatic dengue disease of any severity and due to any dengue virus (DENV) serotypes in children and adolescents.

Lancet Glob Health 2024; 12: e257–70

See Comment page e179

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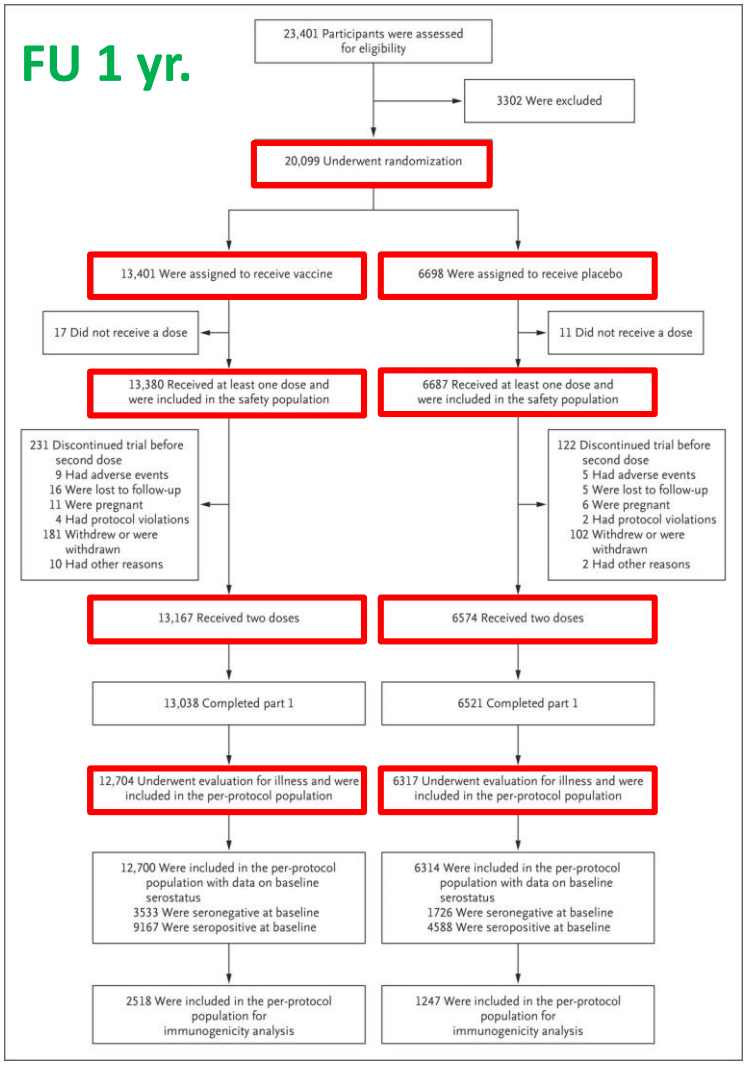
FU 1 yr.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of a Tetravalent Dengue Vaccine in Healthy Children and Adolescents

Table 1. Characteristics of the Participants at Baseline.*

Population and Characteristic	Vaccine Group	Placebo Group	Total
Per-protocol population			
No. of participants	12,704	6317	19,021
Age — yr	9.6±3.35	9.6±3.34	9.6±3.35
Seronegative for dengue virus — no./total no. (%)†	3533/12,700 (27.8)	1726/6314 (27.3)	5259/19,014 (27.7)
Female sex — no. (%)	6314 (49.7)	3098 (49.0)	9,412 (49.5)
Asia-Pacific region — no. (%)	5896 (46.4)	2942 (46.6)	8,838 (46.5)
Seronegative for dengue virus — no./total no. (%)†	1503/5895 (25.5)	773/2940 (26.3)	2276/8835 (25.8)
Latin America — no. (%)	6808 (53.6)	3375 (53.4)	10,183 (53.5)
Seronegative for dengue virus — no./total no. (%)†	2030/6805 (29.8)	953/3374 (28.2)	2983/10,179 (29.3)
Safety population‡			
No. of participants	13,380	6687	20,071
Age — yr	9.6±3.36	9.6±3.34	9.6±3.35
Seronegative for dengue virus — no./total no. (%)†	3714/13,375 (27.8)	1832/6684 (27.4)	5547/20,063 (27.6)
Female sex — no. (%)	6651 (49.7)	3276 (49.0)	9,929 (49.5)
Safety subpopulation‡§			
No. of participants	2663	1329	3993
Seronegative for dengue virus — no. (%)†	740 (27.8)	369 (27.8)	1,109 (27.8)

Biswal S, *et al*. N Engl J Med 2019; 381:2009-2019.

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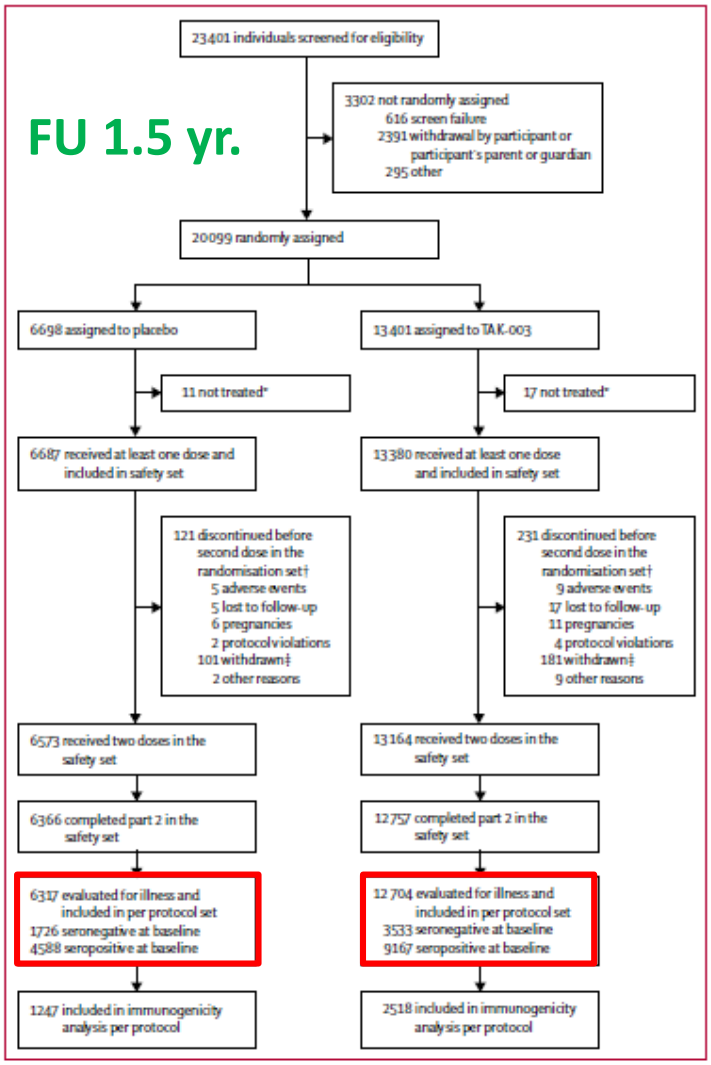
FU 1.5 yr.



FU 2 yrs.

Table 2. Vaccine Efficacy (95% CI) of TAK-003 in Prevention of VCD Occurring Between 30 Days After Second Dose and End of Part 1 (Year 1, Month 4–15), and over 12 Months After End of Part 1 (Year 2, M 16–27) Per Protocol Set Data

	TAK-003 VCD Cases[a]		Placebo VCD Cases[a]		Vaccine Efficacy, % (95% CI)	
	Year 1	Year 2	Year 1	Year 2	Year 1	Year 2
Overall	61/12 700 (0.5)	97/12 577 (0.8)	149/6316 (2.6)	106/6268 (1.8)	80.2 (73.3–85.3)	56.2 (42.3–66.8)
SP	[illegible]	[illegible]	[illegible]	[illegible]	82.2 (74.5–87.6)	60.3 (44.7–71.5)
SN	20/3531 (0.6)	33/3498 (1.0)	39/1726 (2.5)	29/1715 (1.8)	71.9 (57.0–85.4)	45.3 (9.9–66.8)
DENV-1	16/12 700 (0.1)	41/12 577 (0.3)	30/6316 (0.5)	49/6268 (0.8)	73.7 (51.7–85.7)	59.4 (38.5–73.2)
DENV-2	3/12 700 (< 0.1)	14/12 577 (0.1)	64/6316 (1.1)	27/6268 (0.4)	97.7 (92.7–99.3)	75.0 (52.3–86.9)
DENV-3	39/12 700 (0.3)	37/12 577 (0.3)	51/6316 (0.9)	26/6268 (0.4)	62.6 (43.3–75.4)	32.8 (–10.9 to 59.3
DENV-4	3/12 700 (< 0.1)	5/12 577 (< 0.1)	4/6316 (< 0.1)	4/6268 (< 0.1)	63.2 (–64.4 to 91.8)	41.2 (–119.0 to 84.2
SP						
DENV-1	7/9165 (< 0.1)	26/9077 (0.3)	17/4587 (0.4)	31/4552 (0.7)	79.8 (51.3–91.6)	59.1 (31.1–75.7)
DENV-2	3/9165 (< 0.1)	11/9077 (0.1)	42/4587 (1.0)	22/4552 (0.5)	96.5 (88.8–98.9)	75.5 (49.5–88.1)
DENV-3	28/9165 (0.3)	25/9077 (0.3)	47/4587 (1.1)	21/4552 (0.5)	71.4 (54.3–82.1)	44.9 (1.5–69.1)
DENV-4	3/9165 (< 0.1)	2/9077 (< 0.1)	4/4587 (< 0.1)	3/4552 (< 0.1)	63.8 (–61.8 to 91.9)	69.0 (–85.8 to 94.8
SN						
DENV-1	9/3531 (0.3)	15/3498 (0.4)	13/1726 (0.8)	18/1715 (1.1)	67.2 (23.2–86.0)	60.7 (22.1–80.2)
DENV-2	0/3531 (0)	3/3498 (< 0.1)	22/1726 (1.4)	5/1715 (0.3)	100 (–)	70.5 (–23.4 to 93.0
DENV-3	11/3531 (0.3)	12/3498 (0.3)	4/1726 (0.3)	5/1715 (0.3)	–38.7 (–335.7 to 55.8)	–18.5 (–236.2 to 58
DENV-4	0/3531 (0)	3/3498 (< 0.1)	0/1726 (0)	1/1715 (< 0.1)	…	–476 (–1319.1 to 8
Age 4–5 y	13/1619 (0.9)	30/1603 (1.9)	23/801 (3.2)	19/795 (2.5)	72.8 (46.4–86.2)	24.5 (–34.2 to 57.5)
Age 6–11 y	34/7009 (0.5)	55/6961 (0.8)	85/3491 (2.7)	67/3476 (2.0)	80.7 (71.3–87.0)	60.6 (43.8–72.4)
Age 12–16 y	14/4072 (0.4)	12/4013 (0.3)	41/2024 (2.2)	20/1997 (1.0)	83.3 (69.4–90.9)	71.2 (41.0–85.9)
SP						
Age 4–5 y	7/957 (0.8)	15/948 (1.6)	18/464 (4.3)	13/461 (3.0)	81.9 (56.6–92.4)	46.4 (–12.7 to 74.5)
Age 6–11 y	22/4806 (0.5)	39/4775 (0.8)	58/2423 (2.7)	48/2415 (2.1)	82.0 (70.7–89.0)	60.8 (40.2–71.3)

FU 3 yrs.

Table 2. Vaccine efficacy (95% CI) of TAK-003 in preventing VCD and hospitalized VCD during year 3 after the second dose (per protocol set data)

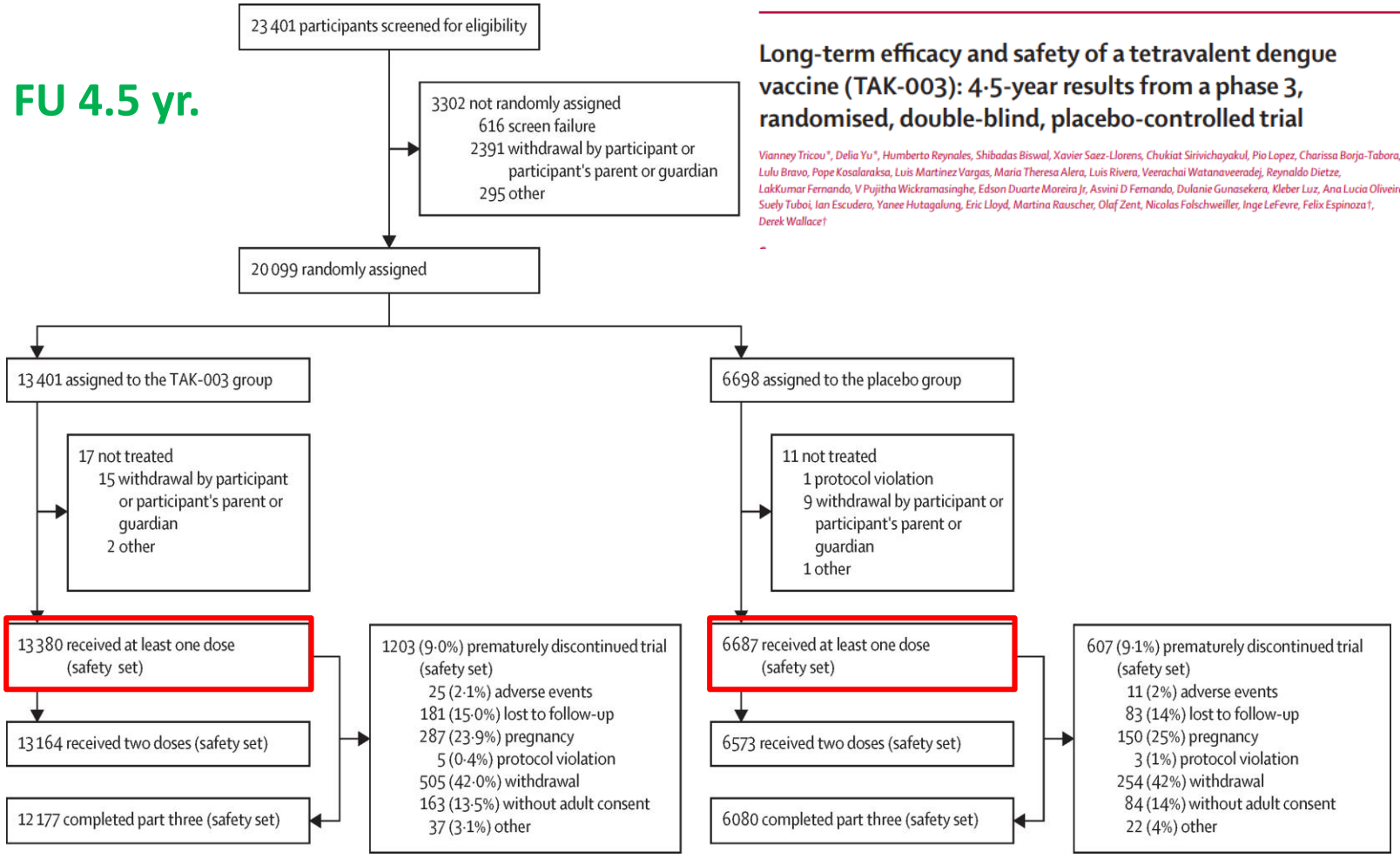
		Placebo (N = 6317)	TAK-003 (N = 12 704)	Efficacy % (95% CI)
VCD				
Overall		179/6201 (3.1)	208/12 435 (1.7)	44.7 (32.5–54.7)
SP		128/4502 (3.1)	139/8968 (1.6)	48.3 (34.2–59.3)
SN		51/1698 (3.2)	69/3465 (2.1)	35.5 (7.3–55.1)
SP	DENV-1	69/4502 (1.7)	77/8968 (0.9)	45.4 (24.5–60.6)
	DENV-2	34/4502 (0.8)	20/8968 (0.2)	72.1 (51.6–84.0)
	DENV-3	20/4502 (0.5)	37/8968 (0.4)	15.2 (–46.1 to 50.8)
	DENV-4	6/4502 (0.1)	5/8968 (<0.1)	61.9 (–24.9 to 88.4)
SN	DENV-1	28/1698 (1.8)	49/3465 (1.5)	17.2 (–31.8 to 47.9)
	DENV-2	16/1698 (1.0)	5/3465 (0.1)	84.9 (58.7–94.5)
	DENV-3	6/1698 (0.4)	11/3465 (0.3)	9.5 (–144.7 to 66.5)
	DENV-4	1/1698 (<0.1)	4/3465 (0.1)	–99.0 (–1680.3 to 77.8)
SP	4–5 y	16/457 (3.9)	34/941 (3.8)	2.5 (–76.6 to 46.2)
	6–11 y	75/2401 (3.4)	75/4743 (1.6)	51.9 (33.8–65.1)
	12–16 y	37/1644 (2.4)	30/3284 (0.9)	61.1 (37.1–76.0)
SN	4–5 y	16/331 (5.2)	17/652(2.8)	47.4 (–4.3 to 73.4)

Tricou V, *et al*. Lancet. 2020;395(10234):1434-1443. doi: 10.1016/S0140-6736(20)30556-0.
López-Medina E, *et al*. J Infect Dis. 2022;225(9):1521-1532. doi: 10.1093/infdis/jiaa761.
Rivera L, *et al*. Clin Infect Dis. 2022;75(1):107-117. doi: 10.1093/cid/ciab864.

FU 4.5 yr.

Long-term efficacy and safety of a tetravalent dengue vaccine (TAK-003): 4·5-year results from a phase 3, randomised, double-blind, placebo-controlled trial

Vianney Tricou, Delia Yu*, Humberto Reynales, Shibadas Biswal, Xavier Saez-Llorens, Chukiat Sirivichayakul, Pio Lopez, Charissa Borja-Tabora, Lulu Bravo, Pope Kosalaraksa, Luis Martinez Vargas, Maria Theresa Alera, Luis Rivera, Veerachai Watanaveeradej, Reynaldo Dietze, LakKumar Fernando, V Pujitha Wickramasinghe, Edson Duarte Moreira Jr, Asvini D Fernando, Dulanie Gunasekera, Kleber Luz, Ana Lucia Oliveira, Suely Tuboi, Ian Escudero, Yanee Hutagalung, Eric Lloyd, Martina Rauscher, Olaf Zent, Nicolas Folschweiller, Inge LeFevre, Felix Espinoza†, Derek Wallace†*



Tricou V, *et al*. Lancet Glob Health. 2024;12(2):e257-e270. doi: 10.1016/S2214-109X(23)00522-3.

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Vaccine Efficacy (TAK-003) in Prevention of Virologically Confirmed Dengue

Follow up	1 year (95% CI)	1.5 year (95% CI)	2 years (95% CI)	3 years (95% CI)	4.5 years (95% CI)
Overall	80.2% (73.3-85.3)	73.3% (66.5-78.8)	56.2% (42.3-66.8)	44.7% (32.5-54.7)	61.2% (56.0-65.8)
Seropositive	82.2% (74.5-87.6)	76.1% (68.5-81.9)	60.3% (44.7-71.5)	48.3% (34.2-59.3)	64.2% (58.9-70.1)
Seronegative	74.9% (57.0-85.4)	66.2% (49.1-77.5)	45.3% (9.9-66.8)	35.5% (7.3-55.1)	53.5% (41.6-62.9)
DENV-1	73.7% (51.7-85.7)	69.8% (54.8-79.9)	59.4% (38.5-73.2)	NA	NA
DENV-2	97.7% (92.7-99.3)	95.1% (89.9-97.6)	75.0% (52.3-86.9)	NA	NA
DENV-3	62.6% (43.3-75.4)	48.9% (27.2-64.1)	32.8% (-10.9-59.3)	NA	NA
DENV-4	63.2% (-64.6-91.8)	51.0% (-69.4-85.8)	41.2% (-119.0-84.2)	NA	NA

Biswal S, *et al*. N Engl J Med 2019; 381:2009-2019.
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Vaccine Efficacy (TAK-003) in Prevention of Virologically Confirmed Dengue

Follow up	1 year (95% CI)	1.5 year (95% CI)	2 years (95% CI)	3 years (95% CI)	4.5 years (95% CI)
Seropositive					
DENV-1	79.8% (51.3-91.6)	72.0% (52.2-83.6)	59.1% (31.1-75.7)	45.4% (24.5-60.6)	56.1% (44.6-65.2)
DENV-2	96.5% (88.8-98.9)	93.7% (86.1-97.1)	75.5% (49.5-88.1)	72.1% (51.6-84.0)	80.4% (73.1-85.7)
DENV-3	71.4% (54.3-82.1)	61.8% (43.0-74.4)	44.9% (1.5-69.1)	15.2% (-46.1-50.8)	52.3% (36.7-64.0)
DENV-4	63.8% (-61.8-91.9)	61.2% (-44.3-89.6)	69.0% (-85.8-94.8)	61.9% (-24.9-88.4)	70.6% (39.9-85.6)
Seronegative					
DENV-1	67.2% (23.2-86.0)	67.8% (40.3-82.6)	60.7% (22.1-80.2)	17.2% (-31.8-47.9)	45.4% (26.1-59.7)
DENV-2	100% (-)	98.1% (85.8-99.7)	70.5% (-23.4-93.0)	84.9% (58.7-94.5)	88.1% (78.6-93.3)
DENV-3	-38.7% (-335.7-55.8)	-68.2% (-318.9-32.4)	-18.5% (-236.2-58.3)	9.5% (-144.7-66.5)	-15.5% (-108.2-35.9)
DENV-4	-	-	-47.6 (-1319.1-84.6)	-99.0 (-1680.3-77.8)	-105.6 (-628.7-42.0)

Biswal S, *et al*. N Engl J Med 2019; 381:2009-2019.
Tricou V, *et al*. Lancet. 2020;395(10234):1434-1443. doi: 10.1016/S0140-6736(20)30556-0.
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Vaccine Efficacy (TAK-003) in Prevention of Hospitalized Virologically Confirmed Dengue

Follow up	1 year (95% CI)	1.5 year (95% CI)	2 years (95% CI)	3 years (95% CI)	4.5 years (95% CI)
Overall	95.4% (88.4-98.2)	90.4% (82.6-94.7)	76.1% (50.8-88.4)	70.8% (49.6-83.0)	84.1% (77.8-88.6)
Seropositive	94.4% (84.3-98.0)	91.4% (NA)	85.2% (59.6-94.6)	78.4% (57.1-89.1)	85.9% (78.7-90.7)
DENV-1	NA	NA	NA	71.6% (21.7-89.7)	NA
DENV-2	NA	NA	NA	89.4% (51.1-97.7)	NA
DENV-3	NA	NA	NA	69.6% (-7.9-91.4)	NA
DENV-4	NA	NA	NA	100% (NE-NE)	NA
Seronegative	97.2% (79.1-99.6)	88.1% (NA)	51.4% (-50.7-84.3)	45.0% (-42.6-78.8)	79.3% (63.5-88.2)
DENV-1	NA	NA	NA	80.6% (-0.1-96.2)	NA
DENV-2	NA	NA	NA	100% (NE-NE)	NA
DENV-3	NA	NA	NA	-246.6% (-2716.1-57.3)	NA
DENV-4	NA	NA	NA	NE	NA

Biswal S, *et al*. N Engl J Med 2019; 381:2009-2019.
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Vaccine Efficacy (TAK-003) in Prevention of Hospitalized Virologically Confirmed Dengue

Follow up	1 year (95% CI)	1.5 year (95% CI)	2 years (95% CI)	3 years (95% CI)	4.5 years (95% CI)
DHF	87.3% (-13.5-98.6)	NA	81.2% (29.3-95.0)	NA	NA
Seropositive	NA	91.7% (30.9-99.0)	NA	NA	80.9% (46.3-93.2)
Seronegative	NA	49.4% (-709.2-96.8)	NA	NA	-3.4% (-464.7-81.1)
Severe dengue	NA	NA	66.9% (-97.8-94.5)	NA	NA
Seropositive	NA	NA	NA	NA	90.1% (15.3-98.8)
Seronegative	NA	NA	NA	NA	NE
DHF or Severe dengue	NA	NA	NA	NA	NA
Seropositive	NA	NA	NA	NA	85.4% (60.3-94.6)
Seronegative	NA	NA	NA	NA	-29.2% (-566.1-74.9)

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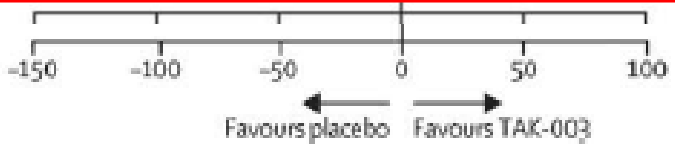
Long-term efficacy and safety of a tetravalent dengue vaccine (TAK-003): 4·5-year results from a phase 3, randomised, double-blind, placebo-controlled trial

Vianney Tricou*, Delia Yu*, Humberto Reynales, Shibadas Biswal, Xavier Saez-Llorens, Chukiat Sirivichayakul, Pio Lopez, Charissa Borja-Tabora,

Tricou V, *et al*. Lancet Glob Health. 2024;12(2):e257-e270. doi: 10.1016/S2214-109X(23)00522-3.

A Virologically confirmed dengue

	n/N (%)		Efficacy, % (95% CI)
	Placebo	TAK-003	
Overall	**547/6687 (8·2%)**	**442/13 380 (3·3%)**	**61·2 (56·0 to 65·8)**
Seropositive	394/4854 (8·1%)	295/9663 (3·1%)	64·2 (58·4 to 69·2)
DENV-1	151/4854 (3·1%)	133/9663 (1·4%)	56·1 (44·6 to 65·2)
DENV-2	135/4854 (2·8%)	54/9663 (0·6%)	80·4 (73·1 to 85·7)
DENV-3	97/4854 (2·0%)	96/9663 (1·0%)	52·3 (36·7 to 64·0)
DENV-4	20/4854 (0·4%)	12/9663 (0·1%)	70·6 (39·9 to 85·6)
Seronegative	153/1832 (8·4%)	147/3714 (4·0%)	53·5 (41·6 to 62·9)
DENV-1	79/1832 (4·3%)	89/3714 (2·4%)	45·4 (26·1 to 59·7)
DENV-2	58/1832 (3·2%)	14/3714 (0·4%)	88·1 (78·6 to 93·3)
DENV-3	16/1832 (0·9%)	36/3714 (1·0%)	−15·5 (−108·2 to 35·9)
DENV-4	3/1832 (0·2%)	12/3714 (0·3%)	−105·6 (−628·7 to 42·0)



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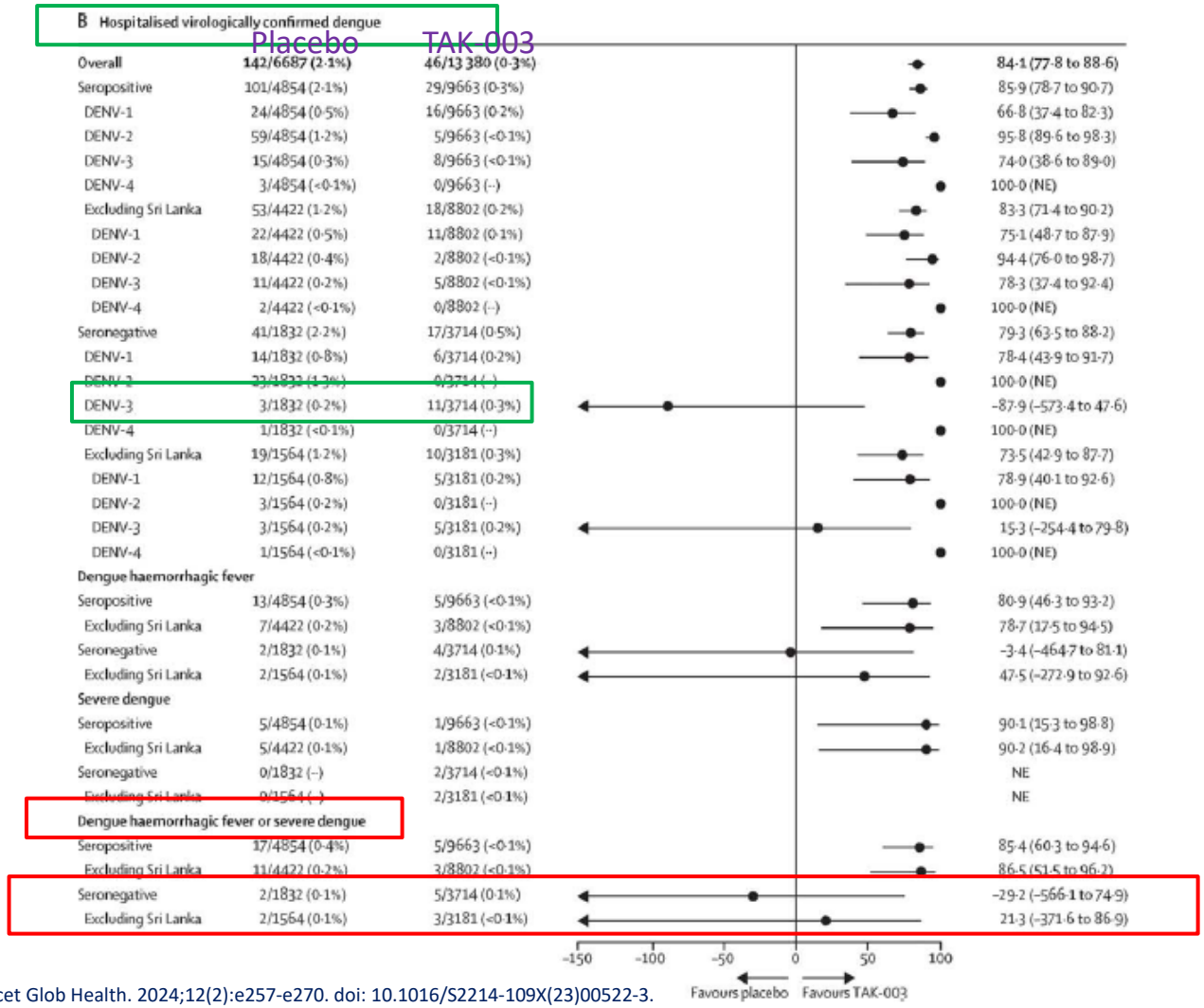

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Comment

TAK-003 dengue vaccine as a new tool to mitigate dengue in countries with a high disease burden

See Articles page e257

Dengue, an arboviral disease of the tropics and subtropics, is caused by infection with one of four distinct serotypes of the dengue virus (DENV-1, DENV-2, DENV-3, and DENV-4).[1] We have seen an exponential increase in dengue incidence over the past few decades, surpassing the growth rate of other communicable diseases, a trend anticipated to continue, fuelled by urbanisation with high population densities, global mobility, and climate change.[2] Dengue incidence is concentrated in southeast and south Asia, with Latin America following closely. The proportion of dengue-related febrile episodes necessitating hospitalisation is 19% in Asia and 11% in Latin America.[1]

The quest for an effective dengue has encountered substantial obstacles, primarily due to the immunological interaction between the four dengue virus serotypes. Therefore, phase 3 clinical trial designs require baseline blood samples of all trial participants to enable determination of serostatus before vaccination. Determining vaccine efficacy for dengue vaccines is complex because there are eight possible scenarios, with four serotypes in combination with seronegative versus seropositive baseline status. This is further complicated

The efficacy trial was done over 5 years, recruiting more than 20 000 children and adolescents (4–16 years of age) residing in dengue-endemic countries in Asia and Latin America. The dengue seroprevalence (the proportion of dengue seropositive people) in the study population before vaccination was approximately 70%, and the predominant circulating strains were serotypes 1 and 2. Despite the 5 year observation period, there was low circulation of serotypes 3 and 4, so that some of the uncertainties identified regarding serotype-stratified efficacy in seronegative people in the earlier interim analyses could not be addressed.

In this study population and study setting, the cumulative vaccine efficacy of TAK-003 over 5 years against virologically confirmed dengue was 61·2% (95% CI 56·0–65·8) and against dengue-related hospitalisations was 84·1% (77·8–88·6). Vaccine efficacy varied by serostatus and serotype, with higher vaccine efficacy in people with a baseline seropositive serostatus compared with people with baseline seronegative serostatus. Vaccine efficacy was highest against DENV-2, both in seropositive and seronegative people.

For individuals who were seropositive at baseline, TAK-003 demonstrated safety and efficacy against all four

- For individuals who were seropositive at baseline, TAK-003 demonstrated safety and efficacy against all four DENV serotypes, showing the greatest vaccine efficacy against DENV-2.
- The vaccine did not show a reduction in virologically confirmed dengue and dengue hospitalizations caused by DENV-3 in dengue-naive participants, with further uncertainties around DENV-4.
- There were higher rates of symptomatic as well as hospitalized DENV-3 cases among seronegative vaccinated people than among seronegative unvaccinated people, but this excess was small and not statistically significant.

Wilder-Smith A. Lancet Glob Health. 2024;12(2):e179-e180. doi: 10.1016/S2214-109X(23)00590-9.

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Comment

TAK-003 dengue vaccine as a new tool to mitigate dengue in countries with a high disease burden

Dengue, an arboviral disease of the tropics and subtropics, is caused by infection with one of four distinct serotypes of the dengue virus (DENV-1, DENV-2, DENV-3, and DENV-4).[1] We have seen an exponential increase in dengue incidence over the past few decades, surpassing the growth rate of other communicable diseases, a trend anticipated to continue, fuelled by urbanisation with high population densities, global mobility, and climate change.[2] Dengue incidence is concentrated in southeast and south Asia, with Latin America following closely. The proportion of dengue-related febrile episodes necessitating hospitalisation is 19% in Asia and 11% in Latin America.[1]

The quest for an effective dengue has encountered substantial obstacles, primarily due to the immunological interaction between the four dengue virus serotypes. Therefore, phase 3 clinical trial designs require baseline blood samples of all trial participants to enable determination of serostatus before vaccination. Determining vaccine efficacy for dengue vaccines is complex because there are eight possible scenarios, with four serotypes in combination with seronegative versus seropositive baseline status. This is further complicated

The efficacy trial was done over 5 years, recruiting more than 20 000 children and adolescents (4–16 years of age) residing in dengue-endemic countries in Asia and Latin America. The dengue seroprevalence (the proportion of dengue seropositive people) in the study population before vaccination was approximately 70%, and the predominant circulating strains were serotypes 1 and 2. Despite the 5 year observation period, there was low circulation of serotypes 3 and 4, so that some of the uncertainties identified regarding serotype-stratified efficacy in seronegative people in the earlier interim analyses could not be addressed.

In this study population and study setting, the cumulative vaccine efficacy of TAK-003 over 5 years against virologically confirmed dengue was 61·2% (95% CI 56·0–65·8) and against dengue-related hospitalisations was 84·1% (77·8–88·6). Vaccine efficacy varied by serostatus and serotype, with higher vaccine efficacy in people with a baseline seropositive serostatus compared with people with baseline seronegative serostatus. Vaccine efficacy was highest against DENV-2, both in seropositive and seronegative people.

For individuals who were seropositive at baseline, TAK-003 demonstrated safety and efficacy against all four

Wilder-Smith A. Lancet Glob Health. 2024;12(2):e179-e180. doi: 10.1016/S2214-109X(23)00590-9.

- In September 2023, WHO's Strategic Advisory Group of Experts on Immunization (SAGE) addressed this question.
- SAGE came to the conclusion that pre-vaccination screening would significantly reduce the public health impact of TAK-003.
- Pre-vaccination screening has limited sensitivity and would exclude seropositive people who would benefit from vaccination.
- In contrast to Dengvaxia, where all seronegative people were at increased risk for severe dengue.
- TAK-003, there is a statistically significant protection in seronegative people for two of the four serotypes (DENV-1 and DENV-2).
- Pre-vaccination screening would unnecessarily increase the complexities and costs of roll-out and, hence, vaccine uptake. SAGE endorsed the use of TAK-003 without pre-vaccination screening.
- However, the policy recommendation is targeted for use in high disease burden settings only, as vaccine performance is higher in such populations and any potential, not yet proven, risk in a subset of seronegative people exposed to DENV-3 and DENV-4, would be mitigated.

WHO recommendations for endemic areas

- In September 2023, WHO officially recommended that countries should consider introducing TAK-003 vaccine into their routine immunization programs for age 6–16 years, but only in high-risk geographic locations.
- Specific locations should be decided at the national level until the efficacy-risk profile in seronegative persons for DENV3 and DENV4 has been more precisely assessed, WHO does not recommend the programmatic use of this vaccine in low to moderate dengue transmission settings.

Freedman DO. J Travel Med. 2023;30(7):taad132. doi: 10.1093/jtm/taad132. PMID: 37847608.

WHO recommendations for endemic areas

Administration considerations:

- Two-doses subcutaneously to be spaced at a minimum interval of 3 months.
- TAK-003 is not recommended for pregnant women, and women of childbearing potential should avoid pregnancy for at least 1 month following vaccination.
- TAK-003 is contraindicated in persons with congenital or acquired immune deficiency, including immunosuppressive therapies within 4 weeks prior to vaccination
- TAK-003 is contraindicated in persons with symptomatic HIV or with asymptomatic HIV and laboratory or other evidence of impaired immune function.
- No current recommendation has been made for a booster dose due to lack of data.
- Co-administration of TAK-003 with yellow fever and hepatitis A vaccines is supported by data.
- Countries could consider coadministration with other inactivated, sub-unit or messenger RNA vaccines, except for live vaccines (pending more data).

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Thank you for your attention

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