보건학석사학위논문

Passive Fever Surveillance for Dengue in Nha Trang City, Vietnam: Association between Clinical and Laboratory-Confirmed Diagnoses of Dengue

베트남 냐짱 지역의 뎅기 역학조사: 뎅기의 임상진단과 실험실진단의 연관성

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Abstract

Passive Fever Surveillance for Dengue in Nha Trang City, Vietnam: Association between Clinical and Laboratory-Confirmed Diagnoses of Dengue

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Dengue is a leading cause of morbidity in Vietnam with gradual increase from 32.5 per 100,000 population in 2000 to 120.0 per 100,000 population in 2009. In Vietnam, almost all cases of dengue virus (DENV) infection are diagnosed clinically based on the WHO guideline (2009), but it is commonly under-reported and many cases are misclassified due to its broad spectrum of symptoms shared with other febrile diseases. On behalf of the Dengue Vaccine Initiative (DVI), the International Vaccine Institute (IVI)

assessed the strength of association between clinical and laboratory-confirmed diagnoses of dengue infection from a passive hospital-based surveillance study in Nha Trang City, in Khanh Hoa province, Vietnam from July 2014 to December 2015. The study was designed to determine the true burden of dengue, symptomatic infection of all fever cases among children and adults between 1 and 55 years of age in a defined population. Clinical signs and symptoms of 553 dengue patients and 1,152 non-dengue patients (laboratory-confirmed by IgM and IgG capture ELISA or real-time PCR) were analyzed. Leucopenia (OR = 6.03), thrombocytopenia (OR = 1.97), rash (OR = 1.90), headache (OR = 1.75), arthralgia (OR = 1.75), petechiae (OR = 1.71), and nausea/vomiting (OR = 1.42) were highly associated with laboratory-positive dengue cases in the absence of respiratory signs and symptoms such as rhinorrhea (OR = 0.41) and expectoration (OR = 0.39). A comparison between adults and children of laboratory-confirmed dengue cases revealed that the frequency of clinical signs and symptoms was different between two age groups. DENV infected adults were more likely to present flushed face (OR = 2.13), headache (OR = 2.10), rash (OR = 1.96), thrombocytopenia (OR = 1.91), and arthralgia (OR = 1.83) which were not apparent to DENV infected children. Overall sensitivity and specificity of clinical diagnoses were 57.7% and 92.0% with diagnostic accuracy of 80.9%. Once validated, those key clinical features for children and adult patients with dengue infection may improve the future clinical outcomes, especially in the resource-poor dengue

endemic countries, as they would allow more closely monitoring of selected patients and it may affect the sensitivity of clinical diagnosis.

Keywords: Dengue, Vietnam, clinical diagnosis, fever, rash, thrombocytopenia, leucopenia

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I. Introduction

1. Dengue virus infection and its clinical manifestations

Dengue virus (DENV) is a single-stranded RNA flavivirus transmitted to humans mainly by Aedes mosquitoes including A. aegypti and A. albopictus. It is endemic in most tropical and subtropical regions of the world with four different serotypes (DENV-1 to DENV-4) circulating. Primary DENV infection with one serotype confers long-term immunity against the infecting serotype, but not to the others (1-3).

DENV infection causes a wide spectrum of illness ranging from clinically inapparent to severe and fatal hemorrhagic diseases. It is known that the most majority of infections especially in children under age of 15 years are asymptomatic or minimally symptomatic. After typical incubation period of 4 to 7 days, ranging from 3 to 14 days, fever commonly occurs during the acute febrile state associated with headache, nausea, vomiting, and body pains as well as rash (4). In addition to frequent manifestation of leucopenia and mild thrombocytopenia, hemorrhagic manifestations such as petechiae, epistaxis, gingival bleeding, gastrointestinal bleeding, haematuria, and hypermenorrhoea are less frequently but not rarely associated with DENV infection (2). Dengue hemorrhagic fever (DHF) / dengue shock syndrome

(DSS) occurs mostly in individuals during their secondary DENV infection with a different serotype and also in infants with a primary infection born to mothers immunized to DENV (3). DHF/DSS is characterized by rapid onset of capillary leakage accompanied by thrombocytopenia, altered haemostasis, and damage to the liver (5).

Dengue is commonly under-reported and many cases are misclassified with other febrile diseases (6). The key to reduce dengue mortality is early recognition and understanding of the clinical problems during the different phases of the disease. Effective and accurate clinical diagnosis can help in identifying those at risk of developing severe disease and needing hospital care. However, it is complicated to clinically distinguish dengue from undifferentiated febrile illnesses (e.g. Japanese encephalitis, malaria, chikungunya, Zika, and influenza) in the early febrile phase, as DENV infection produces a broad spectrum of symptoms, many of which are non-specific to dengue (Table 1). It would be ideal to confirm dengue infection based on laboratory diagnostics (e.g. virus isolation, serologic tests, and molecular methods); on the other hand, laboratory tests are not feasible in local settings in scarce of resources, unless samples are prepared and tested appropriately in such resource-poor settings especially in dengue-endemic developing countries. Therefore, WHO criteria (2009) (7) have been widely used for clinical diagnosis of dengue in endemic areas, but accuracy of clinical diagnoses varies in different settings of the clinical practice.

Table 1. Non-dengue febrile diseases sharing clinical features of DENV infection

Conditions similar to the febrile phase of dengue infection	
Flu-like syndromes	Influenza, measles, chikungunya, Zika, infectious mononucleosis, HIV seroconversion illness
Illnesses with a rash	Rubella, measles, scarlet fever, meningococcal infection, chikungunya, Zika, drug reactions
Diarrheal diseases	Rotavirus, other enteric infections
Illnesses with neurological manifestations	Meningo/encephalitis, febrile seizures

2. Global burden of dengue

Dengue is a continuing global threat (8), with an estimate of 3.9 billion people at risk of DENV infection in 128 countries (9). DENV transmission occurs in American, South-East Asian, Western Pacific, Eastern Mediterranean, and African regions, with new cases spreading to non-endemic regions in Europe and the United States as well as North-East Asia (4). 390 million annual dengue infections are estimated worldwide based on the global population in 2010 (10). According to an analysis from the Global Burden of Disease Study 2013, the global incidence of dengue increased significantly from 8.3 million apparent cases in 1990 to 58.4 million apparent cases in 2013 (11).

Dengue exacts a global economic burden on both individuals and governments especially in the endemic countries in tropical and subtropical regions. Dengue epidemics brings high costs to families, health services, and the economic systems of affected countries (12). The total global cost of dengue illness per year was estimated to be USD 8.9 billion (13). Dengue illness was estimated to cost USD 2.1 billion per year on average in the Americas (14), USD 1.2 billion per year in South-East Asia, and USD 76 million per year in Africa (12)

3. Dengue in Vietnam

Dengue is recognized as a leading cause of mortality and morbidity in Vietnam (15). Since its first case report in 1959 and the first outbreak reported in 1963 resulting in 116 deaths (16), dengue has been endemic across the whole country. DENV transmission occurs year-round, whereas infection peaks during the summer rainy season from June to October annually. All four serotypes of dengue circulate in the country (Figure 1) and epidemics usually occur in the cycle of 3-5 years (17).

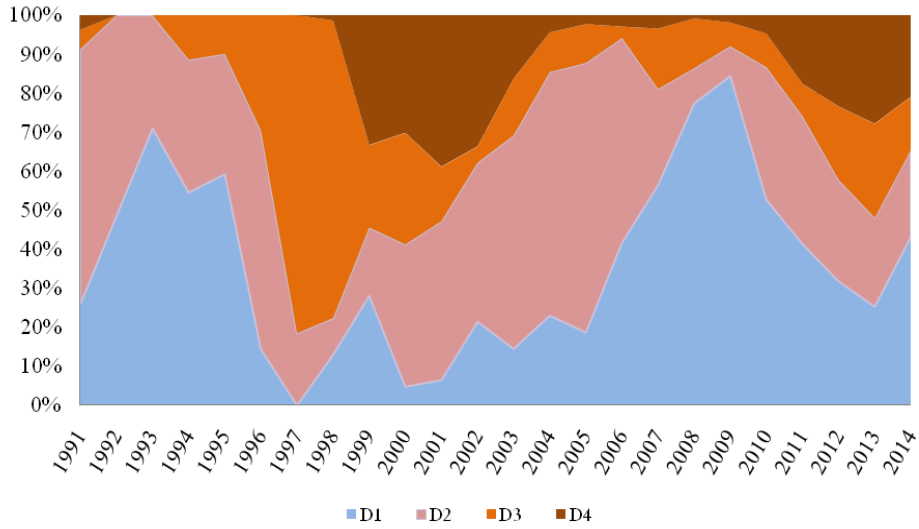


Figure 1. Prevalence of DENV serotypes in Vietnam

Vietnam has been successful in controlling dengue fever mortality; on the other hand, the country has been less successful in reducing the number of dengue cases (17). In 1998, there was a substantial outbreak occurred in Vietnam resulting in 119,429 dengue hemorrhagic fever (DHF) cases and 342 deaths (18). Dengue morbidity per 100,000 population in the country increased gradually from 32.5 (24,434 cases) in 2000, to 120.0 (105,370 cases) in 2009 (17).

From January to December in 2016, Vietnam reported a total of 122,020 cases of dengue including 43 deaths to the World Health Organization Western Pacific Regional Office (WHO WPRO). Cumulative number of cases in 2016 increased by 25.2% compared to 2015 and also increased by 73.6% compared to median in 2011-2015 period, respectively

(19). Main factors responsible for the emergence and re-emergence of dengue in Vietnam include high density of the dengue vector and wide geographic distribution of the vector, as well as circulation of all four types of dengue virus (17).

Dengue also imposes a substantial economic burden on households and healthcare systems in Vietnam. The cost of illness study conducted in Ho Chi Minh City in 2015-2016 estimated that the average cost per dengue case was USD 139.3±61.7, and more specifically, average direct medical cost, direct nonmedical cost and indirect cost per case were USD 47.1±31.9, USD 41.1±38 and USD 51±22.7, respectively (20).

In Vietnam, almost all cases of DENV infection are diagnosed clinically. Around 15-20% of dengue cases are serologically diagnosed, and virus isolation is performed only in 3-5% cases (17). The previous fever surveillance conducted in Vietnam in 2001-2002 demonstrated poor agreement between clinical and serological diagnosis of dengue (Cohen's kappa 0.055, p value 0.024) (21). Undifferentiated febrile illnesses are common in South-East Asian countries, including Vietnam, with clinical features of dengue similar to co-circulating pathogens, such as Japanese encephalitis, chikungunya, malaria, leptrospirosis, influenza A, Salmonella Typhi, and Rickettsia (21-26). A diagnosis based only on clinical symptoms is unreliable; therefore, early laboratory confirmation of clinical diagnosis may

be helpful to prevent progress from mild to severe disease and death (7). It might be valuable to evaluate accuracy of clinical diagnosis of dengue for the improved efficacy of the clinical measurement.

4. Objective of the study

On behalf of the Dengue Vaccine Initiative (DVI), the International Vaccine Institute (IVI) conducted a passive hospital-based surveillance study in Nha Trang City, in Khanh Hoa province, Vietnam from July 2014 to December 2015 with a primary objective to determine the true burden of dengue, symptomatic infection among children and adults between 1 and 55 years of age in a defined population. Secondary objectives of the study were:

1. To provide general epidemiological information of patients with DENV infection
2. To specify key clinical features highly associated with DENV infection and differentiate those key clinical features in children and adult groups
3. To evaluate accuracy of clinical diagnosis of DENV infection

II. Methods

1. Study area and population

Nha Trang city is the capital of Khanh Hoa province, located in the South central coast of Vietnam. The city has 420,521 inhabitants in an area of 251 km^2 resulting 1,675 people/km^2 of population density (2015 Census). The city is a middle-income country where residents primarily rely on tourism, agricultural and manufacturing industries. Based on Khanh Hoa Health Services database, the reported incidence of DENV infection was high in Nha Trang city ranging from 70.0-361.1/100,000 between 2008 and 2012, much higher than the national level (40.9-182.1/100,000 between 2003 and 2012) but slightly lower than provincial level (50.6-497.7/100,000 between 2003 and 2012). Khanh Hoa province reported an annual dengue incidence ranging from 77.7-875.03/100,000 among children less than 15 years of age.

Vietnamese healthcare system is composed of communal health centers (CHCs) where primarily outpatients are treated and suspected dengue cases are referred to the next level, district-level polyclinics where only minimal testing, such as blood tests, are available without ELISA/PCR testing capacity, and provincial hospitals like Khanh Hoa General Hospital (KHGH). KHGH is the largest hospital in the province as a tertiary care facility with 1,000 beds.

By implementing surveillance in the KHGH and the selected polyclinics (Figure 2) for the catchment area of 16 communes, the study captured most of the patients that may be representative of the residents of Nha Trang city. KHGH relies on clinical diagnosis of DENV infection as well as laboratory-confirmation.

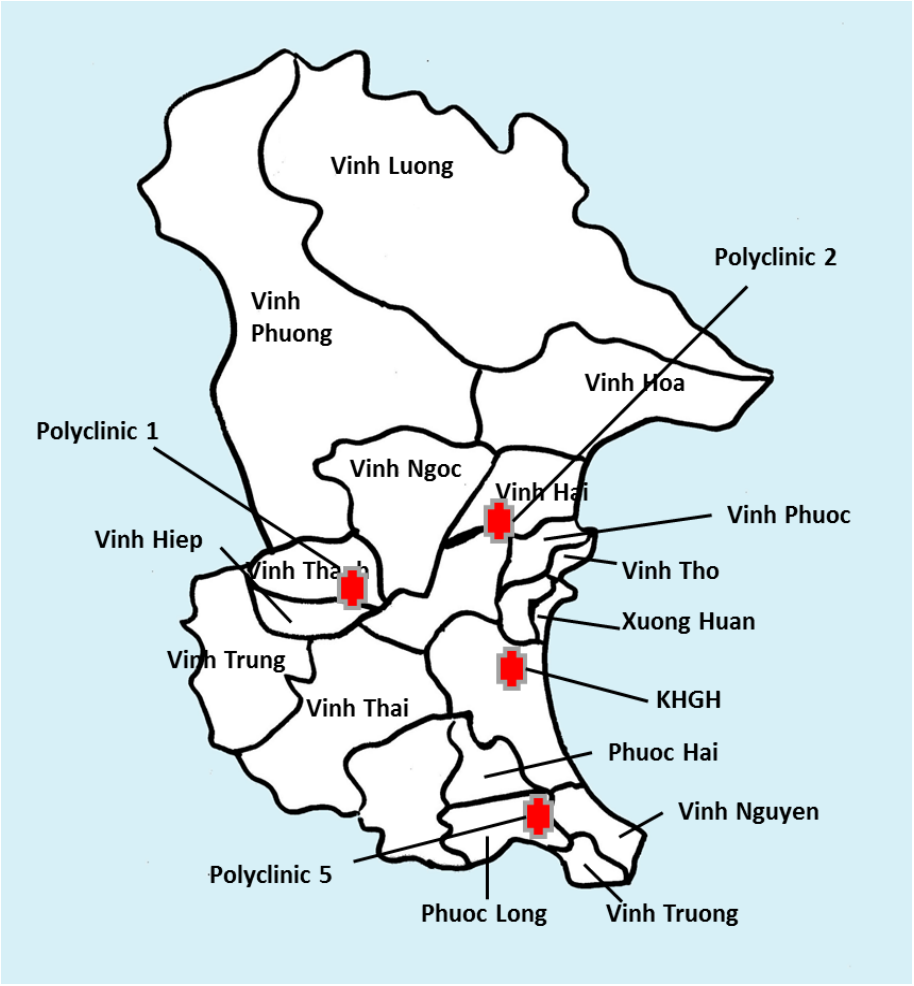


Figure 2. Location of study sites in Nha Trang city

2. Study Design

From August 2014 to December 2015, a passive hospital-based surveillance for dengue infection was conducted in patients between 1 and 55 years of age, residents of the selected 16 communes of Nha Trang city in Khanh Hoa province, Vietnam, who presented to KHGH and the selected 3 polyclinics (1, 2 and 5) with current fever (Axillary Temp $\geq$ 37.5º C) or history of fever for duration of less than 7 days without localizing signs. Individuals suffering from known cause or etiology listed in the patient identification SOP and/or planning to move out of the catchment area within the study period that could prevent the convalescent blood sample visit were excluded.

An acute sample of blood was taken when the patient first visited the hospital/polyclinics with fever and he/she was asked to return to the hospital/polyclinics for a convalescent sample collection between 10-14 days from the first visit. After the 14^{th} day, if the patient has not come to the hospital or polyclinics, phone calls or a house visit was made and the second blood sample was collected within 21 days from the first visit. At this follow up visit, case report forms (CRF) were completed after the clinical assessment. The consent documents and CRF were transported to Khanh Hoa Health Services (KHHS) regularly. Both acute and convalescent blood samples were tested at the National Institute of Hygiene and Epidemiology (NIHE) using

ELISA IgM/IgG. A subset of samples tested by IgM or rising of IgG were further evaluated with real-time PCR.

3. Sample collection

A blood draw of 5-7ml for acute and convalescent febrile sample was performed by phlebotomists with aseptic measures using disposable needles and syringes. Every laboratory specimen was labeled and identified using bar-coded surveillance participant's ID number and initials. A sticker was placed on at least one other form where the sample, time of collection, and subject ID number were all listed. Whole-blood samples collected at the KHGH and the polyclinics were stored at the KHGH microbiology lab and transported to the NIHE every month. The specimens were scanned and logged into a computerized database.

4. Laboratory testing

When the sera samples collected from the hospital and polyclinics arrived at the NIHE, both acute and convalescent samples underwent ELISA dengue IgM/IgG. The cut-off value of IgM and IgG capture ELISA was calculated by adding 0.3 to the mean absorbance of the negative controls. Samples that had results higher than the cut-off value were considered as positive, and samples that had results lower than the cut-off value were

considered as negative.

Presence of positive IgM dengue specific antibody by ELISA in acute (within 7 days of fever) serum specimen indicated dengue-positive case. In addition, samples with seroconversion of anti-dengue IgM from negative in the acute phase to positive in the convalescent phase, as well as samples with virus detection through real-time PCR in the acute serum specimen were considered as laboratory-confirmed. Samples resulted higher than the cut-off value for the IgG capture ELISA indicated that elevated IgG antibodies were detectable, identifying the evidence of past or recent dengue infection. Samples resulted less than the cut-off value indicated the absence of elevated IgG antibody level as an evidence of no recent dengue infection.

5. Case definitions of clinical diagnosis

In accordance with the WHO guideline (2009) (7), clinically diagnosed dengue cases were defined as individuals who presented with acute fever lasting up to 7 days combined with at least two of the following: nausea, vomiting, rash, aches or pains, positive tourniquet test, and leucopenia. Warning signs included: abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy or restlessness, liver enlargement over 2cm, and an increase in the hematocrit with a simultaneous decrease in platelets. Severe dengue was classified with severe plasma

leakage leading to dengue shock syndrome (DSS) and fluid accumulation with respiratory distress; severe bleeding; and severe organ involvement with liver (AST or ALT higher than 1,000IU/L), CNS (impaired consciousness), and heart and other organs.

6. Data management

Data entry, processing and maintenance were implemented by the Data Management Unit of KHHS in the use of Microsoft FOXPRO-based database created by the IVI''s Data Management Team. Data entry was validated regularly, and the data entered and screened/resolved for error were sent to the IVI data management team in a zip-file on a weekly basis during the surveillance study was conducted. In order to ensure the confidentiality of information about individual study participants, all personal names and other identifiers were removed from the data and replaced with study identification numbers and subject initials.

Once data collection was completed in the field, the study site was closed and IVI's Data Manager conducted a data cleaning process. For this particular study focusing on the association between clinical and laboratory-confirmed diagnoses of dengue, IVI's Data Manager exported cleaned data from the Microsoft FOXPRO-based database in the format of Microsoft Excel with only selected variables for secondary analysis of data.

7. Statistical analysis

Descriptive statistics were used to describe the distribution of the general characteristics of subjects, as well as signs and symptoms. The statistical analysis was carried out using R-3.4.2 software for Windows. Relevant clinical features were examined to find the association with DENV infection. Student's t test was used to determine differences in continuous variables, and chi-square tests were applied for comparing categorical proportions. Variables that were significant from exploratory analysis were selected for inclusion in a multiple logistic regression model to compare significant factors that accurately confirmed dengue among febrile patients. Sensitivity and specificity of clinical diagnoses given by local physicians were compared with laboratory-confirmed cases, and a receiver-operating characteristic (ROC) curve was plotted. P-value smaller than 0.05 ($p>0.05$) was considered as statistically significant.

8. Ethics

The study obtained ethical approvals from the Ethics Committee of NIHE, Hanoi, Vietnam; the Ethical Review Committee in the Ministry of Health (MoH), Vietnam; and Institutional Review Board (IRB) of the International Vaccine Institute (IVI). All participants (or the parents/legal

guardians for children) gave written informed consents and assents by signature or fingerprint. In order to protect the rights and confidentiality of the study participants and to ensure accuracy, reliability, and integrity of data, the study adhered to the principles of the Helsinki Declaration and the International Conference on Harmonization's Good Clinical Practice Guidelines (ICH-GCP).

III. Results

1. Study enrollment and lab results

From a total of 2,216 subjects enrolled, acute and convalescent samples of 1,858 participants who met the study criteria were collected for laboratory confirmation of DENV infection (Figure 3). Total 358 subjects were withdrawn, and most of withdrawal resulted during the second visit due to loss of follow-up (n=179) and consent withdrawal (n=175). Total of 1,705 patients classified as dengue (n=553) or non-dengue (1,152) by IgM and IgG capture ELISA or real-time PCR were evaluated with exclusion of 153 probable dengue cases.

Table 2 demonstrates laboratory results of IgM/IgG capture ELISA with or without real-time PCR for confirmation of dengue infection. It was mostly based on seroconversion from negative to positive of either IgM or IgG. From a total of 1,705 samples tested by IgM/IgG ELISA, a subset of 414 samples were further analyzed by real-time PCR.

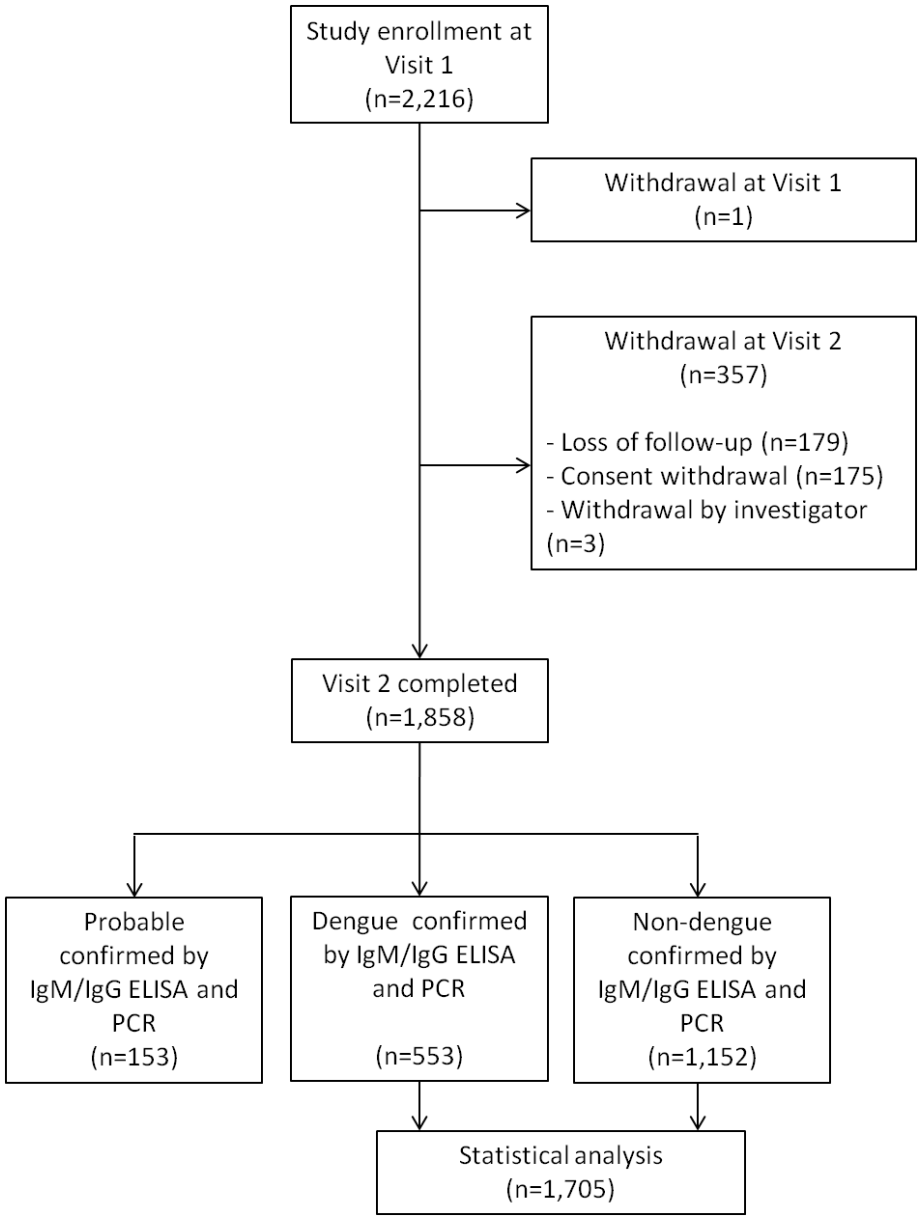


Figure 3. Flow chart of enrollment, participation and laboratory confirmation of dengue cases

Table 2. Laboratory-confirmation of dengue cases

IgM		IgG		Real-time PCR	Frequency n=1,858	Lab-confirmed
Acute	Conv.	Acute	Conv.			
+	+	+	+	+	42 (2.26)	**Dengue**
+	+	+	+	-	22 (1.18)	Non-dengue
+	+	+	+	Not done	120 (6.46)	Probable
+	+	+	-	Not done	1 (0.05)	Probable
+	+	-	+	+	26 (1.40)	**Dengue**
+	+	-	+	-	11 (0.59)	**Dengue**
+	+	-	+	Not done	61 (3.28)	**Dengue**
+	+	-	-	+	3 (0.16)	**Dengue**
+	+	-	-	-	10 (0.54)	Non-dengue
+	+	-	-	Not done	32 (1.72)	Probable
-	+	+	+	+	12 (0.65)	**Dengue**
-	+	+	+	-	3 (0.16)	**Dengue**
-	+	+	+	Not done	25 (1.35)	**Dengue**
-	+	-	+	+	101 (5.44)	**Dengue**
-	+	-	+	-	18 (0.97)	**Dengue**
-	+	-	+	Not done	87 (4.68)	**Dengue**
-	+	-	-	+	29 (1.56)	**Dengue**
-	+	-	-	-	5 (0.27)	**Dengue**
-	+	-	-	Not done	19 (1.02)	**Dengue**
-	-	+	+	+	3 (0.16)	**Dengue**
-	-	+	+	-	62 (3.34)	Non-dengue
-	-	+	+	Not done	175 (9.42)	Non-dengue
-	-	+	-	Not done	13 (0.70)	Non-dengue
-	-	-	+	+	12 (0.65)	**Dengue**
-	-	-	+	-	46 (2.48)	**Dengue**
-	-	-	+	Not done	50 (2.69)	**Dengue**
-	-	-	-	-	9 (0.48)	Non-dengue
-	-	-	-	Not done	861 (46.3)	Non-dengue

2. Demographic information of dengue patients

Among 553 dengue confirmed patients, 253 were male (45.8%) and 300 were female (54.2%) as shown in Table 3. Individuals with laboratory-confirmed dengue were more likely to be female than those who were laboratory-negative for dengue, but this difference did not reach statistical significance (p-value 0.768).

Patients with laboratory-positive for dengue were older (mean 21.6±13.0) than patients who were laboratory-negative for dengue (16.3±15.4). From a total of 553 individuals with laboratory-confirmed dengue, 345 were adults (61.4%) between 16-55 years of age and 208 were children (38.6%) between 1-15 years of age (p-value < 0.001). Table 4 and figure 4 shows that most dengue cases occurred in subjects 21-30 years old (n=137), while the highest number of enrollees who sought care for non-dengue illnesses were younger children between 1-5 years of age (n=405). Primary infection of DENV was more prevalent in the younger age group, especially in 6-10 years of age, while secondary infection was more common in the older age group in 31-55 years of age.

Table 3. Characteristics of laboratory-confirmed dengue patients

Characteristics	Total n=1,705	Dengue n=553	Non-dengue n=1,152	*p*-value
Sex				0.768
Male, n (%)	800 (46.9)	253 (45.8)	547 (47.5)	
Female, n (%)	905 (53.1)	300 (54.2)	605 (52.5)	
Age				
Age, years, mean±SD	18.3±14.6	21.6±13.0	16.3±15.4	**<0.001**
Children, n (%)	937 (55.0)	208 (38.6)	729 (62.9)	**<0.001**
Adults, n (%)	768 (45.0)	345 (61.4)	423 (37.1)	**<0.001**
Hospital visit				**<0.001**
IPD, n (%)	620 (36.4)	304 (56.2)	316 (26.8)	
OPD, n (%)	1,085 (63.6)	249 (43.8)	836 (73.2)	

Characteristics	Total n=1,705	Dengue n=553	Non-dengue n=1,152	*p*-value
Vital signs				
Axillary temperature, ℃, mean±SD	38.5±0.6	38.7±0.7	38.5±0.6	**<0.001**
Duration of fever, days, mean±SD	4.56±1.48	5.01±1.31	4.19±1.47	**<0.001**
Systolic blood pressure, mmHg, mean±SD	105.6±11.9	106.0±11.4	105.2±12.4	0.238
Diastolic blood pressure, mmHg, mean±SD	65.7±7.6	66.0±7.9	65.7±7.3	0.497
Pulse rate, mean±SD	93.5±13.9	91.2±12.7	95.1±14.5	**<0.001**
Respiratory rate, mean±SD	24.0±6.2	21.8±4.0	25.4±6.9	**<0.001**
Hematological tests				
Platelet, 1,000/ ul, mean±SD	208.7±95.6	169.7±85.7	241.5±85.7	**<0.001**
Hematocrit, %, mean±SD	37.7±5.6	38.4±5.4	37.1±5.6	**<0.001**
Hemoglobin, g/ ul, mean±SD	12.9±4.7	13.2±4.6	12.6±4.4	0.013
Leukocytes, 1,000/ ul, mean±SD	8.0±7.1	5.7±5.0	9.5±7.7	**<0.001**
Neutrophils, %, mean±SD	63.4±17.0	66.1±15.1	63.3±17.1	**<0.001**
Lymphocytes, %, mean±SD	25.6±14.2	22.2±12.6	26.7±14.5	**<0.001**

Table 4. Primary dengue infection, secondary dengue infection, and non-dengue infection among different age groups

Age Group	Dengue		Non-dengue	Total
	Primary	Secondary		
1-5	19 (7.25)	18 (6.19)	368 (31.9)	405 (23.8)
6-10	43 (16.4)	28 (9.62)	209 (18.1)	280 (16.4)
11-15	49 (18.7)	51 (17.5)	152 (13.2)	252 (14.8)
16-20	46 (17.6)	46 (15.8)	63 (5.47)	155 (9.09)
21-30	69 (26.3)	68 (23.4)	126 (10.9)	263 (15.4)
31-40	18 (6.87)	31 (10.7)	91 (7.90)	140 (8.21)
41-50	13 (4.96)	33 (11.3)	98 (8.51)	144 (8.45)
51-55	5 (1.91)	16 (5.50)	45 (3.91)	66 (3.87)
Total	262	291	1152	1,705

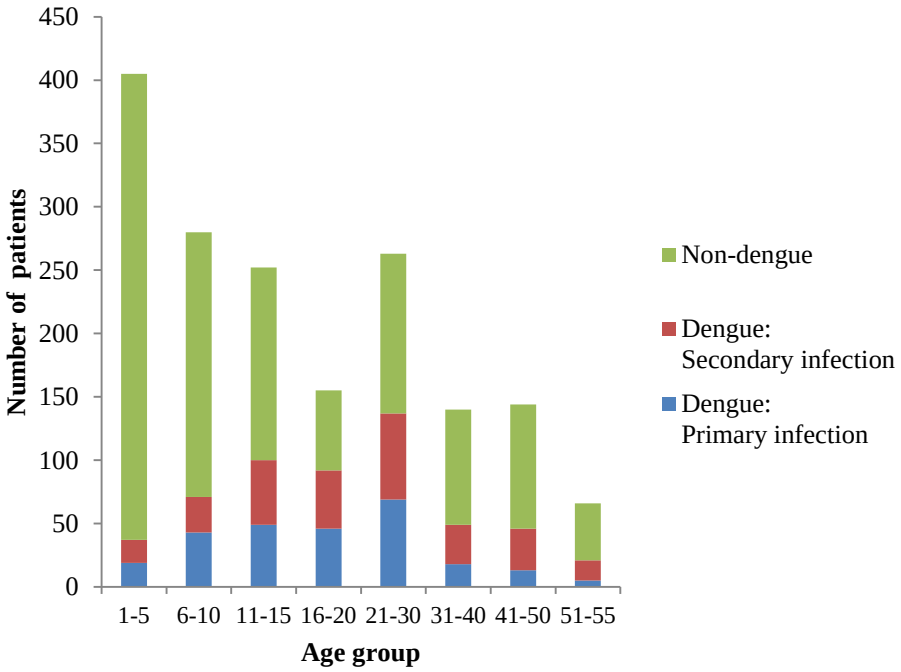


Figure 4. Proportion of primary dengue infection, secondary dengue infection, and non-dengue per age group

3. Medical information of dengue patients

As shown in Table 3, dengue frequency was higher in hospitalized cases (56.2%) than in outpatients (43.8%) with the IPD to OPD ratio of 1.22 (*p*-value < 0.001). Dengue cases were manifested with higher temperature (mean 38.7±0.6 ℃) and longer duration of fever (mean 5.01±1.31 days) compared to those measured for laboratory-negative for dengue (mean 38.5±0.6 ℃ and 4.19±1.47 days, respectively). Pulse rate and respiratory rate were lower in the dengue group (91.2±12.7 and 21.8±4.0, respectively) compared to those measured in the non-dengue group (95.1±14.5 and 25.4±6.9, respectively). Lower count of platelets (mean 169,700±85,700/uL) and leukocytes (5,700±5,000/uL), as well as higher hematocrit (mean 38.4±5.4 %) were significantly associated with dengue cases (*p*-value <0.001).

4. Dengue serotypes

There were total 193 samples from which DENV serotypes were detectable through real-time PCR. All four serotypes of dengue virus was prevalent (Figure 5), and DENV-1 was predominant (67%) followed by DENV-2 (27%). There was only one patient infected with DENV-4. These findings were in accordance with the national data in Figure 1 where DENV-1 was predominant with increase starting in 2013 after the highest peak during 2008-2010 (27).

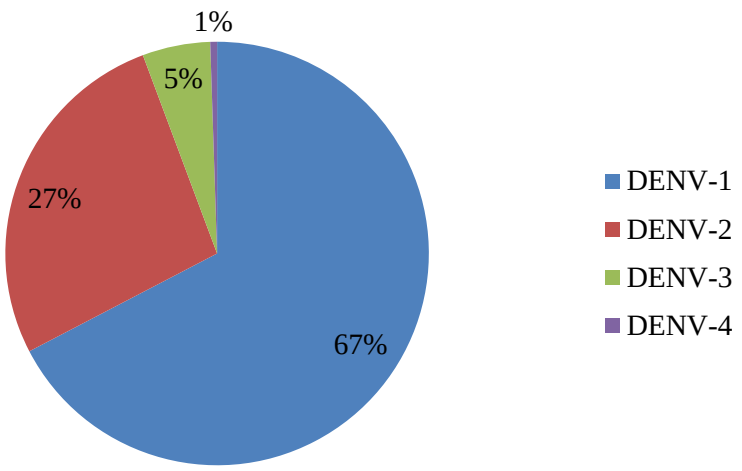


Figure 5. Proportion of DENV serotypes from real-time PCR results

5. Seasonal and regional distribution of dengue cases

Infection of dengue virus occurred year-round, and infection peaked during August to November especially in the second year of the study in 2015 (Figure 6). Highest number of dengue cases occurred in September 2015 (n = 135) and October 2015 (n = 136) which were almost half of febrile cases in the months. Fairly high number of non-dengue febrile cases were recorded in June 2015 (n = 115), but number of dengue cases was not significantly high (n=12).

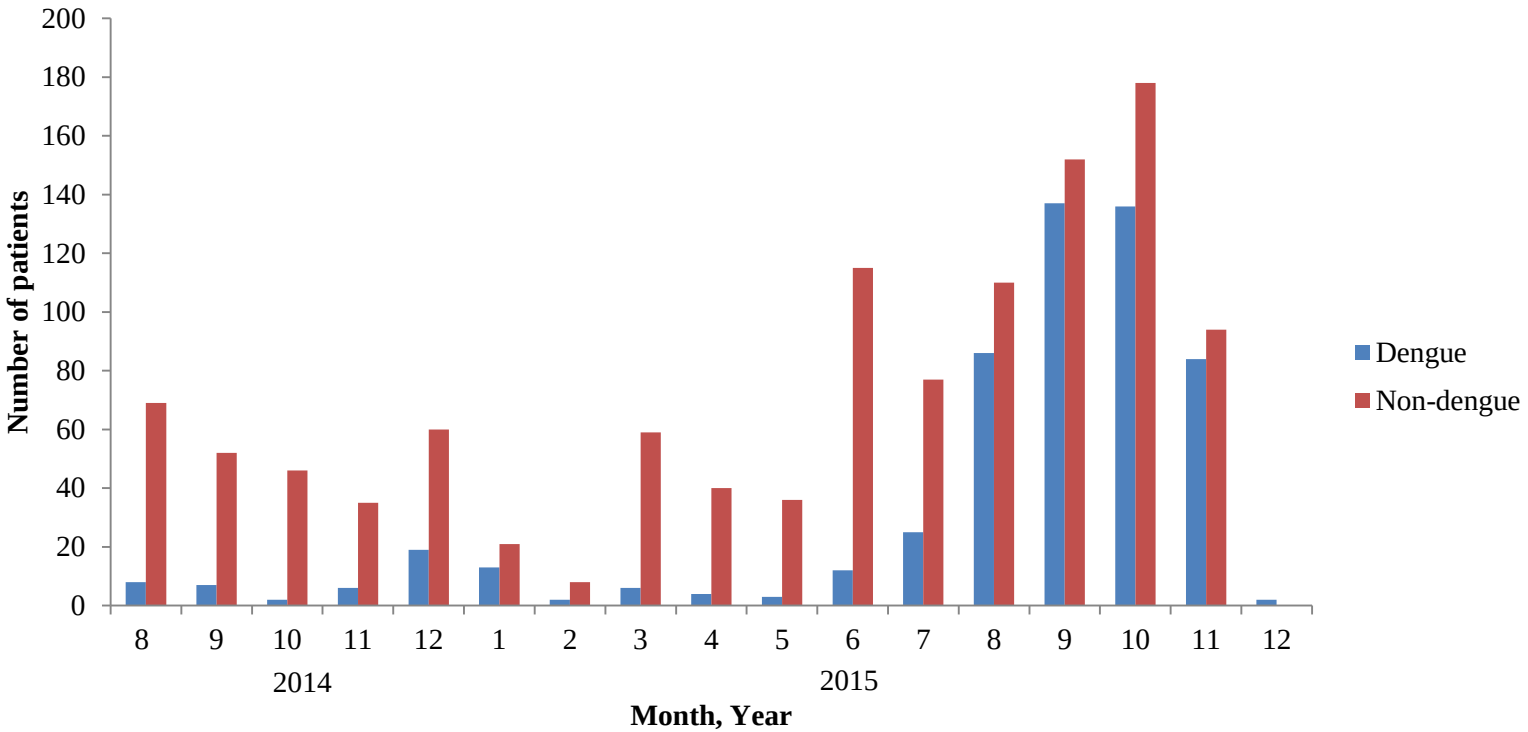


Figure 6. Monthly distribution of dengue and non-dengue patients

Infection of dengue virus occurred year-round, and infection peaked during August to November especially in the second year of the study (Figure 6). Highest number of dengue cases occurred in September 2015 (n = 135) and October 2015 (n = 136) which were almost half of febrile cases in the months. Fairly high number of non-dengue febrile cases were recorded in June 2015 (n = 115), but number of dengue cases was not significantly high (n=12).

More than a half of dengue infection occurred in communes around Polyclinic 2 (Table 5). Vinh Phuoc had the highest number of dengue cases (n = 95) followed by Vinh Hai (n = 86) and Vinh Hoa (n = 57). The rest of dengue cases were shared by communes located nearby Polyclinic 1 (28.79%) and Polyclinic 5 (21.5%).

Table 5. Regional distribution of dengue cases

Commune	Polyclinic	Dengue	Non-dengue	Total
Vinh Hai	2	86 (16.1)	156 (13.5)	242 (14.2)
Vinh Phuoc	2	95 (17.8)	158 (13.7)	253 (14.8)
Vinh Tho	2	29 (5.42)	36 (3.13)	65 (3.81)
Vinh Hoa	2	57 (10.7)	104 (9.03)	161 (9.44)
Vinh Luong	2	10 (1.87)	56 (4.86)	66 (3.87)
Xuong Huan	2	6 (1.12)	8 (0.69)	14 (0.82)
Phuoc Hai	5	10 (1.87)	31 (2.69)	41 (2.40)
Vinh Nguyen	5	29 (5.42)	56 (4.86)	85 (4.99)
Vinh Truong	5	31 (5.79)	54 (4.69)	85 (4.99)
Phouc Long	5	46 (8.60)	135 (11.7)	181 (10.6)
Vinh Phuong	1	42 (7.85)	104 (9.03)	146 (8.56)
Vinh Ngoc	1	46 (8.60)	86 (7.47)	132 (7.74)
Vinh Thanh	1	16 (2.99)	46 (3.99)	62 (3.64)
Vinh Hiep	1	12 (2.24)	37 (3.21)	49 (2.87)
Vinh Thai	1	24 (4.49)	41 (3.56)	65 (3.81)
Vinh Trung	1	14 (2.62)	44 (3.82)	58 (3.40)
Total		553	1,152	1,705

6. Clinical features of dengue patients

The most frequent clinical feature in dengue patients was fatigue/weakness (91.0%); however, it was also highly prevalent among non-dengue patients (74.8%) without significant association with dengue infection (Table 6). Multivariate analysis indicated that rash (OR = 1.90; CI 95% = 1.30-2.80), arthralgia (OR = 1.75; CI 95% = 1.30-2.36), headache (OR = 1.75; CI 95% = 1. 25-2.48), petechiae (OR = 1.71; CI 95% = 1.10-2.65), and nausea/vomiting (OR = 1.42; CI 95% = 1.05-1.93) were independently associated with laboratory-confirmed dengue. Conversely, respiratory symptoms such as rhinorrhea (OR = 0.41; CI 95% = 0.28-0.60) and expectoration (OR = 0.39; CI 95% = 0.23-0.63) had higher associations with non-dengue patients.

For further evaluation of the significant hematologic parameters in Table 3, thrombocytopenia, leucopenia, and hemoconcentration were analyzed. Thrombocytopenia was defined as a platelet count < 150,000/ul, leucopenia was defined as a leukocyte count < 4,000/ul, and hemoconcentration was defined as a hematocrit > 45%.While leucopenia (OR = 6.03; CI 95% = 4.30-8.53) and thrombocytopenia (OR = 1.97; CI 95% = 1.42-2.74) were highly associated with dengue cases, hemoconcentration was not a significantly associated feature of hematologic parameters.

Table 6. Clinical features associated with laboratory-positive dengue

	Dengue	Non-dengue	Univariate			Multivariate		
	n= 553	n= 1,152	OR	95% CI	*p*-value	OR	95% CI	*p*-value
General								
Rash	119 (21.5)	68 (5.90)	4.37	3.19-6.03	<0.001	**1.90**	**1.30-2.80**	**0.001**
Flushed face	99 (17.9)	248 (21.5)	0.80	0.61-1.03	0.0971	-	-	NS
Fatigue/weakness	503 (91.0)	862 (74.8)	3.38	2.48-4.71	<0.001	-	-	NS
Headache	481 (87.0)	766 (66.5)	3.36	2.56-4.45	<0.001	**1.75**	**1.25-2.48**	**0.001**
Retro-orbital pain	73 (13.2)	50 (4.34)	3.35	2.31-4.90	<0.001	-	-	NS
Neck pain	19 (3.44)	58 (5.03)	0.67	0.39-1.12	0.1715	-	-	NS
Myalgia	314 (56.8)	327 (28.4)	3.31	2.68-4.09	<0.001	-	-	NS
Arthralgia	253 (45.8)	235 (20.4)	3.29	2.64-4.10	<0.001	**1.75**	**1.30-2.36**	**<0.001**
Loss of appetite	253 (45.8)	417 (36.2)	1.49	1.21-1.83	<0.001	-	-	NS

	Dengue	Non-dengue	Univariate			Multivariate		
	n= 553	n= 1,152	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Respiratory								
Otalgia	6 (1.08)	18 (1.56)	0.69	0.25-1.66	0.5715	-	-	NS
Nasal congestion	33 (5.97)	206 (17.9)	0.29	0.20-0.42	<0.001	-	-	NS
Rhinorrhea	45 (8.14)	397 (34.5)	0.17	0.12-0.23	<0.001	**0.41**	**0.28-0.60**	**<0.001**
Sore throat	114 (20.6)	493 (42.8)	0.35	0.27-0.44	<0.001	-	-	NS
Cough	132 (23.9)	620 (53.8)	0.27	0.21-0.34	<0.001	-	-	NS
Expectoration	26 (4.70)	194 (16.8)	0.24	0.16-0.37	<0.001	**0.39**	**0.23-0.63**	**<0.001**
Dyspnea	6 (1.08)	19 (1.65)	0.65	0.24-1.56	0.489	-	-	NS
Gastrointestinal								
Nausea/vomiting	184 (0.33)	196 (17.0)	2.43	1.92-3.08	<0.001	**1.42**	**1.05-1.93**	**0.021**
Diarrhea	45 (0.08)	84 (7.29)	1.13	0.77-1.63	0.603	-	-	NS
Constipation	7 (0.01)	6 (0.52)	2.45	0.81-7.64	0.174	-	-	NS
Abdominal pain	104 (0.19)	128 (11.1)	1.85	1.40-2.45	<0.001	-	-	NS

	Dengue	Non-dengue	Univariate			Multivariate		
	n= 553	n= 1,152	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Hemorrhagic								
Epistaxis	17(0.03)	15 (1.30)	2.40	1.19-4.91	0.0196	-	-	NS
Gum bleeding	24 (0.04)	10 (0.87)	5.18	2.53-11.42	<0.001	-	-	NS
Ecchymosis	8 (0.01)	1 (0.09)	0.17	3.09-313.8	0.001	-	-	NS
Petechiae	140 (0.25)	52 (4.51)	7.17	5.15-10.13	<0.001	**1.71**	**1.10-2.65**	**0.017**
Others								
Hepatomegaly	8 (0.01)	6 (0.52)	2.80	0.97-8.55	0.090	-	-	NS
Oliguria	5 (0.01)	1 (0.09)	1.05	1.69-201.5	0.026	-	-	NS
Convulsion/seizure	3 (0.01)	30 (2.60)	0.20	0.05-0.58	0.007	-	-	NS
Hematologic								
Thrombocytopenia	246 (0.44)	123 (10.7)	6.63	5.16-8.55	<0.001	**1.97**	**1.42-2.74**	**<0.001**
Leucopenia	232 (0.42)	68 (5.90)	11.50	8.58-15.60	<0.001	**6.03**	**4.30-8.53**	**<0.001**
Hemoconcentration	35 (0.06)	56 (4.86)	1.30	0.83-2.00	0.289	-	-	NS

Receiver-operating characteristic (ROC) curve was plotted to find the best combination of clinical features identified for dengue diagnosis (Figure 7). Combination of leucopenia, thrombocytopenia, rash, and petechiae resulted in the highest sensitivity (70.8%) with 79.9% of specificity and 0.784 of AUC. When all of key clinical features identified from this study were combined including leucopenia, thrombocytopenia, rash, petechiae, arthralgia, and headache, AUC increased to 0.815 with relatively decreased sensitivity (64.4%).

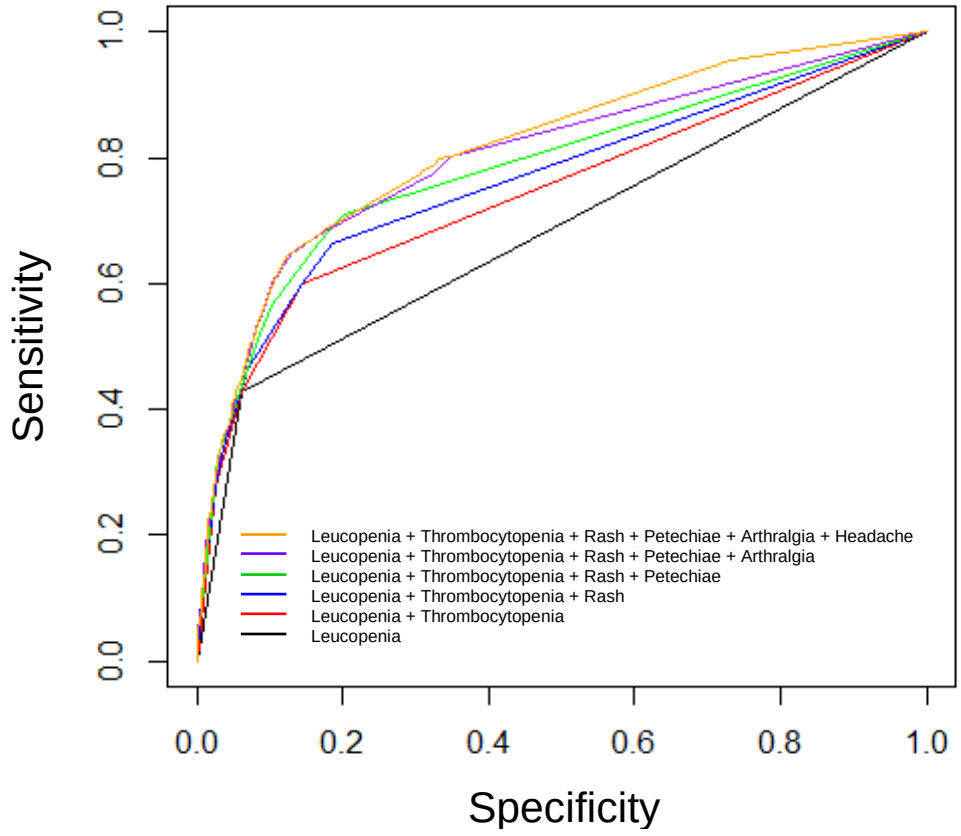


Figure 7. Receiver-operating characteristic (ROC) curve for lab-confirmed dengue cases with clinical predictive markers specified

7. Comparison of clinical features between adults and children

A comparison between adults and children of laboratory-confirmed dengue cases revealed that the frequency of clinical signs and symptoms was different between two age groups (Table 7). In children, dengue was associated with higher odds ratios of leucopenia (OR = 5.64; CI 95% = 3.28-9.89), and petechiae (OR = 2.74; CI 95% = 1.38-5.45), in absence of rhinorrhea (OR = 0.46; CI 95% = 0.27-0.74), and expectoration (OR = 0.34; CI 95% = 0.14-0.72), whereas dengue infected adults had odds ratios of leucopenia (OR = 5.01; CI 95% = 3.21-7.94), petechiae (OR = 2.74; CI 95% = 1.38-5.45), in absence of rhinorrhea (OR = 0.48; CI 95% = 0.26-0.84), and expectoration (OR = 0.42; CI 95% = 0.21-0.79).

Laboratory-confirmed adult patients were more likely to have headache (OR = 2.10; CI 95% = 1.13-4.04), rash (OR = 1.96; CI 95% = 1.18-3.28), thrombocytopenia (OR = 1.91; CI 95% = 1.24-2.95), and arthralgia (OR = 1.83; CI 95% = 1.26-2.66) compared with dengue laboratory-negative adults, but they were not associated with DENV infected children. Flushed face was highly associated with dengue laboratory-positive adults (OR = 2.13; CI 95% = 1.16-3.99); in contrast, children patients with laboratory-positive dengue infections were significantly less likely than laboratory-negative children to present flushed face (OR = 0.36; CI 95% = 0.20-0.62).

Table 7. Clinical features associated with dengue-confirmed children and adults

Clinical features	Dengue	Non-dengue	Univariate			Multivariate		
			OR	95% CI	*p*-value	OR	95% CI	*p*-value
Children	n= 208	n= 729						
Flushed face	40 (19.2)	223 (30.6)	0.54	0.37-0.79	0.002	0.36	0.20-0.62	<0.001
Rhinorrhea	26 (12.5)	287 (39.4)	0.22	0.14-0.33	<0.001	0.46	0.27-0.74	0.002
Expectoration	7 (3.37)	116 (15.9)	0.18	0.08-0.37	<0.001	0.34	0.14-0.72	0.009
Petechiae	45 (21.6)	28 (3.84)	6.91	1.51-11.53	<0.001	2.74	1.38-5.45	0.004
Leucopenia	68 (32.7)	28 (3.84)	11.89	7.46-19.43	<0.001	5.64	3.28-9.89	<0.001
Adults	n= 345	n= 423						
Rash	85 (24.6)	36 (8.51)	3.51	2.33-5.40	<0.001	**1.96**	**1.18-3.28**	**0.010**
Headache	323 (93.6)	366 (86.5)	2.29	1.39-3.90	0.002	**2.10**	**1.13-4.04**	**0.022**
Arthralgia	200 (58.0)	169 (40.0)	2.07	1.55-2.77	<0.001	**1.83**	**1.26-2.66**	**0.001**
Flushed face	59 (17.1)	25 (5.91)	3.28	2.03-5.45	<0.001	**2.13**	**1.16-3.99**	**0.016**
Rhinorrhea	19 (5.51)	110 (26.0)	0.17	0.10-0.27	<0.001	0.48	0.26-0.84	0.013
Expectoration	19 (5.51)	78 (18.4)	0.26	0.15-0.43	<0.001	0.42	0.21-0.79	0.009

Clinical features	Dengue	Non-dengue	Univariate			Multivariate		
			OR	95% CI	*p*-value	OR	95% CI	*p*-value
Petechiae	95 (27.5)	24 (5.67)	6.32	3.99-10.36	<0.001	2.74	1.38-5.45	0.004
Thrombocytopenia	185 (53.6)	75 (17.7)	5.44	3.93-7.58	<0.001	**1.91**	**1.24-2.95**	**0.003**
Leucopenia	164 (47.5)	40 (9.46)	8.93	6.11-13.33	<0.001	5.01	3.21-7.94	<0.001

8. Evaluation of clinical diagnostic accuracy

Based on the number of true positive, false positive, false negative, and true negative in comparison of the clinical diagnosis to the laboratory diagnosis (Table 8), accuracy of clinical diagnosis of dengue was assessed as shown in Table 9. Among total of 1,705 febrile patients, 319 were true positive, 92 were false positive, 234 were false negative, and 1,060 were true negative. The number of true positive, false positive, false negative, and true negative of children was 97, 33, 111, and 696 respectively, whereas adults had 222, 59, 123, and 364 respectively. Overall sensitivity and specificity of clinical diagnoses were 57.7% and 92.0% with diagnostic accuracy of 80.9%. Sensitivity and positive predictive value of clinical diagnoses for children (46.6% and 74.6%) were relatively lower than adults (64.4% and 79.0%), but specificity and negative predictive value for children (95.5% and 86.3%) were higher than adults (86.1% and 74.7%).

As shown in Figure 8, adjusting clinically non-dengue cases in children group manifested with leucopenia improved sensitivity of clinical diagnosis from 47.6% to 64.0% with increase of AUC from 0.72 to 0.79. Sensitivity and AUC of clinical diagnosis for adults (66.5% and 0.77) was increased by adjustment of clinically non-dengue adults with leucopenia (77.3% and 0.83); leucopenia and thrombocytopenia (81.3% and 0.85); and leucopenia, thrombocytopenia, and rash (85.8% and 0.87).

Table 8. Number of dengue and non-dengue cases in clinical and laboratory diagnosis of dengue

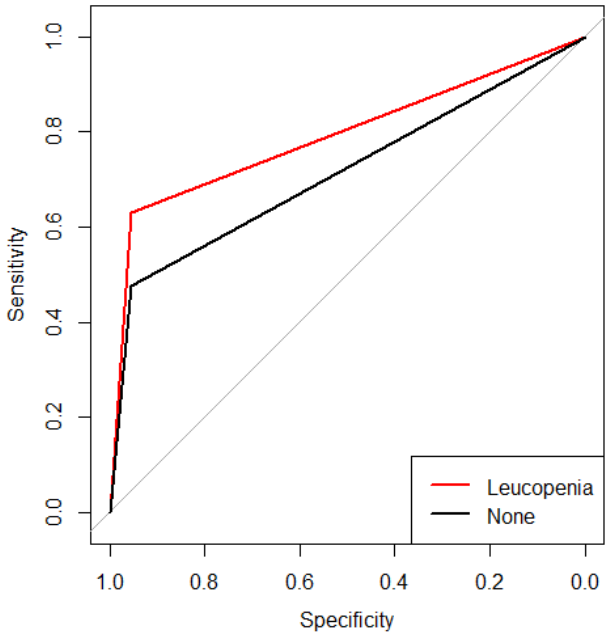
	All	Laboratory-confirmed		
		Dengue	Non-dengue	Total
Clinical diagnosis	Dengue	319	92	411
	Non-dengue	234	1,060	1,294
	Total	553	1,152	1,705

	Children	Laboratory-confirmed		
		Dengue	Non-dengue	Total
Clinical diagnosis	Dengue	97	33	130
	Non-dengue	111	696	807
	Total	208	729	937

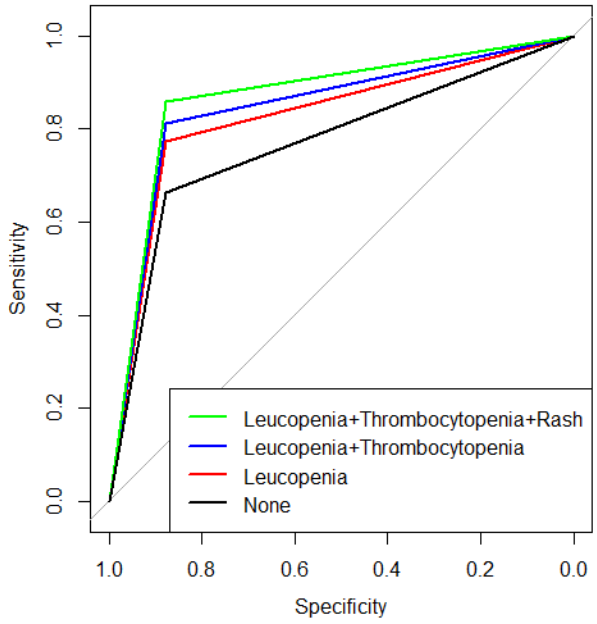
	Adult	Laboratory-confirmed		
		Dengue	Non-dengue	Total
Clinical diagnosis	Dengue	222	59	281
	Non-dengue	123	364	487
	Total	345	423	768

Table 9. Evaluation of clinical diagnostic accuracy

	Total (95% CI)	Children (95% CI)	Adult (95% CI)
Sensitivity	**57.7 (53.5-61.8)**	**46.6 (39.7-53.7)**	**64.4 (59.0-69.4)**
Specificity	92.0 (90.3-93.5)	95.5 (93.7-96.9)	86.1 (82.4-89.2)
PPV	77.6 (73.8-81.0)	74.6 (67.1-80.9)	79.0 (74.6-82.8)
NPV	81.9 (80.4-83.3)	86.3 (84.7-87.7)	74.7 (71.9-77.4)
Diagnostic Accuracy	80.9 (78.9-82.7)	84.6 (82.2-86.9)	76.3 (73.1-79.3)



(a) Children



(b) Adults

Figure 8. Receiver-operating characteristic (ROC) curves for children and adults in adjustment of clinically non-dengue cases associated with leucopenia, thrombocytopenia, and rash

IV. Discussion

The study yielded clear evidence of high prevalence of DENV infection (32.4%) in both adult between 16-55 years of age (44.9%) and children between 1-15 years of age (22.2%) in Nha Trang city, Khanh Hoa province, Vietnam. In accordance with epidemics occurring in the cycle of 3-5 years, increase of dengue cases was expected in the study period from August 2014 to December 2015 following peaks in 1995, 1998, 2005, 2010, and 2012 in Khanh Hoa province (28).

In the dengue-endemic regions, it is common and natural that the secondary infection of DENV is more prevalent in adults (29, 30), as an older group is more exposed to dengue infection in comparison to children in the context of timing as well as spatial setting of daily activities. In contrast to low number of dengue cases in younger children between 1-5 years of age, high number of the group sought care for other febrile illnesses such as influenza. Findings from national surveillance for influenza and influenza-like illness in Vietnam during 2006-2010 imply that influenza is very commonly observed from children younger than 5 years of age in the country (31). It is also known that fever is more common in children than adults with influenza (32, 33). In addition, an active surveillance study in children of 5 Asian countries including Indonesia, Malaysia, Philippines, Thailand, and Vietnam indicated that Chikungunya and Salmonella typhi were also common causes

of febrile illness other than dengue and influenza for children (26).

More frequent DENV infections were observed in the second half of year significantly from August to November, in consistence with the study that analyzed seasonal patterns of dengue fever and associated climate factors in 4 provinces in Vietnam from 1994 to 2013 (28). Khanh Hoa province had mean temperature of 26.9 ± 1.76 ℃ and mean precipitation of 133.6 ± 175.7 mm from 1994 to 2013, and mean temperature increased above 28.0 ℃ during May to August , whereas mean precipitation increased above 200.0 mm during September to November in 1994-2013. Their final model presented that, in Khanh Hoa province, an increase of 1 ℃ in temperature and 100 mm in precipitation were corresponded to an increase of 17% and 11% of dengue fever incidence rate respectively.

Dengue cases were widely distributed in all areas of Nha Trang city but mostly in communes located nearby Polyclinic 2. This may be attributed to the more active surveillance and increased public awareness in the region. There were more DENV infections from communes placed around each polyclinic probably due to easy access to the healthcare system. It is assumed that febrile patients with or without mild signs and symptoms of dengue might have not sought for healthcare service if polyclinics were not adjacent to their home or work places. There may be other social-ecological conditions that could not be analyzed from this study but further investigation might be

helpful in the future.

The study revealed that specific clinical signs and symptoms including petechiae, rash, headache, arthralgia, and nausea/vomiting were significantly associated with laboratory-confirmed dengue, and this finding was fairly consistent with other studies (34-37). Petechiae were the most common hemorrhagic manifestation as observed in previous researches (35, 37-41). Studies which assessed all age groups also demonstrated that the frequency of rash was higher in patients with dengue (35, 41-44). Respiratory symptoms such as rhinorrhea and expectoration were more commonly associated with laboratory-negative cases than laboratory-positive cases, similar to other studies (45, 46). From hematological data, leucopenia and thrombocytopenia were highly associated with dengue cases as reported from other studies (47-49). Although common in other viral illness, leucopenia has been consistently reported as an independent discriminator of dengue diagnosis among febrile patients (50-54). Indeed, it was the most important isolated predictor in this study.

There were similarities and differences in clinical features between dengue infected children and adults. In addition to the shared features of petechiae and leucopenia, adults showed significantly higher incidence of dengue than children of headache and arthralgia, comparable to previous studies (34, 36). These findings may be related to the difficulty in identifying

those signs and symptoms by children and their parents or guardians, whereas adults are more likely to be able to report those specific clinical manifestations. Furthermore, it was notable to find that presence of rash and thrombocytopenia in adults was significantly different from children. Identical to findings from overall data, respiratory signs and symptoms were not involved in dengue cases studied for both children and adults. Interestingly, children patients with laboratory-positive dengue infections were significantly less likely than laboratory-negative children to present flushed face; in opposition, flushed face was highly associated with dengue laboratory-positive adults.

Although clinical diagnoses of dengue based on the WHO guideline (2009) (7) was not as accurate as serologic tests or molecular methods, their accuracy was acceptable with overall accuracy of 80.9%. Meanwhile, sensitivity of clinical diagnosis was relatively low for both groups of adults (64.4%) and children (46.6%). Higher prevalence of flu in children group may have decreased sensitivity of clinical diagnosis for DENV infection. Assuming that the discriminating clinical features significantly associated with dengue laboratory-positive patients identified from this study were applied to clinical diagnosis of dengue, remarkable improvements of diagnostic sensitivity were observed. Sensitivity of clinical diagnosis for adults could be improved up to 85.5% in combination of leucopenia, thrombocytopenia, and rash. Moreover, adjustment of clinically non-dengue

cases in children group manifested with leucopenia could also improve sensitivity of clinical diagnosis up to 64.0%. Consequently, the use of those clinical features identified from this study may enhance the ascertainment of dengue cases by clinical criteria, and enable a more accurate estimation of the disease burden.

The study was unique that it captured most of the patients that may be representative of the residents of Nha Trang city by implementing surveillance in the KHGH and the selected polyclinics for the catchment area of 16 communes. This enhanced the study design to detect mild cases that may not seek care at the hospital, as patients with mild fever may have chosen to go to the polyclinic serving several selected communes. However, the study had several limitations including incomplete laboratory data. First, all samples analyzed in the study were tested by IgM/IgG ELISA, but real-time PCR was conducted for only a subset of samples. It is known that the ELISA cross-reacts with other flaviviruses, specifically, IgM ELISA is cross-reactive with other flaviviruses causing false positives; at the same time, IgG usually lacks specificity within flavivurs serocomplex groups. While IgM/IgG ELISA and real-time PCR are widely used for laboratory-confirmation of DENV infection, sensitivities and specificities of commercial kits also vary in different degrees and some of test kits are not confirmative to be the "gold standard" of laboratory diagnosis. Second, this study may have missed dengue cases at first days of illness due to lack of laboratory tests for dengue

nonstructural protein 1 (NS1). Known as an early antigen presenting in sera of dengue patients, NS1 antigen involves in the pathogenesis of dengue infection. NS1 tests are recommended as a rapid, easy, sensitive, and specific test for the early diagnosis of dengue infection after the onset of fever (55). Sensitivity of NS1 detection is higher at first days of illness (56), so the use of NS1 tests may help to diagnose dengue in patients with samples collected from day 0 to day 2. Third, tourniquet test, one of the clinical features in the WHO guideline (2009) (7), was not routinely performed in the clinical practice of this study. However, the method is considered as an old test for demonstrating vasculopathy or coagulopathy with its low sensitivity for dengue diagnosis (57-59), but it may be a valuable indicator of dengue severity (60). In addition, data collected from memory of patients may be inadequate and unreliable due to omitted or inaccurate information, and the misinformation could add a significant bias to the analyses. Furthermore, there may be other variables that could explain the findings from this study with 161 probable dengue cases excluded from the analyses.

In conclusion, the DVI's dengue fever surveillance study conducted from August 2014 to December 2015 in Nha Trang City, Vietnam identified key clinical features for diagnosis of dengue infection. Petechiae, rash, headache, arthralgia, nausea/vomiting, leucopenia, and thrombocytopenia were highly associated with laboratory-positive dengue cases in the absence of respiratory signs and symptoms such as rhinorrhea and expectoration.

Clinical diagnosis on children and adults should be distinguished as DENV infected adults were more likely to present thrombocytopenia, rash, flushed face, headache, and arthralgia which were not apparent to DENV infected children. Once validated, those key clinical features could influence clinical outcomes as they would allow more closely monitoring of selected patients and it may affect the sensitivity of clinical diagnosis. However, the accuracy of those predictive markers might be subject to change in accordance to the prevalence of dengue infection as well as clinicians' alertness. While implementation of laboratory tests including isolation of the virus, serological tests and molecular methods is highly recommend for accurate diagnosis of dengue infection, improved quality of clinical confirmation of dengue cases accompanied by those key features might be beneficial in resource-poor settings in dengue-endemic developing countries.

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VI. 국문초록

베트남 냐짱 지역의 뎅기역학조사: 뎅기의 임상진단과 실험실진단의 연관성

뎅기열은 베트남에서 주요 질병의 하나로써, morbidity 가 2000 년에 인구 10 만 명당 32.5 명에서 2009 년에 인구 10 만 명당 120.0 명으로 점차 증가하였다. 베트남에서 대부분의 뎅기 바이러스 감염은 WHO guideline (2009 년)을 기준으로 임상적으로 진단되고 있으나, 다른 열성 질환과 공유되는 광범위한 증상으로 인하여 뎅기열은 일반적으로 적게 보고되고 잘못 분류되고 있다. 뎅기백신사업단 (DVI)를 대신하여 국제백신연구소 (IVI)는 2014 년 7 월부터 2015 년 12 월까지 베트남 칸호아 성 냐짱 에서 열을 동반한 1-55 세 사이의 어린이와 성인을 대상으로 뎅기열 역학조사를 수행하였으며, 이 연구에서 얻어진 데이터를 통하여 뎅기의 임상진단과 실험실진단의 연관성을 평가하였다. IgM/IgG ELISA 와 RT-PCR 을 통한 실험실진단 결과, 553 명의 뎅기열 환자와 1,152 명의 비 뎅기열 환자가 보고 되었으며, 뎅기열 환자의 임상 징후 및 증상을 분석하였다. 백혈구감소증 (OR = 6.03), 혈소판감소증

(OR = 1.97), 발진 (OR = 1.90), 관절통 (OR = 1.75), 두통 (OR = 1.75), 점상출혈 (OR = 1.71), 그리고 메스꺼움/구토 (OR = 1.42)는 뎅기열감염과 높은 연관성을 보였으며, 비루 (OR = 0.41)와 가래 (OR = 0.39)와 같은 호흡기 증상은 뎅기열감염과 연관성이 없는것으로 확인되었다. 실험실진단으로 확인 된 뎅기열 환자 중 성인과 어린이를 비교 한 결과, 임상 적 징후 및 증상이 두 연령 그룹 간에 차이가 있는 것으로 나타났다. 뎅기 바이러스에 감염된 성인은 얼굴홍조 (OR = 2.13), 두통 (OR = 2.10), 발진 (OR = 1.96), 혈소판감소증 (OR = 1.91) 및 관절통 (OR = 1.83)의 임상학적 증상과 질환이 크게 나타났으나, 뎅기 바이러스에 감염된 어린이에게서는 특이적으로 나타나지 않았다. 본 연구의 임상진단의 민감도와 특이도는 각각 57.7%와 92.0%였고, 정확도는 80.9 %였다. 본 연구에서 확인된 뎅기열 환자의 주요 임상 징후 및 증상들의 유효성이 검증된다면, 이를 적용하여 선택된 환자들을 보다 면밀히 감시할 수 있고, 또 임상진단의 민감도에 영향을 줄 수 있을 것으로 기대된다.

표제어: 뎅기, 베트남, 임상신단, 실험실진단, 열, 발진, 혈소판감소증, 백혈구감소증

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