Clinical Manifestations, Diagnosis and Treatment of Dengue Fever

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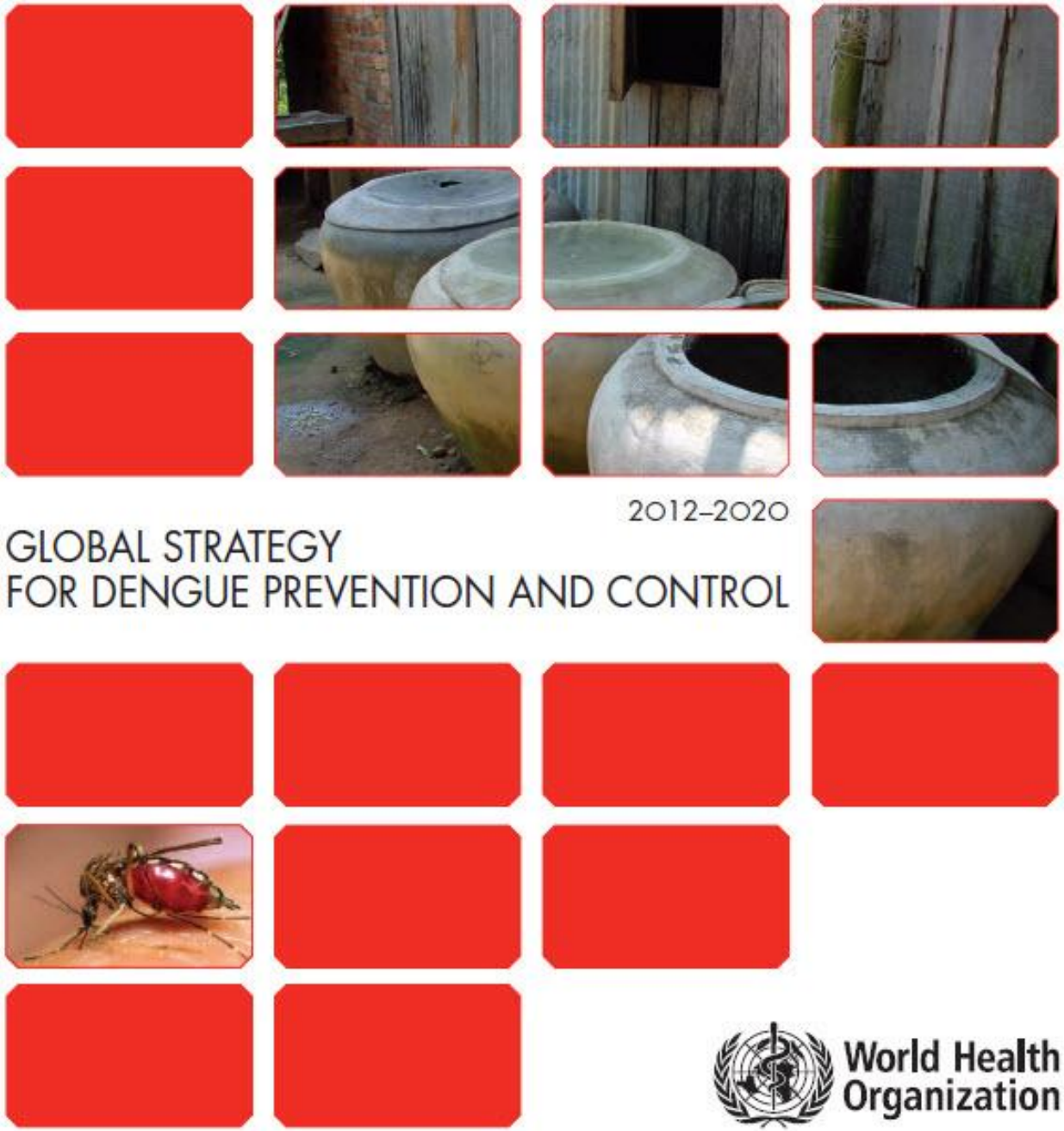
Section of infectious diseases

Department of Internal Medicine

Chi Mei Hospital



ASEAN DENGUE DAY

12 June 2013 | Geneva --The World Health Organization (WHO) joins the Association of Southeast Asian Nations (ASEAN) to observe ASEAN Dengue Day on 14 June 2013.

Number of suspected or laboratory-confirmed dengue cases notified to WHO, 1990–2015

- 撒哈拉以南非洲地區（AFRO）
- 東地中海地區（EMRO）
- 西太平洋地區(WPRO)

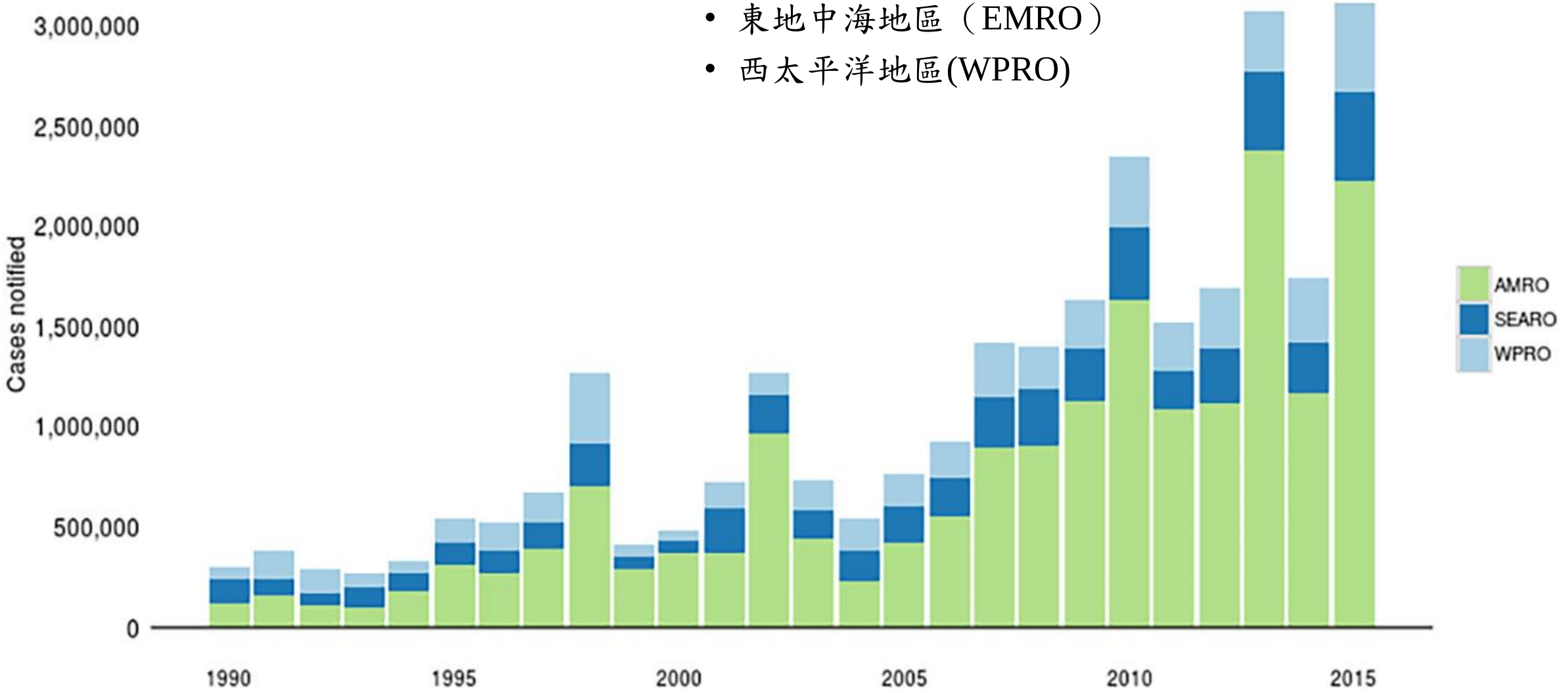
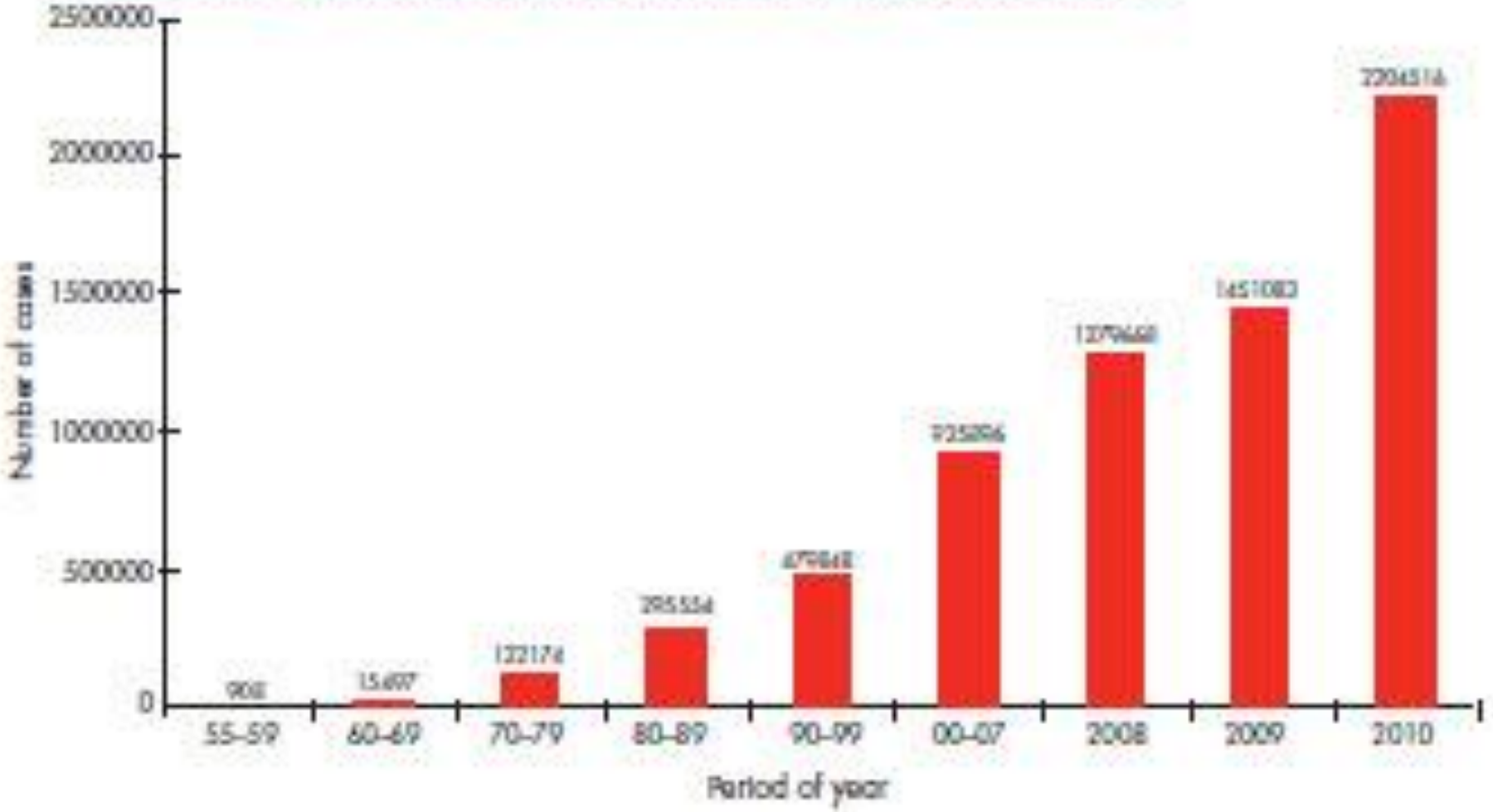
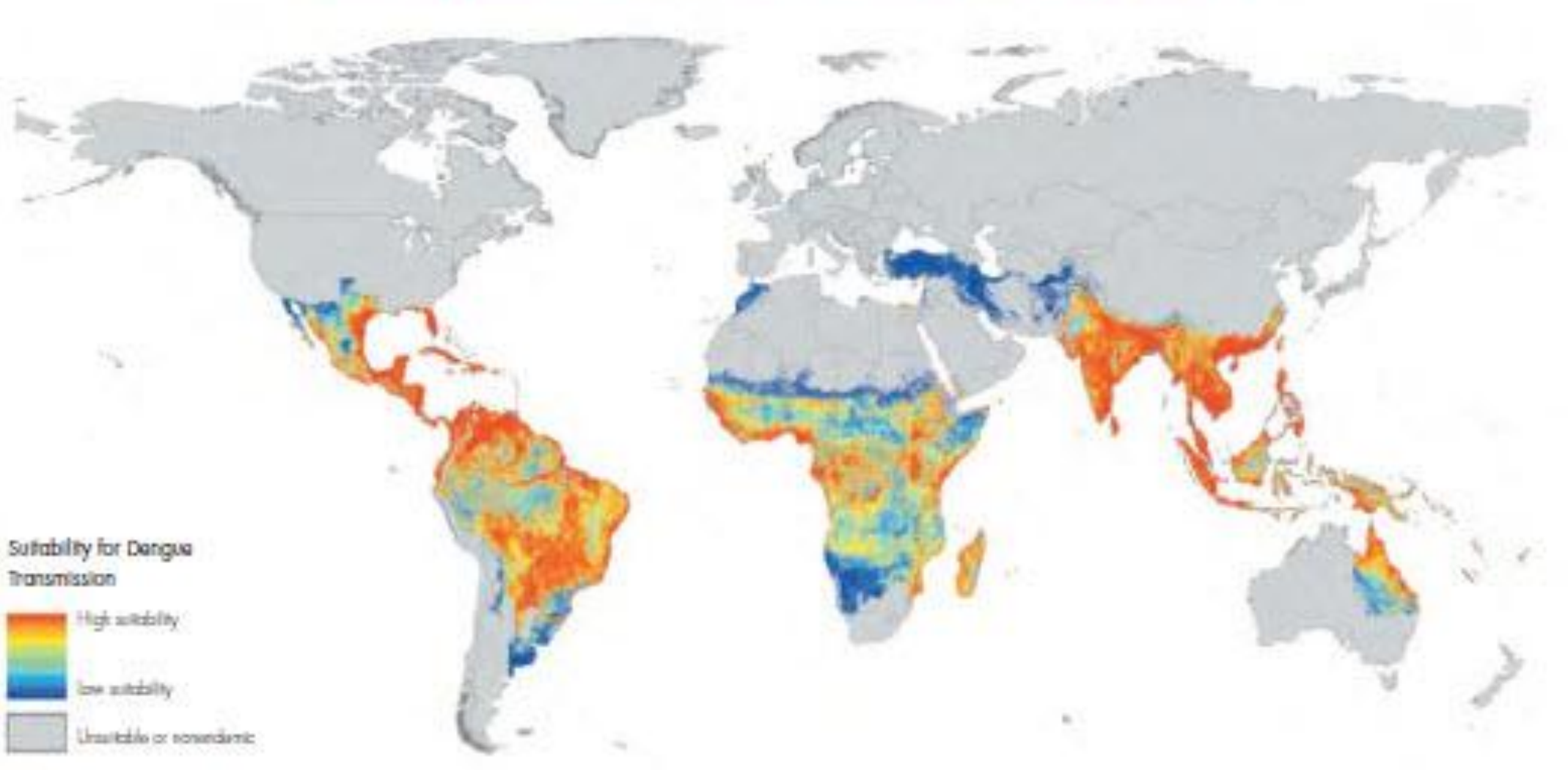


Figure 1. Average number of dengue and severe dengue cases reported to WHO annually in 1955–2007 and number of cases reported in recent years, 2008–2010

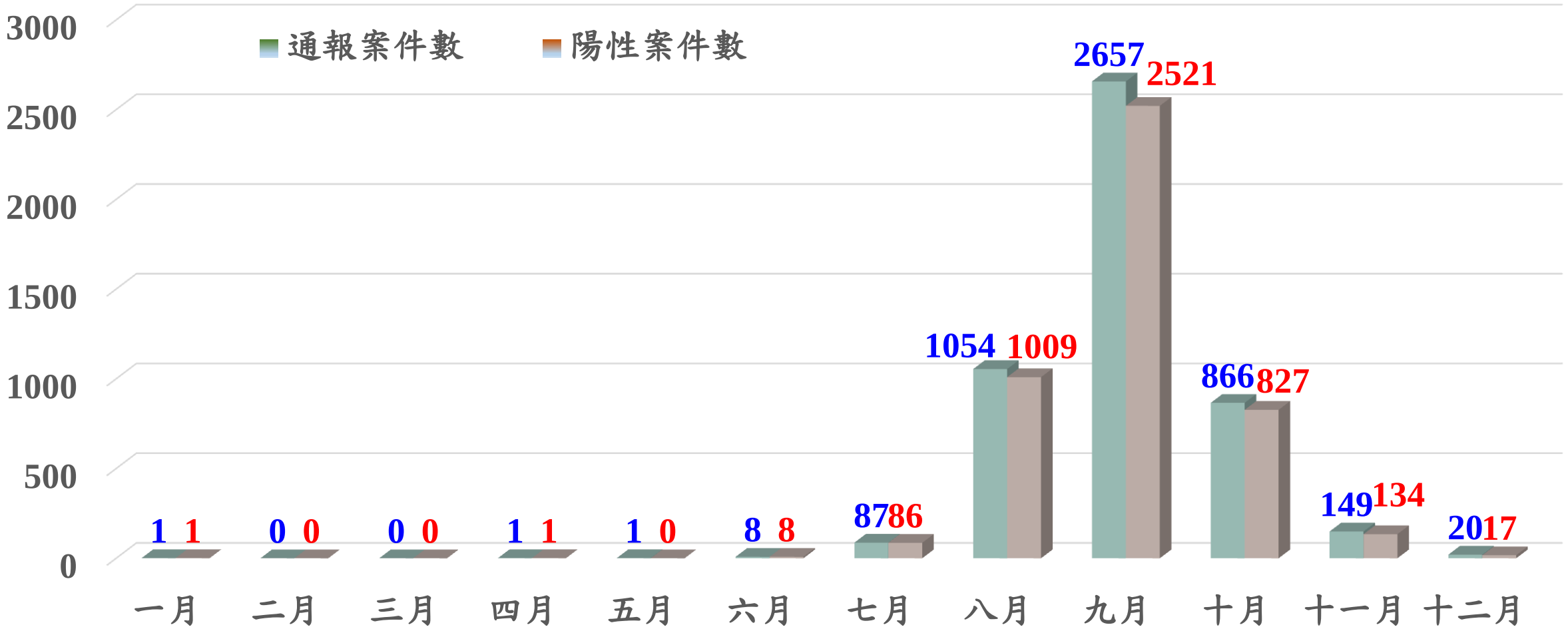


12 June 2013 | Geneva --The World Health Organization (WHO) joins the Association of Southeast Asian Nations (ASEAN) to observe ASEAN Dengue Day on 14 June 2013.

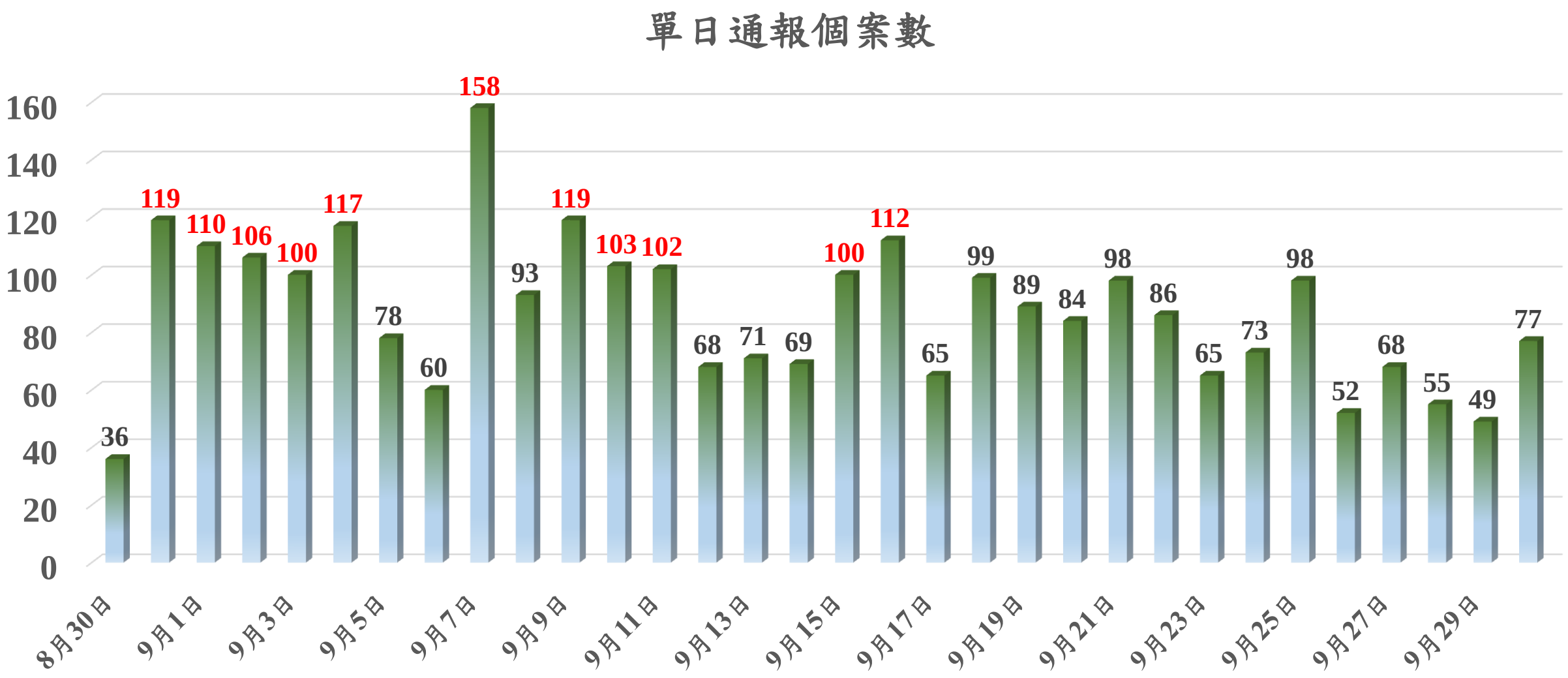
Figure 2. Distribution of global dengue risk (determination of risk status based on combined reports from WHO, the United States Centers for Disease Control and Prevention, Gideon online, ProMED, DengueMap, Eurosurveillance and published literature (Simmons CP et al, 2012).



104年度通報登革熱病例數_以奇美醫院為例



104年8~9月單日通報登革熱病例數_以奇美醫院為例

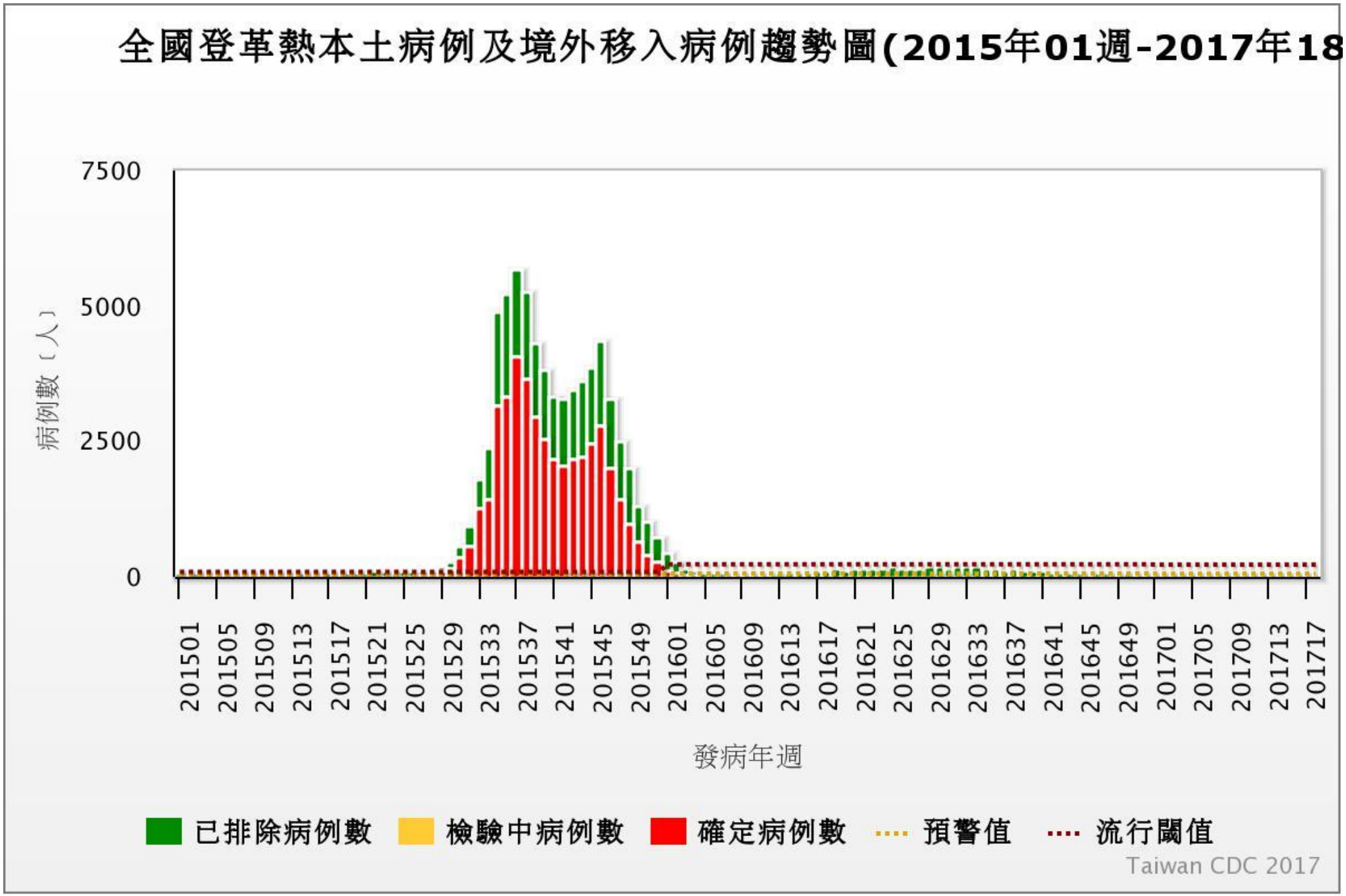


登革熱住院病人累計人數調查表

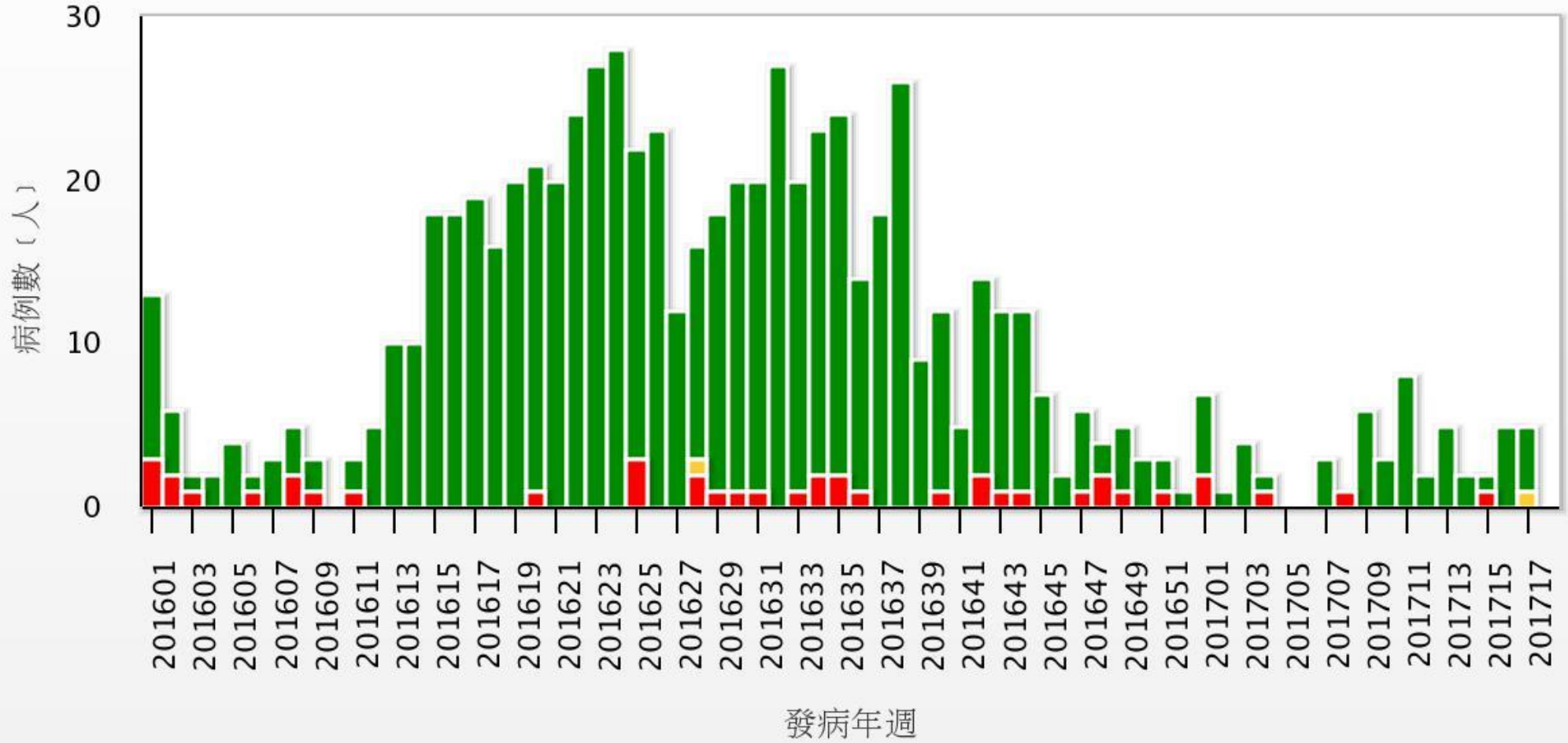
	累計住院人數	累計住院人數動向統計					急診留觀人數
		出院	一般病床	ICU	死亡	其他	
9/10	819	673	121	16	7	2 (RCC及嬰兒病床)	33
9/11	861	700	135	17	7	2 (RCC及嬰兒病床)	20
9/12	887	723	137	18	7	2 (RCC及嬰兒病床)	13
9/13	894	728	141	17	7	1(RCC)	25
9/14	930	785	123	14	7	1(RCC)	21
9/15	945	815	112	10	7	1(RCC)	23
9/16	969	850	99	12	7	1(RCC)	23
9/17	983	869	93	13	7	1(RCC)	27
9/18	1011	895	94	13	8	1(RCC)	29
9/19	1055	911	122	13	8	1(RCC)	12
9/20	1072	913	136	14	8	1(RCC)	31

登革熱病人每日動態調查表

	急診留觀人數	一般病床	ICU	總住院人數
9/10	16	128	12	140
9/11	33	124	12	136
9/12	20	145	17	162
9/13	13	114	18	132
9/14	25	141	17	158
9/15	21	131	13	144
9/16	23	118	7	125
9/17	23	103	12	115
9/18	27	97	13	110
9/19	29	87	13	100
9/20	12	109	13	122
9/21	31	104	14	118

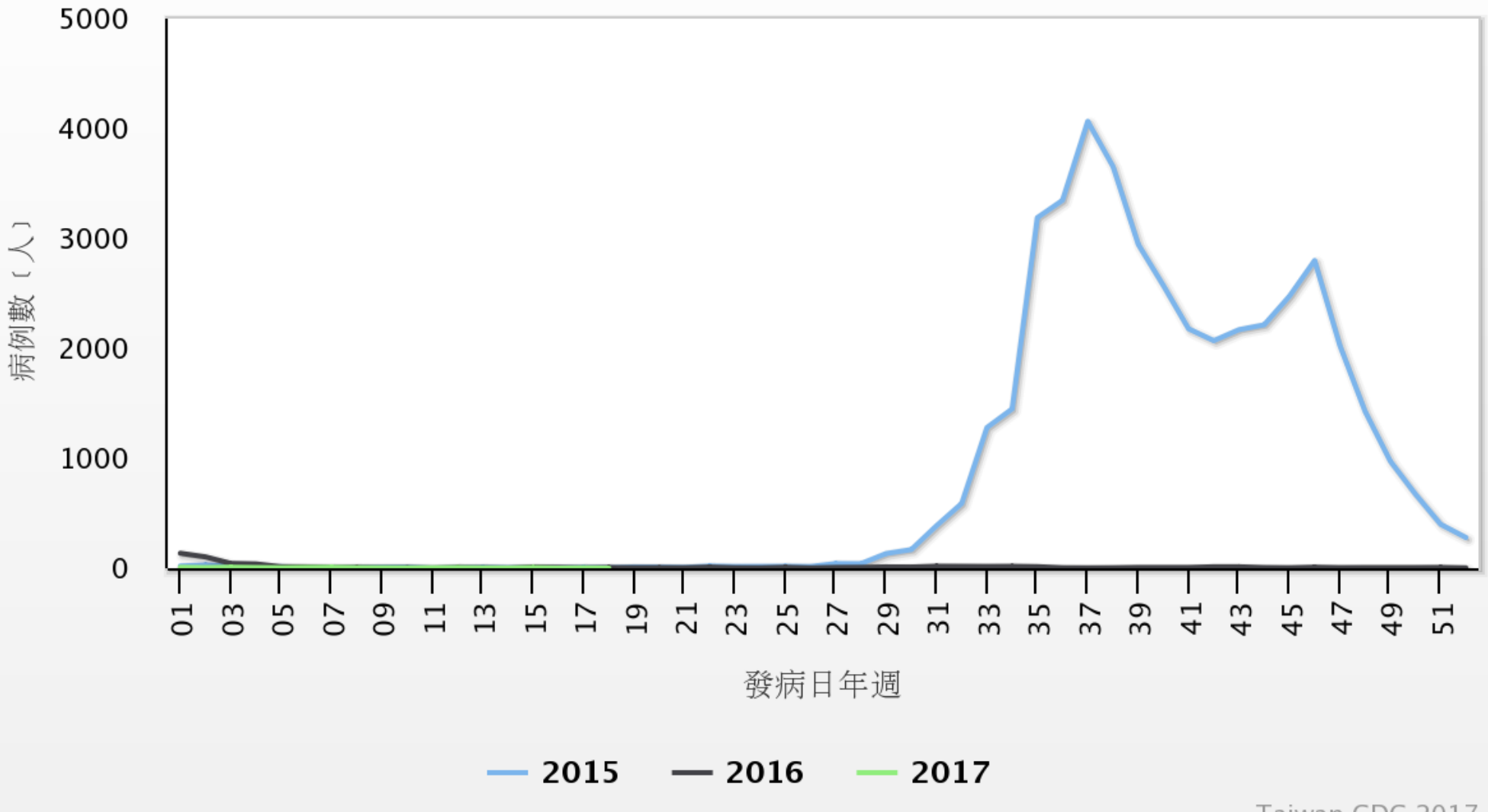

全國登革熱本土病例及境外移入病例趨勢圖(2015年01週-2017年18
7500
5000
2500
0
病例數〔人〕
201501
201505
201509
201513
201517
201521
201525
201529
201533
201537
201541
201545
201549
201601
201605
201609
201613
201617
201621
201625
201629
201633
201637
201641
201645
201649
201701
201705
201709
201713
201717
發病年週
已排除病例數
檢驗中病例數
確定病例數
預警值
流行閾值
Taiwan CDC 2017

南區台南市登革熱本土病例及境外移入病例趨勢圖(2016年01週-2017年18週)



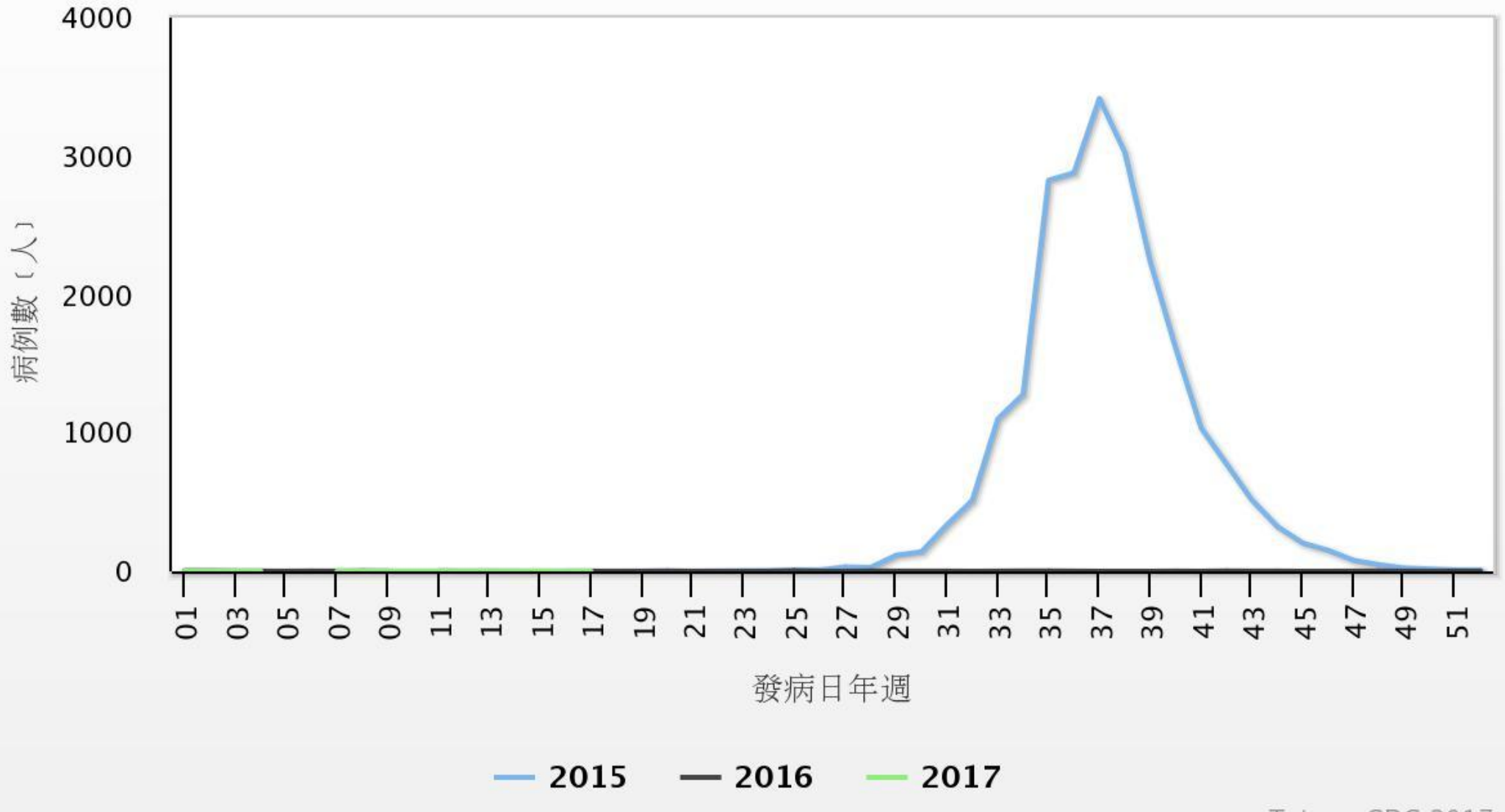
Taiwan CDC 2017

全國登革熱本土病例及境外移入病例同期比較趨勢圖(2015年01週-2017年18週)



Taiwan CDC 2017

南區台南市登革熱本土病例及境外移入病例同期比較趨勢圖(2015年01週-2017年18週)



Taiwan CDC 2017

資料來源


防疫學苑系列 015
登革熱
臨床症狀・診斷與治療
Clinical Manifestations, Diagnosis and Treatment of Dengue Fever
衛生福利部疾病管制署 編著・出版
2015年5月

登革熱的簡介

- 俗稱「天狗熱」或「斷骨熱」
  - 病媒蚊叮咬而感染的急性傳染病
    - 南臺灣以埃及斑蚊為主要病媒蚊
  - 主要症狀為發燒、出疹、肌肉骨骼疼痛…等
- 屬第二類法定傳染病， 24小時內要通報

病媒蚊及登革病毒傳播模式

- Dengue virus: Flaviviridae（Flavivirus)
- RNA virus，直徑約40~50 nm，基因大小約11 kb，主要製造3 種病毒結構蛋白和7 種非結構蛋白
- 依抗原性可分為Ⅰ、Ⅱ、Ⅲ、Ⅳ型
  - The fifth variant DENV-5 has been isolated in October 2013
- 病媒蚊: 埃及斑蚊/白線斑蚊
- 室內或住家積水容器
- 局部的淋巴結內繁殖: 淋巴系統和血行傳播

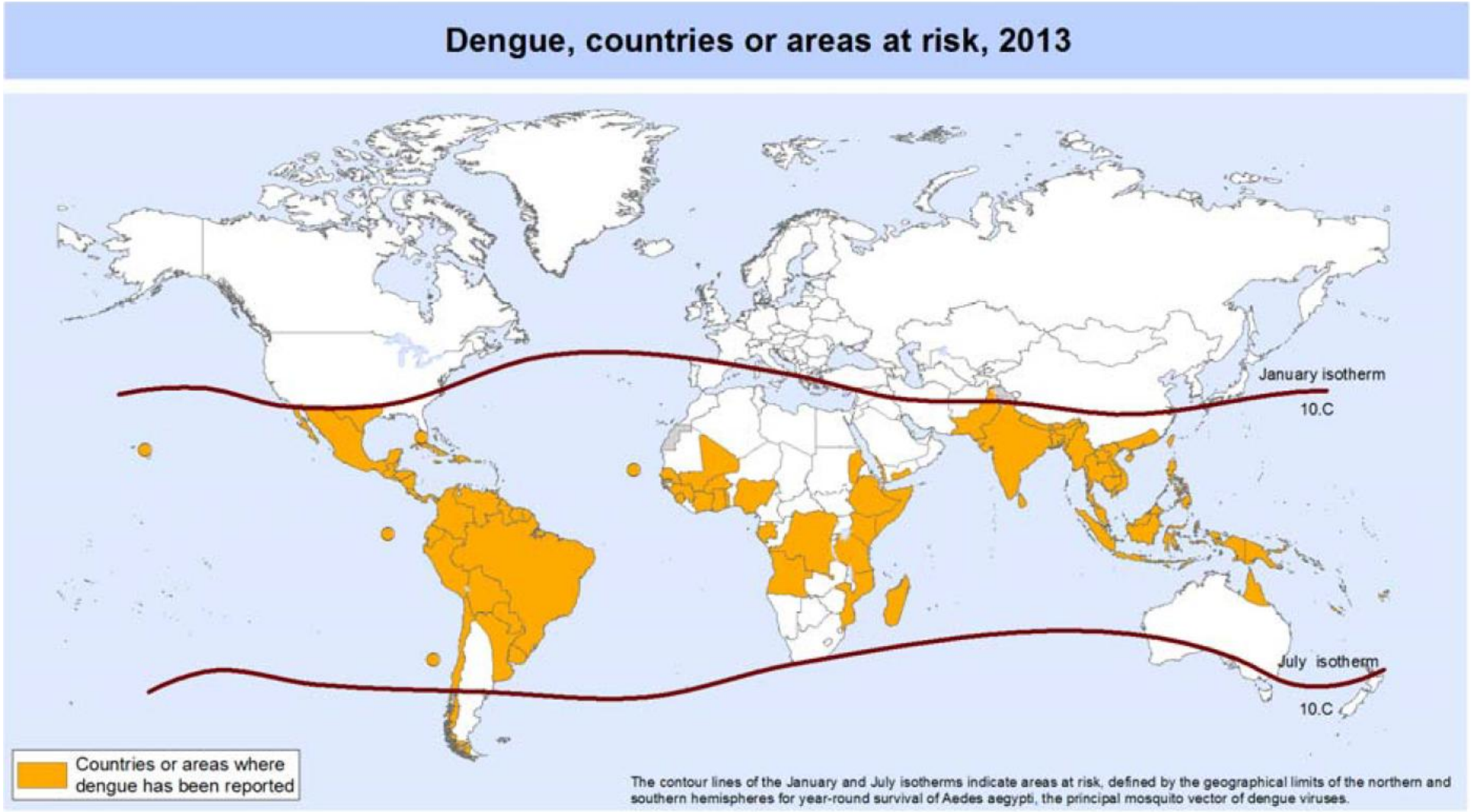
Type 5 DF

The fifth variant DENV-5 has been isolated in October 2013

- This serotype follows the sylvatic cycle unlike the other four serotypes which follow the human cycle. The likely cause of emergence of the new serotype could be genetic recombination, natural selection and genetic bottlenecks.
- There is no indication of the presence of DENV-5 in India. Recent clinical trials with the promising Chimerivax tetravalent vaccine suffered a setback.
- Discovery of DENV-5 and more such sylvatic strains in future may further impede the Dengue Vaccine Initiative.
- Integrated Vector Management holds the key to sustainable dengue control.

Ref.1 Med J Armed Forces India.2015 Jan;71(1):67-70. Epub 2014 Nov 24. **Discovery of fifth serotype of dengue virus (DENV-5): A new public health dilemma in dengue control.** Mustafa MS et al. Ref.2 Science. 2013;342:415 Surprising new dengue virus throws a spanner in disease control efforts Normile D.

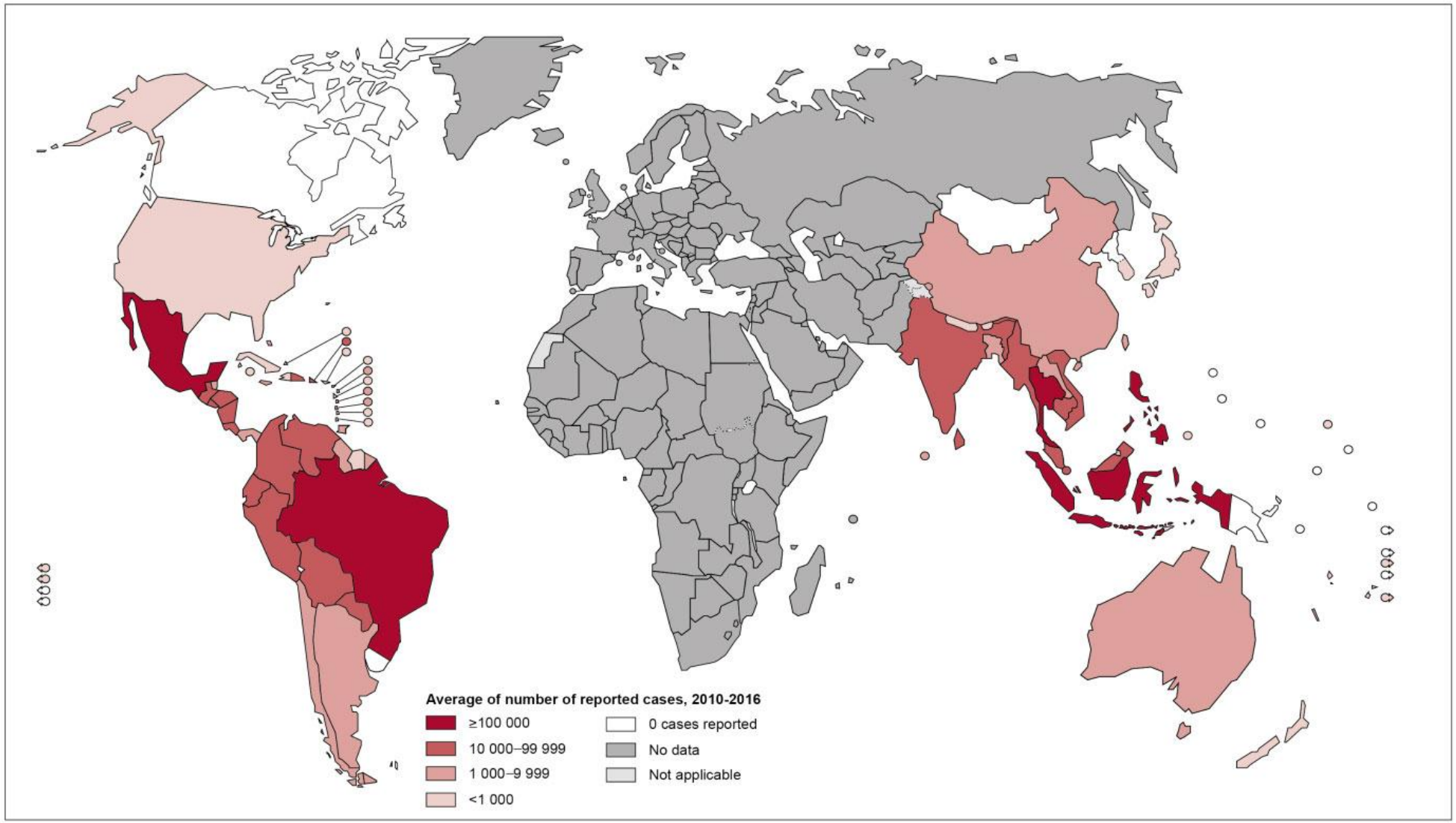
全球登革熱流行分佈圖



Data Source: World Health Organization
Map Production: Health Statistics and Information Systems (HSI)
World Health Organization

World Health Organization

Distribution of dengue, worldwide, 2016



Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization

World Health Organization

典型登革熱

- 突發性高燒（體溫驟升至39~40℃，持續5~6 天）
- 畏寒、頭痛、四肢酸痛、骨關節酸痛、肌肉痛、背痛、後眼窩痛、畏光、虛弱及全身倦怠。
- 臉部潮紅、眼皮水腫、結膜充血、味覺改變、噁心、嘔吐、食慾不振及肝腫大，但脾腫大則不常見。
- 發燒及全身症狀約3~4 天後消失，部份病人會在體溫下降後再度上升，即雙峰型發燒，發燒後期可能會出現斑疹，尤其是下肢。
- 有些會在第3~4 日出現短暫性皮疹，在發燒將退時出現皮疹，特徵為「紅海中的白島」引起全身發癢。
- 其他較少見的症狀，則包括喉嚨痛、相對性緩脈及中樞神經症狀等。

皮疹變化

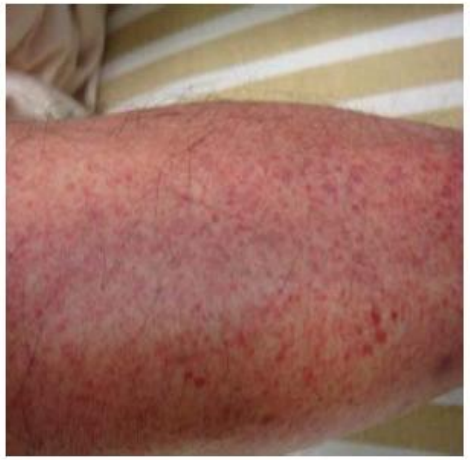


圖 4 皮下點狀出血

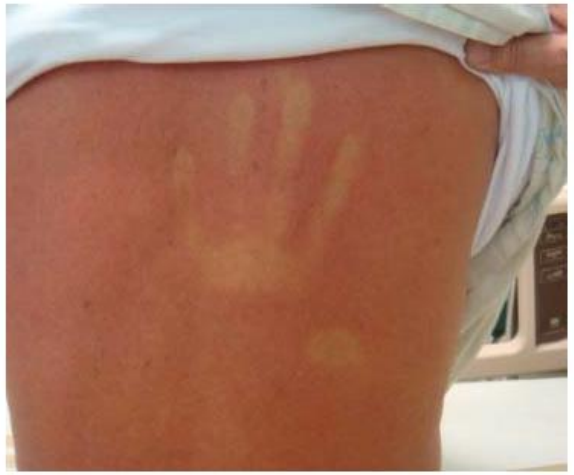


圖 5 融合性紅色丘疹

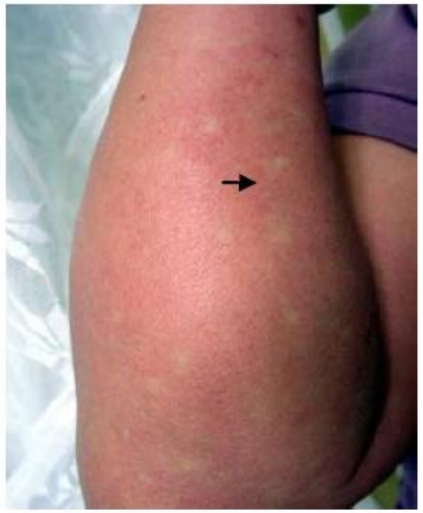


圖 6 登革熱皮疹： White islands in a red sea

眼部臨床表徵

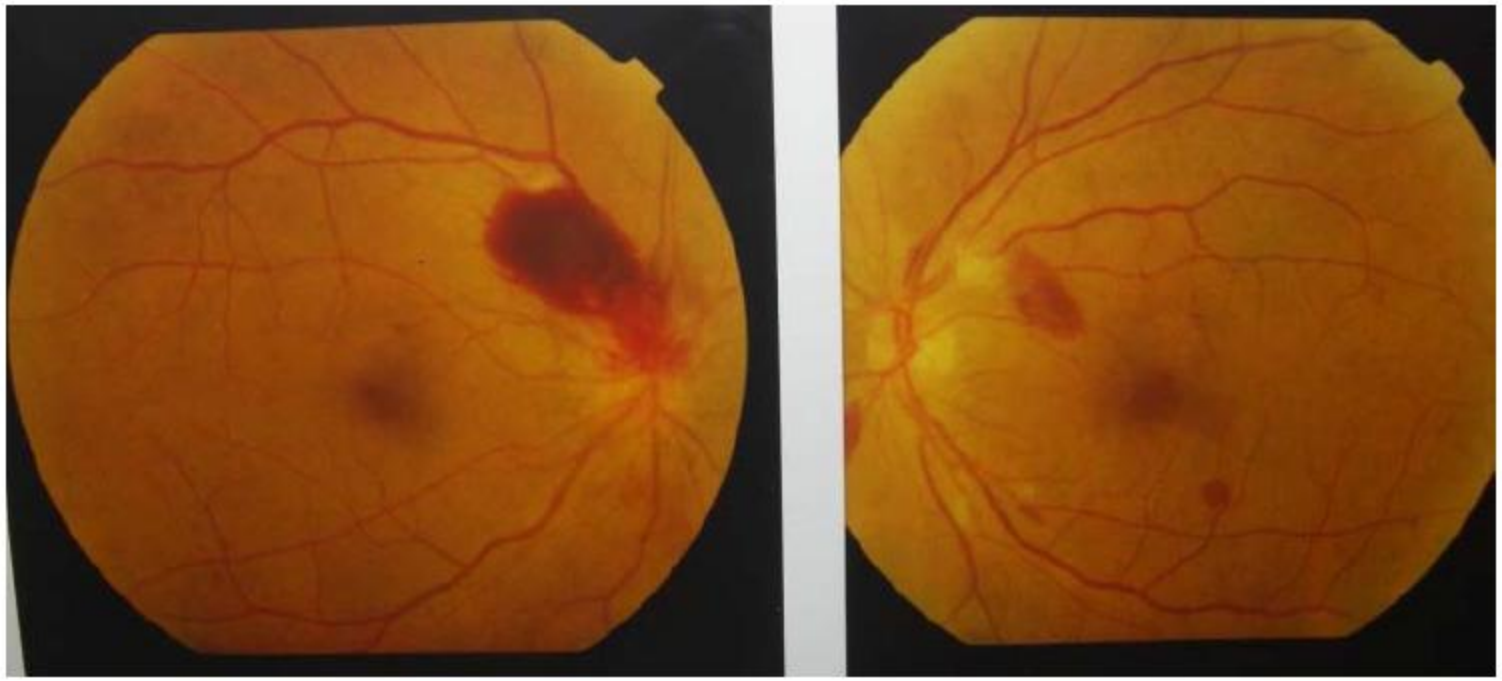
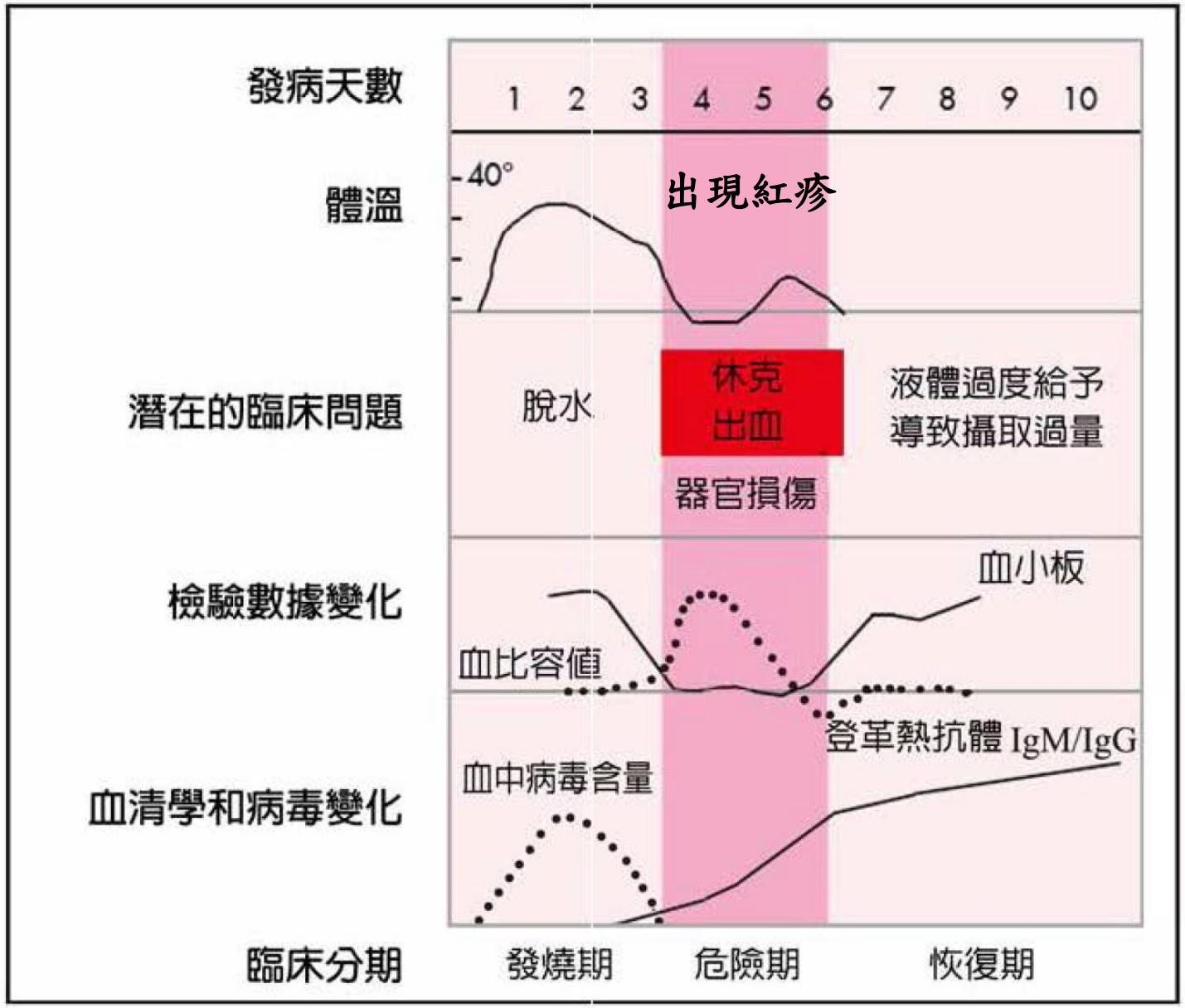
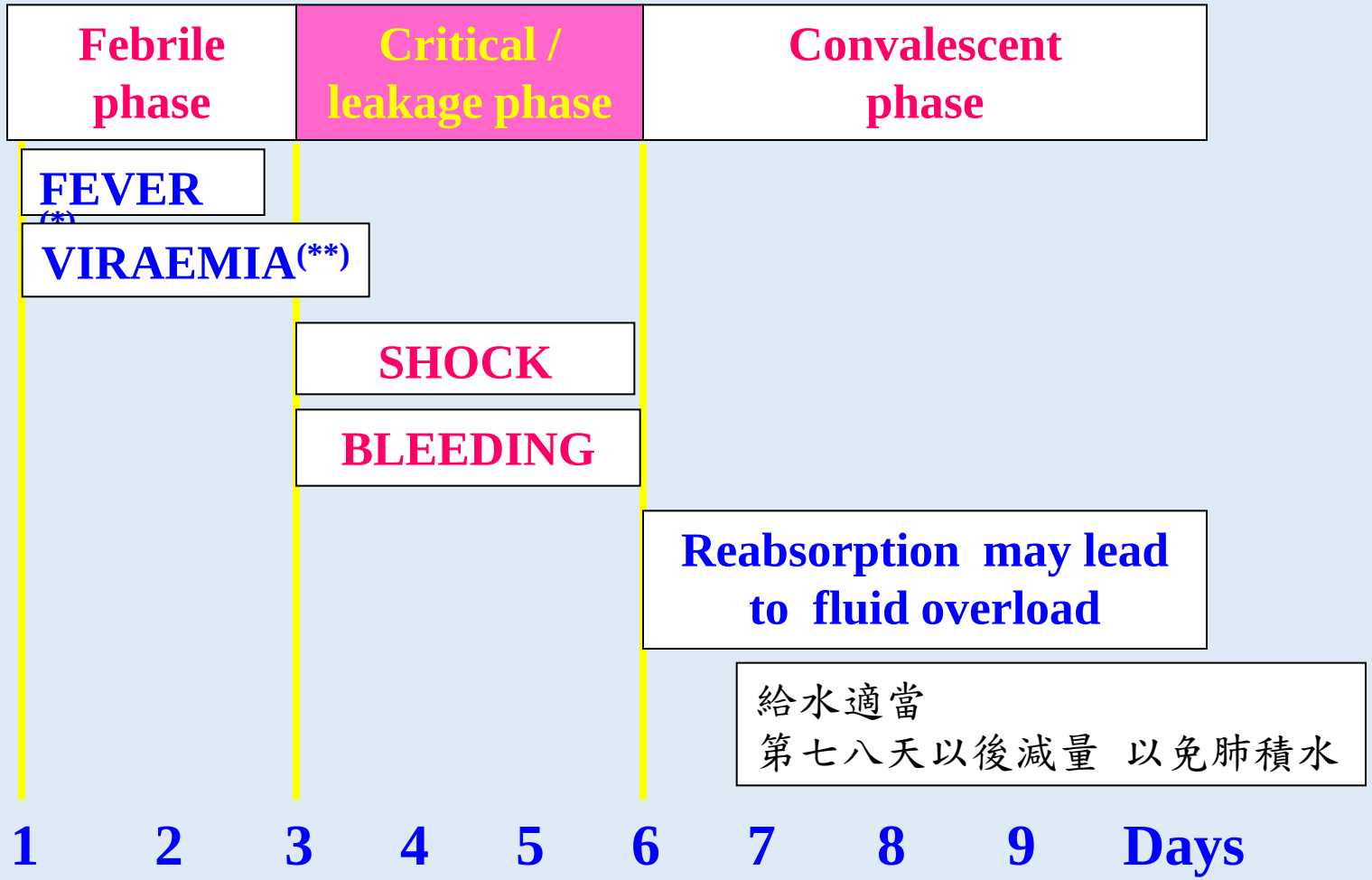


圖 7 登革熱所造成的視網膜出血（李允吉醫師提供）

圖10 登革熱臨床病程


發病天數
1 2 3 4 5 6 7 8 9 10
體溫
40°
出現紅疹
潛在的臨床問題
脫水
休克
出血
器官損傷
液體過度給予
導致攝取過量
檢驗數據變化
血小板
血比容值
血清學和病毒變化
登革熱抗體 IgM/IgG
血中病毒含量
臨床分期
發燒期
危險期
恢復期



Complications

Disease course of DHF

Dengue fever Lab diagnosis

(1)白血球都會降低並出現非典型淋巴球,白血球降低和登革熱疾病的嚴重

度並不成正比。

(2)血小板<100,000/μL,血小板減少的程度和登革熱疾病嚴重度有相關。

(3) 常見**aPTT 延長，但PT 正常**。

(4)重症病患有時會有: DIC

(aPTT and PT prolong)

(5)Elevated liver function test

(6) NS1Ag, IgG, IgM, PCR confirm test

Dengue NS1 Rapid Test Kit Sensitivity in Primary Inf. (Bio-Rad)

Dengue infection	Positive /Total case	Positive rate
DENV-1	39/40	97.5%
DENV-2	10/18	56%
DENV-3	15/20	75%
DENV-4	6/9	67%
Total	70/87	80.5%

※二次感染或檢測時間距離發病已超過6天
可能會假陰性

資料來自疾管局 黃智雄博士

2015/08/26 - 2015/09/03 疫情升溫 + 套組檢測分析

Dengue NS1 Ag VS Dengue virus-PCR

	Dengue virus-PCR		
Dengue NS1 Ag	Positive	Not detected	
Positive	279	3	282
Negative	**19**	284	303
	298	287	585

敏感性: 94 % ; 特異性: 99%

快篩全 (NS1+IgM+ IgG) VS Dengue virus-PCR

	Dengue virus-PCR		
快篩全 (NS1+IgM+ IgG)	Positive	Not detected	
Positive	285	11	296
Negative	**3**	286	289
	288	297	585

敏感性: 99 % ; 特異性: 96%

登革熱病例定義

臨床條件

突發發燒≧38℃並伴隨下列任二（含）項以上症狀

一、 頭痛/後眼窩痛/肌肉痛/關節痛/骨頭痛

二、 出疹

三、 白血球減少（leukopenia）

四、 噁心/嘔吐

五、 血壓帶試驗陽性

六、 任一警示徵象：

六、任一警示徵象：

（一） 腹部疼痛及壓痛

（二） 持續性嘔吐

（三） 臨床上體液蓄積（腹水、胸水...）

（四） 黏膜出血

（五） 嗜睡/躁動不安

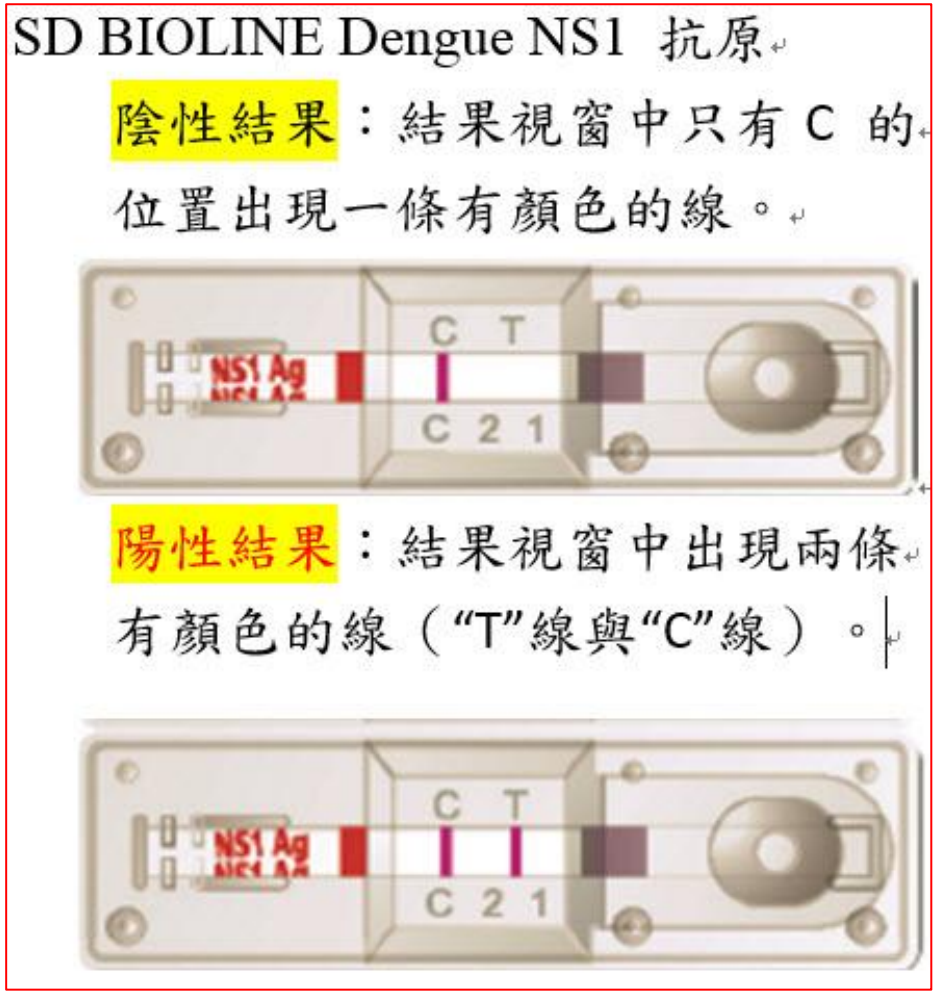
（六） 肝臟腫大超出肋骨下緣2 公分

（七） 血比容增加伴隨血小板急速下降

代辦醫療費用之撥付：於實施日期截止後，由中央健康保署比照代辦疾病管制署其他案件之醫療費用提供相關資料，並依代付之醫療費用向疾病管制署請款

登革熱NS1 抗原抗體快速檢驗試劑標準作業

- 檢驗所使用程序的原理與方法
- 檢驗方法：免疫色層分析法
- NS1原理
  - 以體外免疫色層分析法，單步驟定性測定人類血清、血漿及全血中的登革熱病毒NS1 抗原，診斷早期急性登革熱感染
- 以RT-PCR為標準法之NS1抗原評估結果 ：
  - Sensitivity：92.4%
  - Specificity：98.4%
- 容器與添加劑的種類
  - 抗凝血劑：Heparin、EDTA、sodium citrate
  - 保存於室溫下(1-30˚C)，勿冷凍試劑組或內容物



臺南市105年起「登革熱NS1抗原快速診斷試劑」使用條件截至衛生福利部疾病管制署或本府衛生局書面通知日止

衛生局賦配試劑	一、醫師及防疫人員認為有必要者 二、不明原因發燒≧38℃，未達登革熱病例定義臨床條件 三、潛伏期有國內、外登革熱流行地區活動史，或住家、活動範圍附近有登革熱陽性病例之病患	1.不得申請健保給付 2.不得跟民眾收費	1.陽、陰性一律通報法傳系統，請註明「使用衛生局NS1」 2.快篩陰性，請再將血液送轄區衛生所，後送高雄研檢中心
民眾自費	未符合登革熱任一病例定義臨床條件，民眾要求檢查	1.請使用該院所自購試劑 2.請民眾自費	陽性通報

感謝醫界朋友對「健保網域免帳號通報入口」支持，傳染病通報向多元快捷邁出一大步。（疾病管制署致醫界通函第 301 號）（ 2016-06-13 ）

全國醫界朋友，您好：

疾管署自 4 月 21 日推出醫療院所可透過「**健保網域免帳號通報入口**」通報傳染病，感謝醫界朋友們的支持使用，1 個月以來，已有 95 家醫療院所登入，完成 14 筆傳染病個案通報，更有 15 家過去無法定傳染病通報經驗之診所，加入使用行列。

過去疾管署傳染病通報系統，受限於技術及為保護個人資料安全，僅提供經申請且被核准具有系統帳號的醫療院所通報法定傳染病。為改善第一線照護病人的基層診所需具備固定 IP 位址進行傳染病通報，或另用傳真紙本資料給衛生局等執行程序上之不便，疾管署開放使用「健保網域免帳號通報入口」方式，以兼顧資料安全及方便醫療作業，期待基層診所多加利用該功能，以更便捷的方式進行傳染病通報，提高通報意願與時效，縮短病人發病到通報間之時間，避免疫病在社區傳播。另為減輕醫界朋友

傳染病個案通報系統 - 健保網域免帳號通報入口

醫事憑證卡PIN碼：

代表所屬醫療院所通報：(請點擊放大鏡查詢)

登入系統

相關連結: 使用者操作手冊、 健保網域免帳號通報安裝程式、健保網域免帳號通報常見問題。

系統操作問題: 請洽客服電話:(02)2395-9825 分機3618

卡片元件安裝問題: 請洽(03)563-0200 分機 8 (全景客服) 或參見 客服中心網站 E-mail: help@changingtec.com

本網站以1024*768 設計,建議用Internet Explorer 8 以上版本瀏覽

這個網站想要安裝下列附加元件: 來自 'Changing Information Technology Inc.' 的 'Changing CGHCACSAPIATL Component V1.1.12.1102' 。
有什麼風險?(W)

安裝(I)

Dengue fever score

Table 2. Proposed dengue scoring system

Characteristics	Score
(I) Epidemiology	
Recent travel to Southeast Asia or endemic dengue fever in Taiwan within 1 week	4
(II) Clinical symptom	
Skin rash	3
Bleeding sign*	3
Fever	2
Headache, retrobulbar pain, bone pain, myalgia	1
GI symptoms†	1
Absence of cough and rhinorrhea	1
(III) Differential diagnosis	
Fever > 7 days	–8
Identified infection focus (e.g. eschar of scrub typhus and upperrespiratory infection)	–10

**Included petechia, gum bleeding, epistaxis, gastrointestinal bleeding, hemoptysis, hematuria and menorrhagia; †included poor appetite, abdominal pain, diarrhea and nausea.*

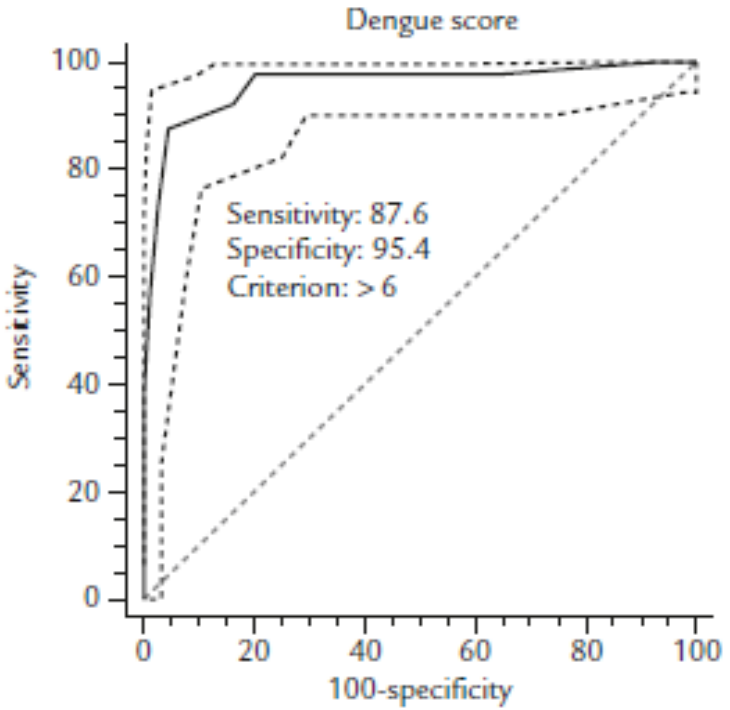


Figure. Receiver operating characteristic curve for dengue scoring system. The dotted lines indicate the 95% confidence interval.

definitively. To confront the confusion in clinical diagnosis, the parameters of relative bradycardia and higher AST than ALT levels can be used for

Ref. J Formos Med 2009 May;108(11):879-85

Predictor markers to promote early diagnosis DF

Early diagnosis of dengue infection remains a challenge to clinicians around the world. The positive predictive value for laboratory-confirmed dengue infection with combination of leukopenia (< 4000/cmm), thrombocytopenia (< 150 × 103/cmm), prolonged aPTT (> 38 sec), elevated aminotransferase (AST/ALT > 1.5) and low CRP (< 20 mg/L) is 93.1%. These clinical and laboratory findings may serve as predictive markers to promote early diagnosis of dengue infection in Taiwan.

Ho *et al. Journal of Biomedical Science* 2013, **20**:75
http://www.jbiomedsci.com/content/20/1/75

Another model : early diagnosis DF

- Prolonged aPTT, normal PT, platelet <100,000 cells/L is useful in evaluating the likehood of DF and/or DHF

Research Article

The Usefulness of Clinical-Practice-Based Laboratory Data in Facilitating the Diagnosis of Dengue Illness

Jien-Wei Liu,[1,2,3] Ing-Kit Lee,[1,2,3] Lin Wang,[4] Rong-Fu Chen,[5] and Kuender D. Yang[5]

BioMed Research International Volume 2013,Article ID 198797,11 pages
http://dx.doi.org/10.1155/2013/198797

1997

- 登革出血熱

1.登革熱的臨床表徵

2.出血現象

3.血小板減少（≦100,000/μL

4.血比容值上升20％以上，或出現血管通透性明顯增加的證據，如低血清蛋白、肋膜或腹膜積水

- 登革休克症候群:合併有低血壓（脈壓差≦20mmHg）
- 嚴重程度

第一級（Grade I）：病患僅血壓帶試驗陽性

第二級（Grade II）：病患有自發性出血的表現

第三級（Grade III）：併有皮膚濕冷、四肢冰涼、坐立不安、脈搏微弱至幾乎測量不到（脈壓差≦20 mmHg）

第四級（GradeIV）：測量不到脈搏，須施行心肺復甦術

登革熱病例定義及分類
WHO 2009

- 有無「警示徵象」

(1)腹部疼痛及壓痛

(2)持續性嘔吐

(3)體液蓄積（腹水、胸水)

(4)黏膜出血

(5)嗜睡/躁動不安

(6)肝臟腫大超出肋骨下緣2 公分

(7)血比容值增加伴隨血小板急速下降

- 潛在疾病因素及特定社經狀況

(1)糖尿病

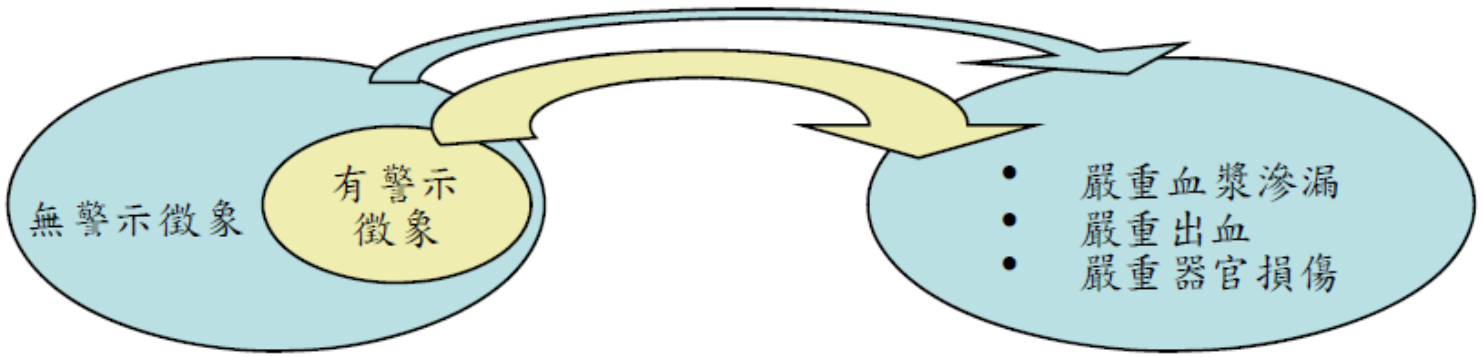
(2)腎衰竭

(3)慢性溶血疾病

(4)肥胖、懷孕婦女、嬰兒、老人

(5)獨居或偏遠地區居民

圖 3 世界衛生組織 2009 年登革熱病例分類



登革熱有無警示徵象的診斷條件

疑似登革熱
居住於或曾至登革熱流行區旅行，出現突發發燒並伴隨以下任二(含)項以上：
-疼痛
-出疹
-白血球低下
-噁心/嘔吐
-血壓帶試驗陽性
-任一警示徵象

實驗室確診登革熱
(在沒有血漿滲漏時特別重要)

警示徵象*
-腹部疼痛及壓痛
-持續性嘔吐
-臨床上體液蓄積（腹水、胸水…..）
-黏膜出血
-嗜睡/躁動不安
-肝臟腫大超出肋骨下緣2公分
-實驗室檢查：血比容增加伴隨血小板急速下降
** 需嚴密監控及醫療介入*

登革熱重症的診斷條件

1.嚴重血漿滲漏導致
-休克（登革休克症候群）
-體液蓄積及呼吸窘迫

2.嚴重出血（由臨床醫師評估）

3.嚴重器官損傷
-肝臟（GOT或GPT≧1000 IU/L）
-中樞神經系統：意識受損
-心臟衰竭
-其他

◆肺部臨床表徵

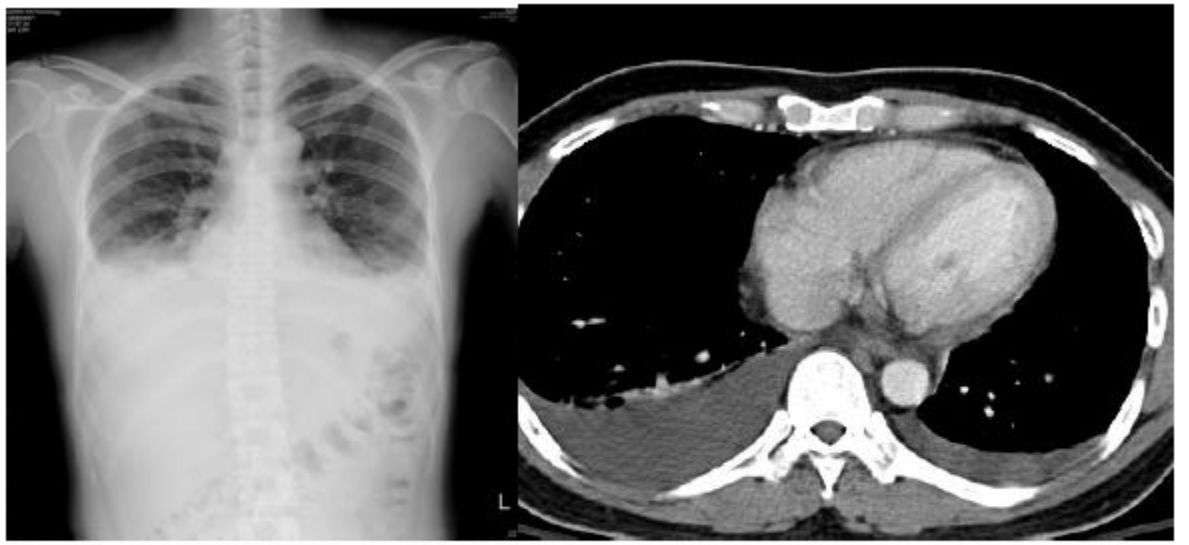


圖 8 胸部 X 光和斷層掃描顯示肋膜積水（李允吉醫師提供）

◆消化系統變化

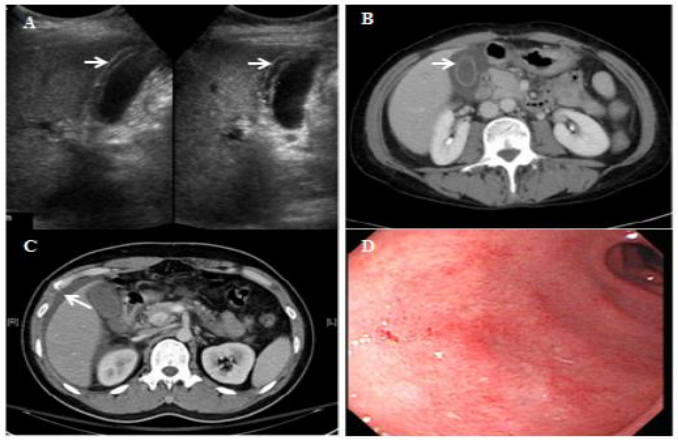


圖9 腹部超音波和斷層掃描顯示膽囊壁水腫（A和B）和腹水（C）；內視鏡檢查顯示點狀出血性胃炎（D）

（李允吉醫師提供）

表5 世界衛生組織之逐步評估法　**不再區分為登革熱與登革出血熱患者**

I.整體評估	
I.1 病史詢問	包括相關症狀，過去病史及家族史
I.2 身體檢查	包括完整的身體及神智評估
I.3 實驗室檢驗	包括常規檢驗及登革熱檢驗
II.診斷	評估疾病期及嚴重度
III.通報及處理	
III.1 法定傳染病通報	診斷後24小時內通報
III.2 處理之決策	依據臨床表現及其他狀況，安排病人處置： Group A（居家追蹤） Group B（安排住院） Group C（需緊急治療或轉院）

Group A Dengue Fever

- 病人無「警示徵象」與**潛在疾病**因素及**特定社經狀況**
  - 須量測血壓、脈搏及體溫、液體補充及流失量、尿量及頻次、檢驗血比容值、白血球及血小板
  - 血比容值正常或只有微升，建議安排隔日或2~3日後門診追蹤
  - *血小板＜100,000/μL*，則應安排每日回診。
- 可居家追蹤
  - 患者有慢性疾病如肝硬化、尿毒症、慢性阻塞性肺病、心臟衰竭、狹心症、消化性潰揚、糖尿病等，則死亡率高，**宜住院**
  - **獨居或偏遠地區居民 宜住院**
- 應避免攝取深咖啡色的飲料，如可樂，以利觀察是否有消化道出血

- **需立刻至醫院就醫的情形**
  - ●臨床症狀未改善
  - ●退燒時症狀惡化
  - ●嚴重腹痛、持續嘔吐
  - ●四肢冰冷濕黏
  - ●嗜睡或煩躁及躁動、出血（如解黑便或咖啡狀嘔吐物）
  - ●超過4～6小時未排尿

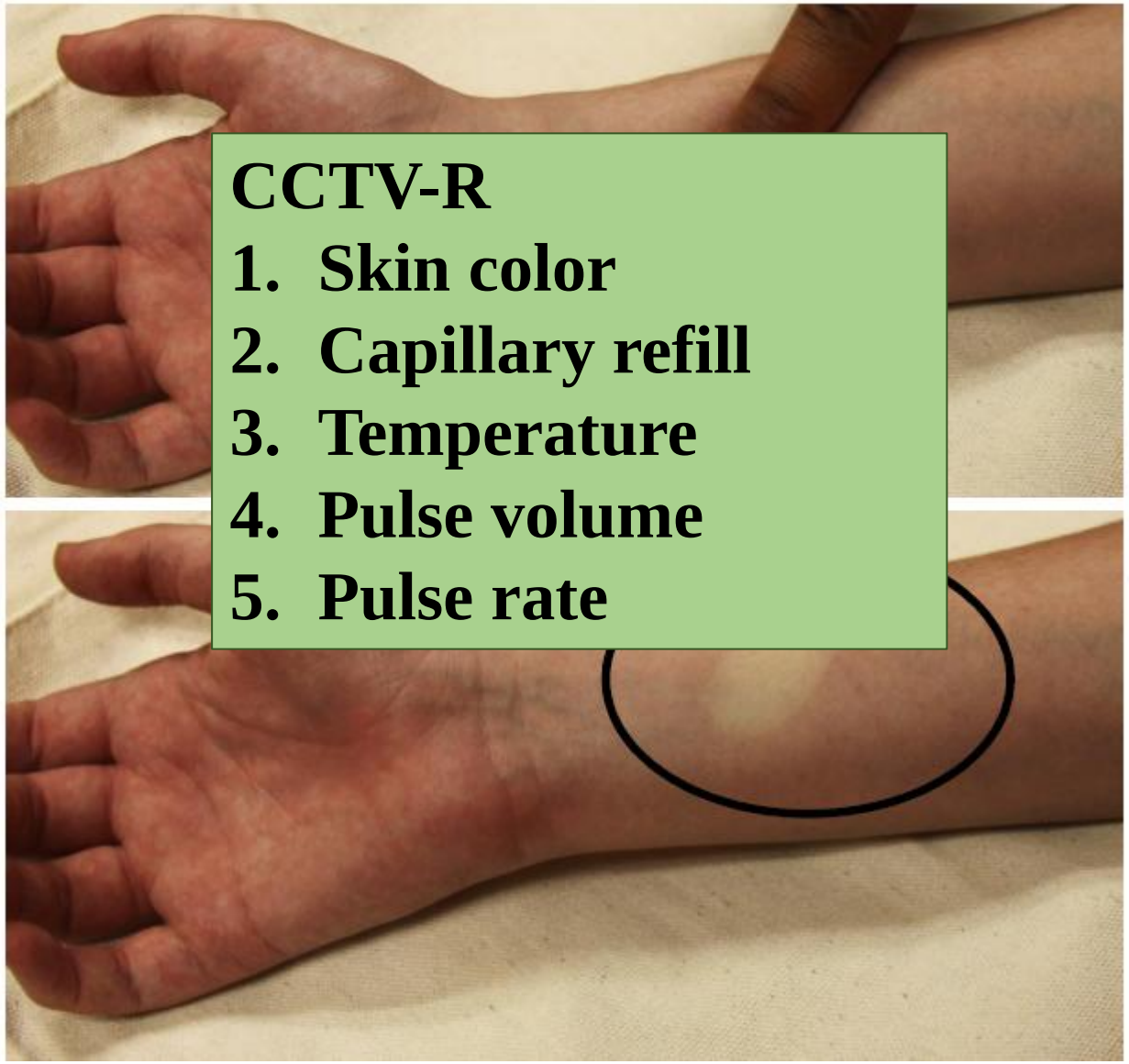
Group B Dengue Fever

- 病人有「警示徵象」或有潛在疾病因素及特定社經狀況；
- **需住院. LMD criteria**

Patient assessment

- **Hemody**
  clinical

Parameters
Conscious l
Capillary re
Extremities
Peripheral p
Heart rate
Pulse pressu
Blood press
Respiratory
Urine outpu



CCTV-R

1. **Skin color**
2. **Capillary refill**
3. **Temperature**
4. **Pulse volume**
5. **Pulse rate**

lengue

hypoxia)

Group C Dengue Fever

- 需住到 ICU
  - 嚴重血漿滲漏導致休克
  - 嚴重血漿滲漏導致體液蓄積及呼吸窘迫
  - 嚴重出血
  - 嚴重器官損傷
    - 如肝臟功能損傷（**GOT或GPT>=1000 IU/L**)、中樞神經系統受損(患者意識變化，如腦病變、腦炎)、心臟衰竭、心肌病變、腎功能損傷等

ICU monitoring

- 血比容值的改變要和血液動力狀況一起判讀
- 高血比容值合併不穩定生命現象
  - ->表示有血漿滲漏且需要體液補充
- 高血比容值但生命現象穩定且有適當尿量排出
  - ->不需額外體液補充
- 血比容值持續降低合併不穩定生命現象
  - ->有大出血， 需要輸血
- 若血比容值持續降低但生命現象穩定且有適當尿量排出
  - ->血液稀釋或血管外體液再吸收的現象，輸液應立刻停止， 以避免肺部積水。

輸血的適應症

- 當**輸注新鮮全血**仍無法妥適處理嚴重出血，或無全血可供輸注時，可考慮輸注血小板濃厚液及新鮮冷凍血漿。故若預期病患會持續出血，可及早準備新鮮全血以備輸注。

(給予5~10毫升/公斤的新鮮濃縮紅血球或10~20毫升/公斤的新鮮全血)

- 因登革熱病患通常血小板數回升迅速，病患即使需要輸注血小板濃厚液，亦應以50,000/μL 為目標即可。
- 對於血小板數極度偏低（通常是指<20,000/μL）的登革熱病患，應嚴格要求病患臥床休息，避免受傷，以減少出血風險。亦應避免執行肌肉注射，以免造成血腫塊。
- 有相當數量的研究指出，登革熱病患通常血小板數回升迅速，所以針對生命徵象穩定、無嚴重出血情形但血小板數偏低的登革熱病患，**實施「預防性」血小板輸注，並不需要也沒有益處。**

Effectiveness of platelet transfusion in DF: a randomized controlled trial

- Almost half the patients showed no response to a high-dose platelet transfusion. Platelet transfusion did not prevent development of severe bleeding or shorten time to cessation of bleeding and was associated with significant side effects. Therefore, platelet transfusion should not be routinely done in the management of dengue fever.

  Ref. Khan Assir Mz et al. Transfus Med Hemother. 2013 Oct;40(5):362-8.

- Lack of efficacy of prophylactic platelet transfusion for severe thrombocytopenia in adults with acute uncomplicated

  dengue infection.

  Ref. Lye DC et al. Clin Infect Dis 2009;48:1262–1265.

- Prophylactic platelets in dengue: survey responses highlight lack of an evidence base.

  Ref. Whitehorn J et al. PLoS Negl Trop Dis. 2012;6(6):e1716.

輸血的適應症

- 對於血小板數<20,000/μL 的登革熱病患，則應檢視是否有下列的危險因子出現：

（1）嚴重無法控制的高血壓（收縮壓>180 mmHg 或舒張壓>110 mmHg）

（2）近期內（半年內）有出血性腦中風、頭部創傷或是顱內手術病史

（3）必須持續接受抗凝血劑治療者

（4）必須接受手術或是其他侵襲性治療者。

若有這些危險因子出現，則可以輸注血小板，使其血小板數達到 20,000/μL 以上。

Prophylaxis platelet transfusion in Dengue Fever

- Platelet count, < 20 X 10^3 /uL

	Patients given platelet transfusion (n = 188)	Patients not given platelet transfusion (n = 68)	P
Age, years	40 (22–64)	39 (22–58)	.54
Any bleeding	1 (1)	2 (3)	.17
Platelet increment the next day, x 10^3 platelets/mL	7(-7 to 50)	11 (-4 to 41)	.26
Time to platelet count ≥50 x 10^3 platelets/mL, days	3 (1–4)	3 (1–5)	.59
Length of hospital stay, days	6 (4–8)	5 (4–7)	.09
Death	1 (1)	0 (0)	1.00

Clin Infect Dis 2009; 48:1262–5

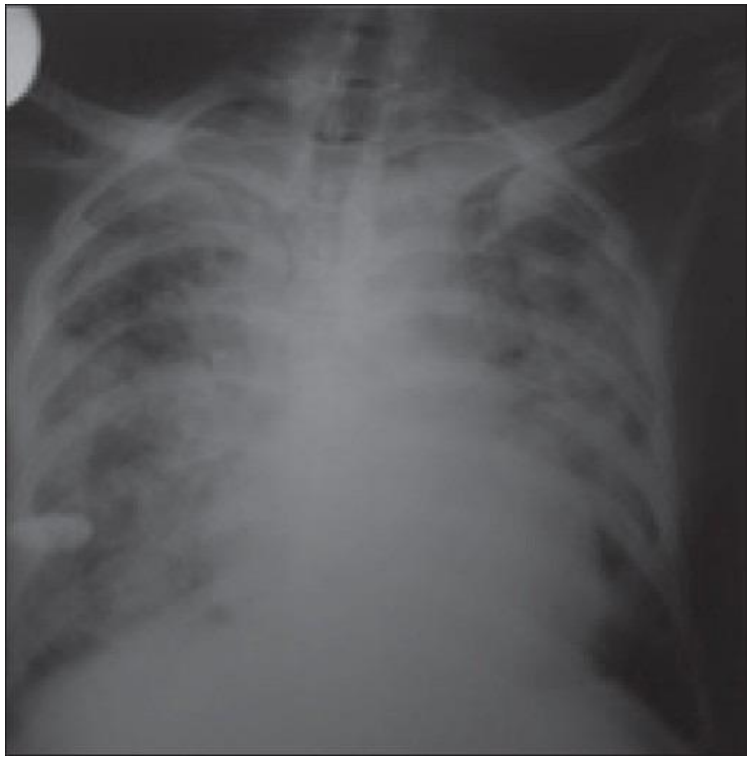
Preventive transfusion in dengue shock syndrome

- Significant differences in the development of pulmonary edema and length of hospitalization (P<.05) (in preventive transfusions group) were observed.
- Preventive transfusions did not produce sustained improvements in the coagulation status in DSS

J Pediatr. 2003 Nov; 143(5):682-4.

Platelet Transfusion in Dengue Fever

- Acute lung injury after platelet transfusion in a patient with dengue fever



Asian J Transfus Sci. 2014 Jul-Dec; 8(2): 131–134

Platelet Transfusion in Dengue Fever

- Prophylactic platelet transfusions are not required in stable patients with platelet count below 20,000/µl.

Blood component	Indication
Platelet	1. In general there is no need to give prophylactic platelets even at 20,000/µl. 2. Prophylactic platelet transfusion may be given at level of <10,000/µl in absence of bleeding manifestations. 3. Prolonged shock; with coagulopathy. 4. In case of massive bleeding, platelet transfusion may be needed in addition to red cell transfusion.

J Indian Med Assoc. 2011 Jan; 109(1):30-5.

可能出現大出血的高危險群

- 具有延長性或頑固性休克。
- 具有低血壓性休克，同時有肝、腎衰竭或嚴重及持續性的代謝性血酸症。
- 使用非類固醇消炎藥。
- 曾有胃潰瘍疾病。
- 現正進行抗擬血治療。
- 有任何型式的受傷，包括肌肉注射。

P-RBC transfusion

- Surviving Sepsis Campaign Guideline中血比容值＜ 30% 被視為是需要輸血的指標，但在登革熱重症並不適用
- Dengue患者的Hct通常一開始會升高，開始下降時就表示有出血->就得開始考慮輸血了…
- 若病患持續出血或血比容無適度改善，必須考慮再度輸血
- 避免插鼻胃管和中央靜脈導管

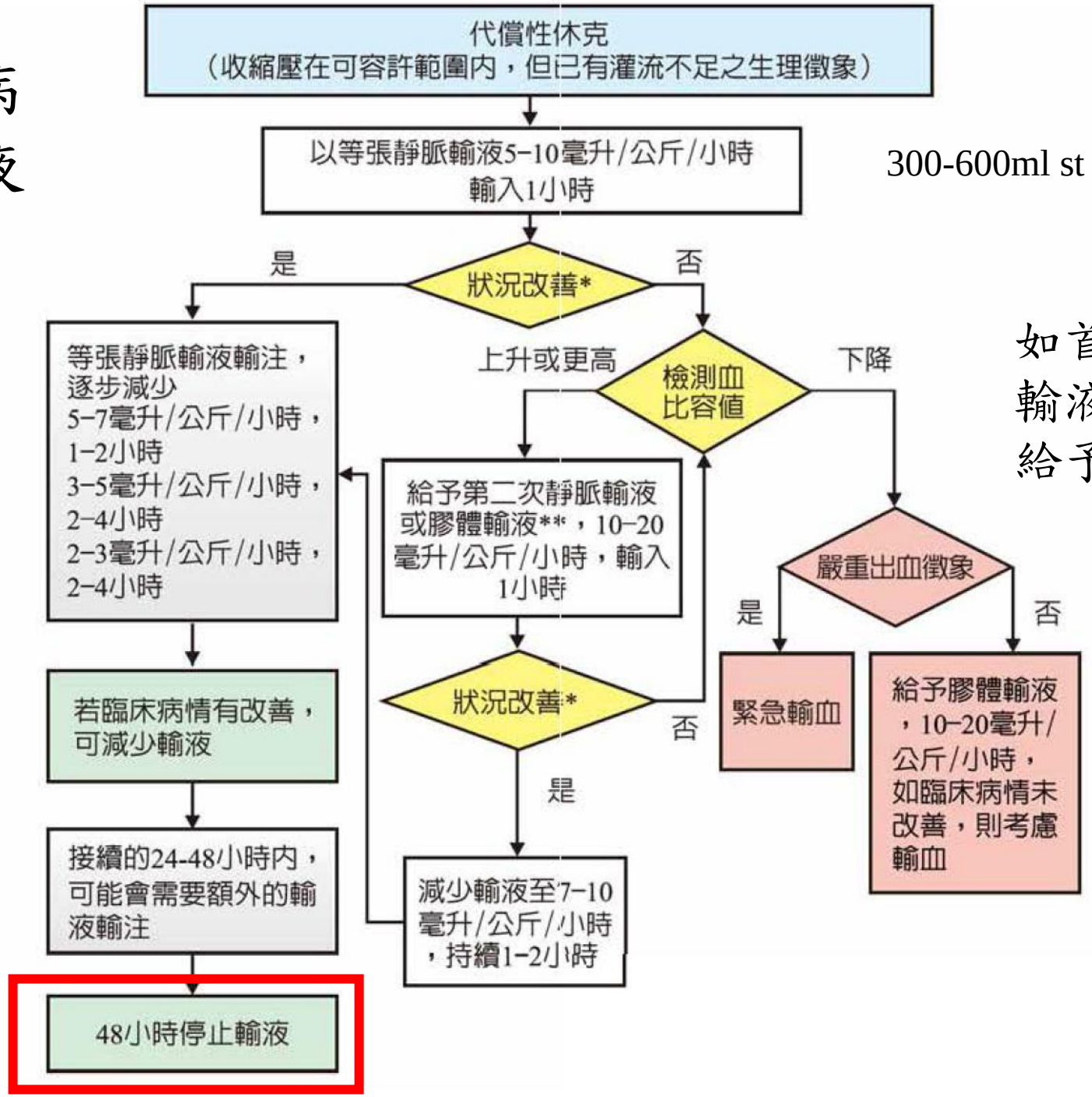
表 9 肥胖或體重過重病患每小時正常維持的輸液量

理想體重(公斤)	正常維持輸液量(毫升/小時)	每小時 2~3 毫升/公斤的輸液量(毫升/小時)	每小時 1.5~2 毫升/公斤的輸液量(毫升/小時)
5	10	10-15	
10	20	20-30	
15	30	30-45	
20	60	40-60	
25	65	50-75	
30	70	60-90	
35	75	70-105	
40	80	80-120	
50	90	100-150	
60	100		90-120
70	110		105-140
80	120		120-150

對理想體重＞50 公斤的成人，1.5~2 毫升/公斤可被用於快速計算每小時維持的輸液量；若理想體重≦50 公斤的成人，2~3 毫升/公斤可被用於快速計算每小時維持的輸液量。

- 出血併發症的治療
針對嚴重血小板下降但血壓穩定的個案，**預防性血小板輸注是無效且沒必要**

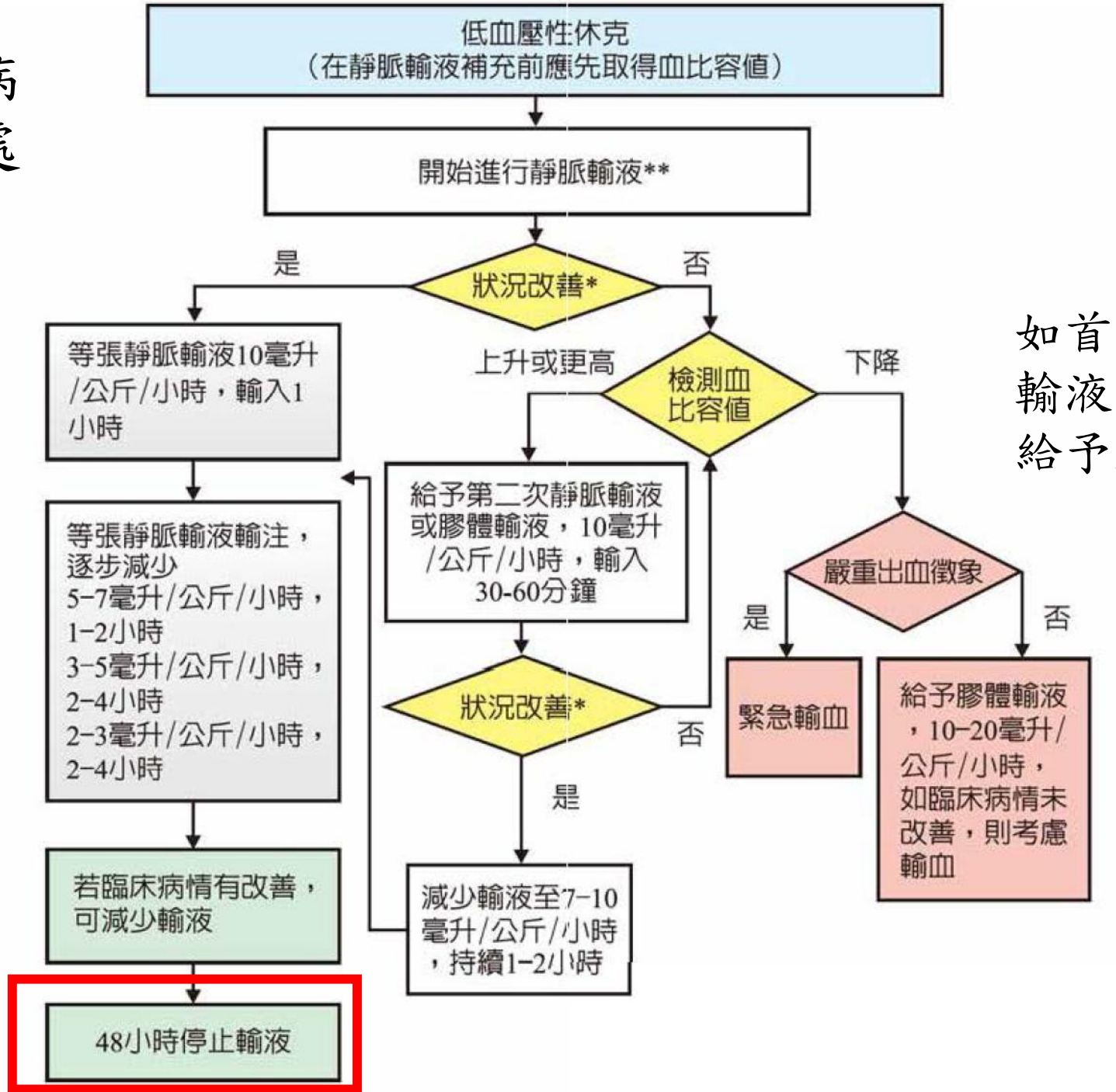
代償性休克病患之靜脈輸液處理流程圖



300-600ml st

如首次靜脈給予晶體輸液，則建議第二次給予膠體輸液

低血壓性休克病患之靜脈輸液處理流程



如首次靜脈給予晶體輸液，則建議第二次給予膠體輸液

Complications of Dengue Fever

- 眼睛
  - 黃斑水腫通常在1～5 天內恢復
  - 視網膜病變所引起的短暫性視力模糊和血小板降低的程度有關係，隨著血小板值的恢復，病患視力也跟著改善
- 肺部
  - 肺出血
  - 肺部浸潤或肋膜積水
- 消化系統
  - 急性膽囊炎、急性胰臟炎
  - 胃腸道出血

DHF patients with acute abdomen: clinical experience of 14 cases.

- 328 patients with DHF/DSS, 14 (4 men, 10 women, median age 44 years) had acute abdomen. DHF/DSS was initially suspected in only 2 of these 14 patients. Presumptive diagnoses of acute cholecystitis (6 acalculus and 4 calculus cholecystitis) were made in 10 patients, non-specific peritonitis in three patients, and acute appendicitis in 1 patients.
- Cholecystectomy, PTGBD, and appendectomy were performed in 3 patients.
- Transfused blood in the 3 patients who underwent invasive procedures and the 11 patients who received supportive treatment included packed RBC

  (24 versus 0 units; P = 0.048), FFP (84 versus 0 units; P = 0.048), and platelets (192 versus 180 units; P = 0.003).
- Patients who underwent invasive procedures also had prolonged time in the hospital (median = 11 versus 7 days; P = 0.015).

Ref. Am J Trop Med Hyg. 2006 May;74(5):901-4. Khor BS et al.

DHF complicated with acute pancreatitis and seizure

- Acute pancreatitis and seizure are rare manifestations of dengue virus infection. A 66 y/o woman with DM presented with epigastralgia, nausea, vomiting, diarrhea and fever. Acute pancreatitis, abnormal liver function and thrombocytopenia were diagnosed at a local hospital.
- After persistent fever, thrombocytopenia and seizure developed she was transferred to our medical center. Dengue virus infection was confirmed and DHF grade II was diagnosed.
- No further neurological symptoms occurred and pancreatitis improved gradually after supportive care.
- Acute pancreatitis, seizure may be manifestations of dengue virus infection, especially in patients with delayed diagnosis, prolonged fever and thrombocytopenia.

Ref. J Formos Med Assoc. 2004 Nov;103(11):865-8. Chen TC et al

Complications of Dengue Fever

- Skin rash
  - 會合併搔癢、灼熱感
  - 冰敷或給予抗組織胺
- Pain
  - pain control
- 登革出血熱合併細菌性感染的獨立危險因子
  - 發燒大於5天
  - 急性腎衰竭
- 營養需求改變
  - 給予靜脈輸液-> 0.9% 生理食鹽水或是乳酸林格氏液

登革熱患者會合併細菌性感染

- 曾有文獻報告指出，登革出血熱病患若合併有細菌性感染者，通常年紀較大、發燒時間較長、有較高比例的急性腎衰竭、胃腸道出血、意識變化、不尋常的登革熱表現與較高比例會演變成登革休克症候群。
- 發燒大於5 天及急性腎衰竭，是登革出血熱合併細菌性感染的獨立危險因子。因此，成人登革出血熱病患，如果持續發燒超過5 天或出現急性腎衰竭，則可能併發細菌性感染。此時，宜抽血做細菌培養後，立即給予經驗性抗生素治療。

Ref. 登革熱臨床症狀、診斷與治療 2015

Prognosis factors of Dengue Fever

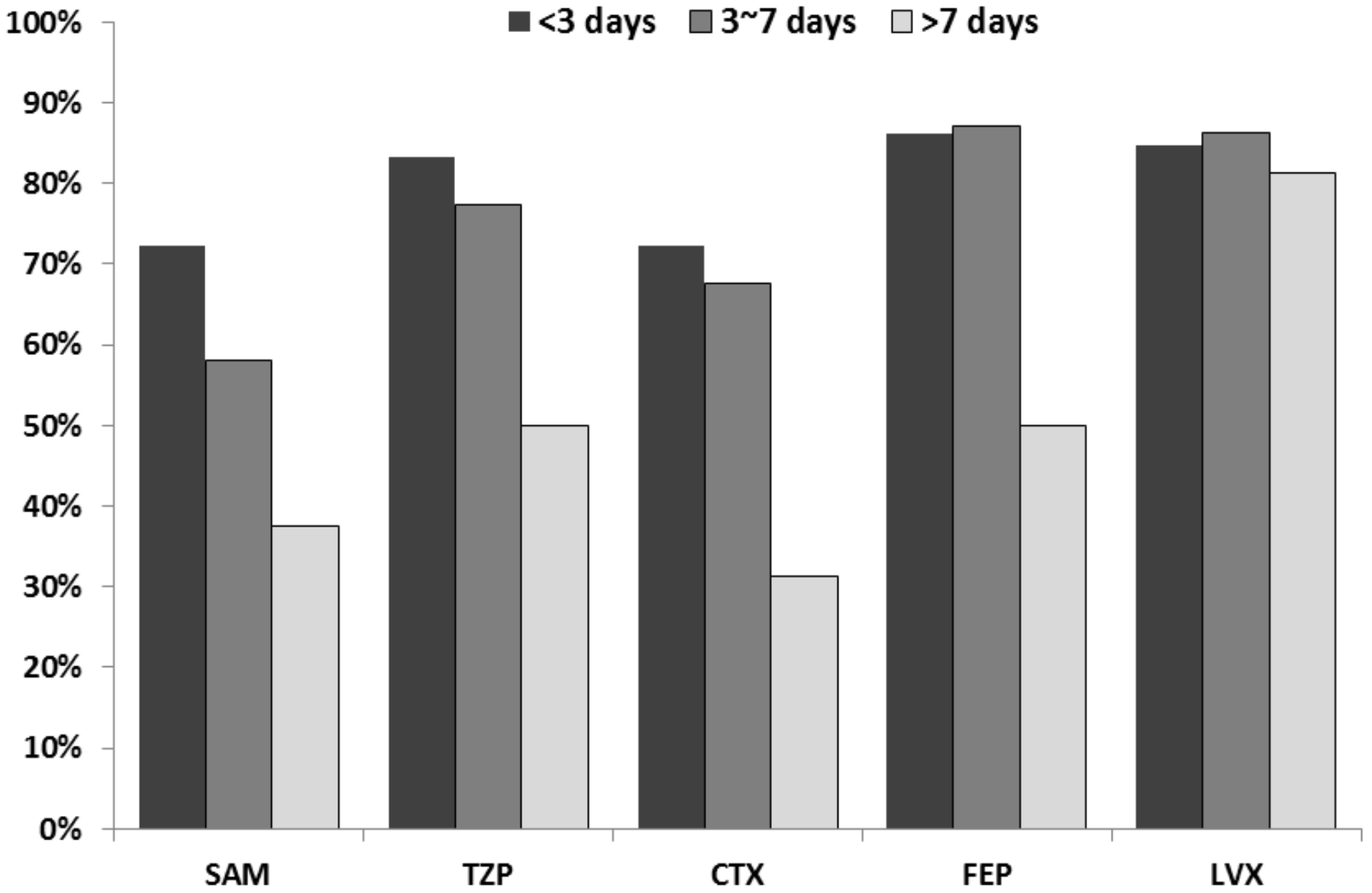
- 有關的
  - thrombocytopenia
  - Hct上升
  - GOT GPT上升
  - GI bleeding
- 無關
  - leukopenia
  - skin rash

Basic characteristics	All cases with BSI, N=80 (%)	Community-onset BSI, N=32 (%)	Hospital-onset BSI, N=48 (%)	*P* value
Age, years (mean ± SD)	73.2 ± 9.4	75.6 ± 7.4	71.6 ± 10.3	0.06
Male	41 (51.3)	15 (46.9)	26 (54.2)	0.52
Comorbidities				
Charlson comorbidity index (mean ± SD)	2.38 ± 1.99	3.13 ± 2.28	1.88 ± 1.61	0.01
Hypertension	59 (73.7)	28 (87.5)	31 (64.6)	0.02
Diabetes mellitus	41 (51.3)	18 (56.3)	23 (47.9)	0.47
Chronic kidney disease	21 (26.3)	9 (28.1)	12 (25)	0.76
Coronary artery disease	16 (20)	6 (18.8)	10 (20.8)	0.82
Cerebrovascular disease	10 (12.5)	6 (18.8)	4 (8.3)	0.17
Malignancy	16 (20)	10 (31.3)	6 (12.5)	0.04
Clinical condition & disease severity				
Admission to BSI, days (mean ± SD)	5.8 ± 8.5	0.4 ± 0.8	9.4 ± 9.4	<0.0001
DF onset to BSI (mean ± SD), days	7.8 ± 8.7	2.3 ± 1.9	11.7 ± 9.6*	<0.0001
APACH II score (mean ± SD)	19.6 ± 11.8	22.0 ± 12.6	18.0 ± 11.0	0.13
Critical illness (Pitt bacteremia score ≥ 4)	30 (37.5)	13 (40.6)	17 (35.4)	0.64
Concurrent gastrointestinal bleeding	32 (40.0)	15 (46.9)	17 (35.4)	0.31
Antibiotic usage before BSI	23 (28.8)	1 (3.1)	21 (45.8)	<0.0001
Leukocytosis (≥ 9,000/mm^3)	32 (40.0)	11 (34.4)	21 (43.8)	0.40
Thrombocytopenia (≤ 100,000/mm^3)	62 (77.5)	25 (78.1)	37 (77.1)	0.91
Inappropriate empirical antibiotic	35 (43.8)	14 (43.8)	21 (43.8)	1.00
Clinical outcomes				
Length of hospitalization (mean ± SD)	17.4 ± 20.6	9.1 ± 8.2	22.9 ± 24.4	0.001
Severe dengue	48 (60.0)	19 (59.4)	29 (60.4)	0.93
Intensive care unit admission	41 (51.2)	16 (50.0)	25 (52.1)	0.86
Ventilation failure	27 (33.8)	10 (31.3)	17 (35.4)	0.70
In-hospital mortality	26 (32.5)	12 (37.5)	14 (29.2)	0.44

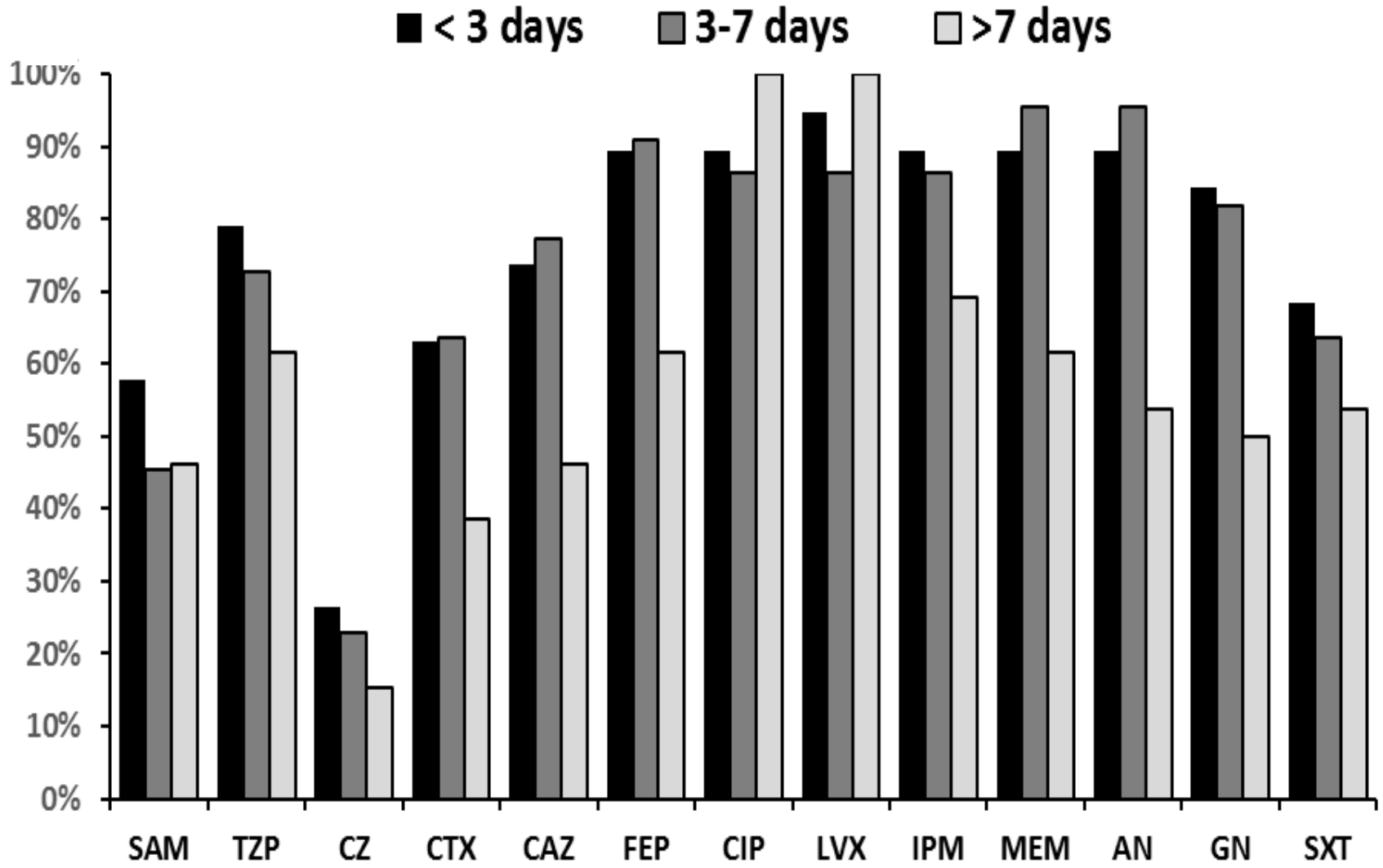
Table 2. A total of 90 bloodstream isolates from 80 hospitalized adults with dengue fever, categorized by the time between admission and BSI onset.

Pathogens	Isolate number (%)			
	All isolates n = 90	<3 days n = 38	3-7 days n = 34	>7 days n = 18
Gram-positive pathogens	29 (32.0)	17 (44.7)	9 (13.2)	3 (16.7)
Streptococcus spp.	15 (16.7) [a]	11 (28.9)	4 (11.8)	0 (0)
Enterococcus spp.	6 (6.7)	2 (5.3) [b]	1 (2.9) [b]	3 (16.7) [c]
Methicillin-susceptible *Staphylococcus aureus*	4 (4.4)	1 (2.6)	3 (8.8)	0 (0)
Methicillin-susceptible *Staphylococcus epidermidis*	2 (2.2)	2 (5.3)	0 (0)	0 (0)
Methicillin-resistant *Staphylococcus aureus*	1 (1.1)	1 (2.6)	0 (0)	0 (0)
Methicillin-resistant coagulase-negative staphylococci	1 (1.1)	0 (0)	1 (2.9)	0 (0)
Gram-negative pathogens	57 (63.3)	21 (55.3)	23 (67.6)	13 (72.2)
Escherichia coli	14 (15.6)	9 (23.7)	4 (11.8)	1 (5.6)
Pseudomonas aeruginosa	8 (8.9)	3 (7.8)	3 (8.8)	2 (11.1)
Acinetobacter spp.	8 (8.9) [d]	3 (7.8)	3 (8.8)	2 (11.1)
Klebsiella pneumoniae	7 (7.8)	1 (2.6)	5 (14.7)	1 (5.6)
Elizabethkingia meningoseptica	3 (3.3)	0 (0)	0 (0)	3 (16.7)
Aeromonas spp.	3 (3.3) [e]	0 (0)	3 (8.8)	0 (0)
Salmonella spp.	2 (2.2)	0 (0)	1 (2.9)	1 (5.6)
Enterobacter cloacae	2 (2.2)	0 (0)	1 (2.9)	1 (5.6)
Others	10 (11.1)	5 (13.2) [f]	3 (8.8) [g]	2 (11.1) [h]
Candida species	4 (4.4)	0 (0)	2 (5.9)	2 (11.1)

[a] Viridans streptococci (13 isolates), *S. agalactiae* (1), and *S. dysgalactiae* (1).
[b] Ampicillin-susceptible *E. faecalis* (3).
[c] Ampicillin-resistant *E. faecium* (1) and vancomycin-resistant *E. faecium* (2).
[d] *A. baumannii* (7) and *A. junii* (1).
[e] *A. caviae* (2) and *A. dhakensis* (1).
[f] *Moraxella urethralis* (1), *Moraxella osloensis* (1), *Ralstonia pickettii* (1), *Shewanella putrefaciens* (1), and *Myroides* spp. (1).
[g] *Moraxella* spp. (1), *Proteus mirabilis* (1), and *Serratia marcescens* (1).
[h] *Morganella morganii* (1) and *Chryseobacterium indologenes* (1).



*Three *Moraxella* isolates were excluded for susceptibility tests due to no interpretation criteria.
Five gram-positive isolates were not available for susceptibility tests.
CTX = cefotaxime; FEP = cefepime; LVX = levofloxacin; SAM = ampicillin-sulbactam; TZP = piperacillin-tazobactam.



*Three *Moraxella* isolates were excluded for susceptibility tests due to no interpretation criteria.

AN = amikacin; CAZ = ceftazidime; CIP = ciprofloxacin; CTX = cefotaxime; CZ = cefazolin; FEP = cefepime; LVX = levofloxacin; IPM = imipenem; MEM = meropenem; SAM = ampicillin-sulbactam; SXT = trimethoprim-sulfamethoxazole; TZP = piperacillin-tazobactam.

DM an epidemiologically identified risk factor for development of DHF/severe dengue in dengue virus affected patients

- In vitro study evaluating the sequential immunological reactions and viral load in the **DENV infected mononuclear cells of adults with type 2 DM (T2DM group, n = 33) and normal adults (control group, n = 29).** In the T2DM group significantly higher **IL-4 level on the first (P = 0.049) and the third (P = 0.022) postinfection days, while higher IL-10 (P = 0.042) and granulocyte-macrophage colony-stimulating factor (GM-CSF) (P = 0.009) were detected on the third postinfection day.**
- Patients with **T2DM are at higher risk for development of DHF/severe dengue and strengthen the previously epidemiologically identified role of DM being a predictive risk factor for progressing into DHF/severe dengue in DENV-affected patients. (DM is a risk factor)**
- Increased production of IL-4, IL-10, and granulocyte-macrophage colony-stimulating factor by type 2 **DM mononuclear cells infected with dengue virus, but not increased intracellular viral multiplication.**

Ref. Biomed Res Int. 2013;2013:965853. Lee IK et al

Discharge criteria

all of the following conditions must be present

- Clinical No fever for 48 hours.
- Improvement in clinical status (general well-being, appetite, haemodynamic status, urine output, no respiratory distress).
- Laboratory Increasing trend of platelet count.
- Stable haematocrit without intravenous fluids.

Ref. WHO 2009 dengue fever guideline

Oral Corticosteroid Therapy in Dengue Infection

- Randomized, Double-Blind Placebo Controlled Trial

Endpoint	Placebo (n = 75)	Low-Dose Prednisolone (n = 74)	High-Dose Prednisolone (n = 74)	Overall Comparison (*P* Value)
DSS	5 (7)	5 (7)	8 (11)	.36
ICU admission	8 (11)	6 (8)	8 (11)	.98
Bleeding (any)	58 (77)	52 (70)	54 (73)	.54
Hyperglycemia (random)	3 (4)	5 (7)	9 (12)	.07
Platelet nadir days 3–8, 10^9/L	51 (25–83)	59 (33–89)	60 (29–93)	.36
Maximum hematocrit days 3–8, %	46 (42–49)	45 (42–47)	45 (42–48)	1.00
Percentage hemoconcentration	15 (10–23)	16 (8–22)	17 (10–27)	.28
AUC log viremia days 3–6, $\log_{10}$ copies/mL	20.96 (16.97–23.25)	21.56 (17.99–24.18)	21.29 (18.85–23.79)	.76
Time to undetectable viremia				
No. with undetectable viremia, %	32 (43)	28 (38)	25 (34)	.94
Days from enrollment, median (IQR)	7 (5–8)	7 (5–NE)	8 (5–8)	
Time to negative NS1				
No. with negative NS1, %	44 (59)	41 (55)	37 (50)	.08
Days from enrollment, median (IQR)	5 (3–8)	5 (3–11)	5 (3–NE)	
Patients with any adverse event	22 (29)	16 (22)	23 (31)	.81
Patients with any serious adverse event	10 (13)	6 (8)	14 (19)	.32

Clin Infect Dis 2012;55(9):1216–24

Balapiravir therapy in Dengue Infection

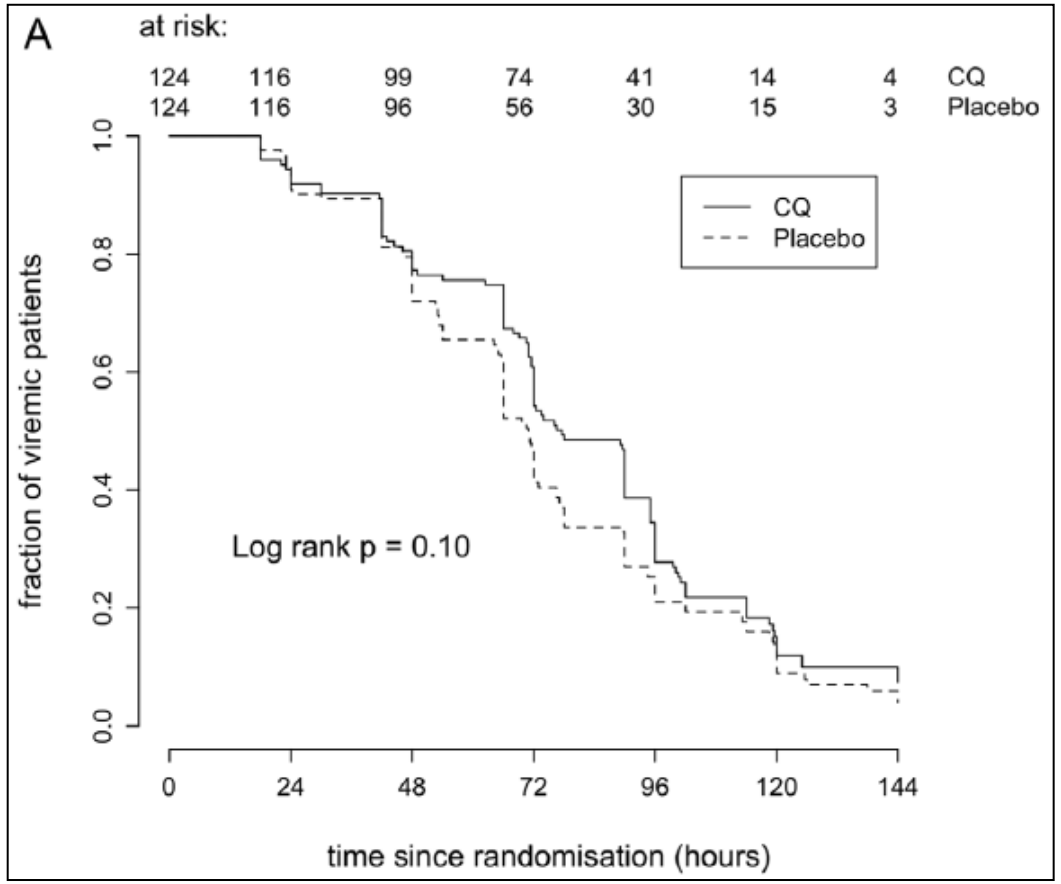
- Randomized, Double-Blind Placebo Controlled Trial

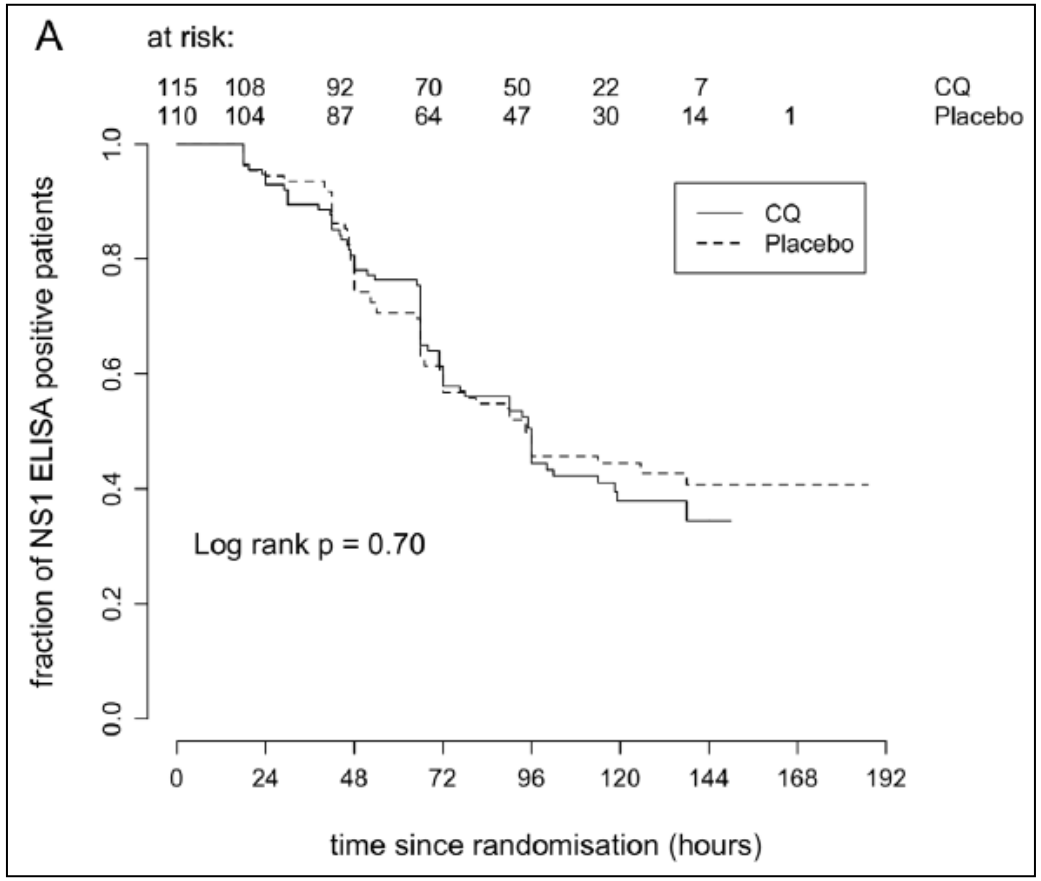
Endpoint	Placebo (n = 32)	Low-dose Balapiravir (n = 10)	High-dose Balapiravir (n = 22)	*P*
AUC viremia, log_{10} copies/mL × d[a]				.623
Mean	32.78	34.49	32.56	
Median (IQR)	32.19 (26.63–39.24)	29.63 (27.41–39.86)	31.98 (27.60–34.98)	
Median time to first viremia level of <1000 copies/mL, d (IQR)[b]	4 (3–6)	5 (4, NA)	4 (3–5)	.476
Median time to first negative NS1 test result, d (IQR)[b]	4 (3–13)	3 (3–14)	4 (3–6)	.852

J Infect Dis 2013;207:1442–50

Chloroquine therapy in Dengue Infection

- Double-blind, randomized, placebo-controlled trial





PLoS Negl Trop Dis 2010; 4(8): e785

Prochlorperazine

Repurposing of Prochlorperazine for Use Against Dengue Virus Infection

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The increasing prevalence of dengue virus (DENV) infection presents serious disease and economic burdens in countries where dengue epidemics are occurring. Despite the clinical importance, no DENV vaccine or anti-DENV drug is available. In this study, we found that prochlorperazine (PCZ), a dopamine D2 receptor (D2R) antagonist approved to treat nausea, vomiting, and headache in humans has potent in vitro and in vivo antiviral activity against DENV infection. PCZ can block DENV infection by targeting viral binding and viral entry through D2R- and clathrin-associated mechanisms, respectively. Administration of PCZ immediately or 6 hours after DENV infection in a *Stat1*-deficient mouse model completely protected against or delayed lethality. Overall, PCZ showed a previously unknown antiviral effect against DENV infection, and D2R may play a role in the DENV life cycle. Prophylactic and/or therapeutic treatment with PCZ might reduce viral replication and relieve the clinical symptoms of patients with dengue.

Ref. The Journal of Infectious diseases 2015;211:394-404

Table 3. Serotype-Specific Vaccine Efficacy.

Variable	Vaccine Group			Control Group			Vaccine Efficacy (95% CI)
	Cases	Person-Yr at Risk	Incidence Density (95% CI)	Cases	Person-Yr at Risk	Incidence Density (95% CI)	
	no.		*no./100 person-yr*	*no.*		*no./100 person-yr*	%
Modified per-protocol analysis*							
Serotype 1	66	12,478	0.5 (0.4–0.7)	66	6,196	1.1 (0.8–1.4)	50.3 (29.1–65.2)
Serotype 2	58	12,495	0.5 (0.4–0.6)	50	6,219	0.8 (0.6–1.1)	42.3 (14.0–61.1)
Serotype 3	43	12,514	0.3 (0.2–0.5)	82	6,213	1.3 (1.1–1.6)	74.0 (61.9–82.4)
Serotype 4	18	12,522	0.1 (0.1–0.2)	40	6,206	0.6 (0.5–0.9)	77.7 (60.2–88.0)
Unknown	6	12,540	<0.1 (0.0–0.1)	3	6,268	<0.1 (0.0–0.1)	0.0 (–517.8–78.6)
Intention-to-treat analysis							
Serotype 1	99	27,016	0.4 (0.3–0.4)	109	13,434	0.8 (0.7–1.0)	54.8 (40.2–65.9)
Serotype 2	84	27,035	0.3 (0.2–0.4)	84	13,461	0.6 (0.5–0.8)	50.2 (31.8–63.6)
Serotype 3	55	27,060	0.2 (0.2. 0.3)	106	13,459	0.8 (0.6–1.0)	74.2 (63.9–81.7)
Serotype 4	32	27,063	0.1 (0.1–0.2)	83	13,442	0.6 (0.5–0.8)	80.9 (70.9–87.7)
Unknown	15	27,079	<0.1 (0.0–0.1)	14	13,514	0.1 (0.1–0.2)	46.5 (–19.6–75.9)

* The modified per-protocol analysis was performed at least 28 days after the third injection in all participants who had received three doses, regardless of protocol deviations.

Ref. N Engl J Med. 2015 Jan 8;372(2):113-23.Villar L et al.

Take Home Message

- Chief Complaint and travel history
- Admission criteria and patient education(fever / skin rash)
- Underlying diseases (DM ESRD and old age)
- General appearance, appetite, toxic sign and consciousness
- Physical examination during admission for warm shock(HR, CCTV-R, urine output)
- CXR or Echo
  - (for effusion, for liver span)

致醫界通函

疾病管制署再次放寬登革熱NS1快速診斷試劑對象為全國各縣市於「潛伏期有國內、外登革熱流行地區活動史，或住家、活動範圍附近有登革熱陽性病例之病患」皆適用(疾病管制署致醫界通函第313號) (2016-12-14)

全國醫界朋友，您好：

為能加強全國的登革熱病例偵測，疾病管制署於105年12月6日修訂「登革熱NS1抗原快速診斷試劑之費用申報及核付作業」，再次放寬適用對象條件。

（一）符合登革熱病例定義；

（二）發病 7 天內；

（三）潛伏期有國內、外登革熱流行地區活動史，或住家、活動範圍附近有登革熱陽性病例之病患。

健保給付「登革熱 NS1 抗原快速篩檢試劑」

已修訂
如P77頁

致醫界通函

疾病管制署已放寬登革熱 NS1 快速診斷試劑適用對象，提升登革熱病例偵測效能(疾病管制署致醫界通函第 294 號)(2016-03-28)

全國醫界朋友，您好：為因應未來登革熱疫情之發生，提升病例偵測效能，疾病管制署放寬 NS1 快速診斷試劑適用對象條件至：

1. 具有健保身分且符合登革熱病例定義
2. 發病 7 日內
3. 居住於臺南市、高雄市與屏東縣，或有登革熱流行地區旅遊活動史的個案，經醫師判定需進一步檢驗者(詳附件)。

Thank You Very Much