# The Predictors of Diagnosis upon Presentation of Patients with Dengue-Like Symptoms at a Public Primary Care Clinic in Selangor

Zhuo-Lin Chong, chongzl@moh.gov.my
Rafidah Ali, rafidah_a@moh.gov.my
Noor Aliza Lodz, draliza.lodz@moh.gov.my
Institute for Public Health, National Institutes of Health, Ministry of Health, Malaysia

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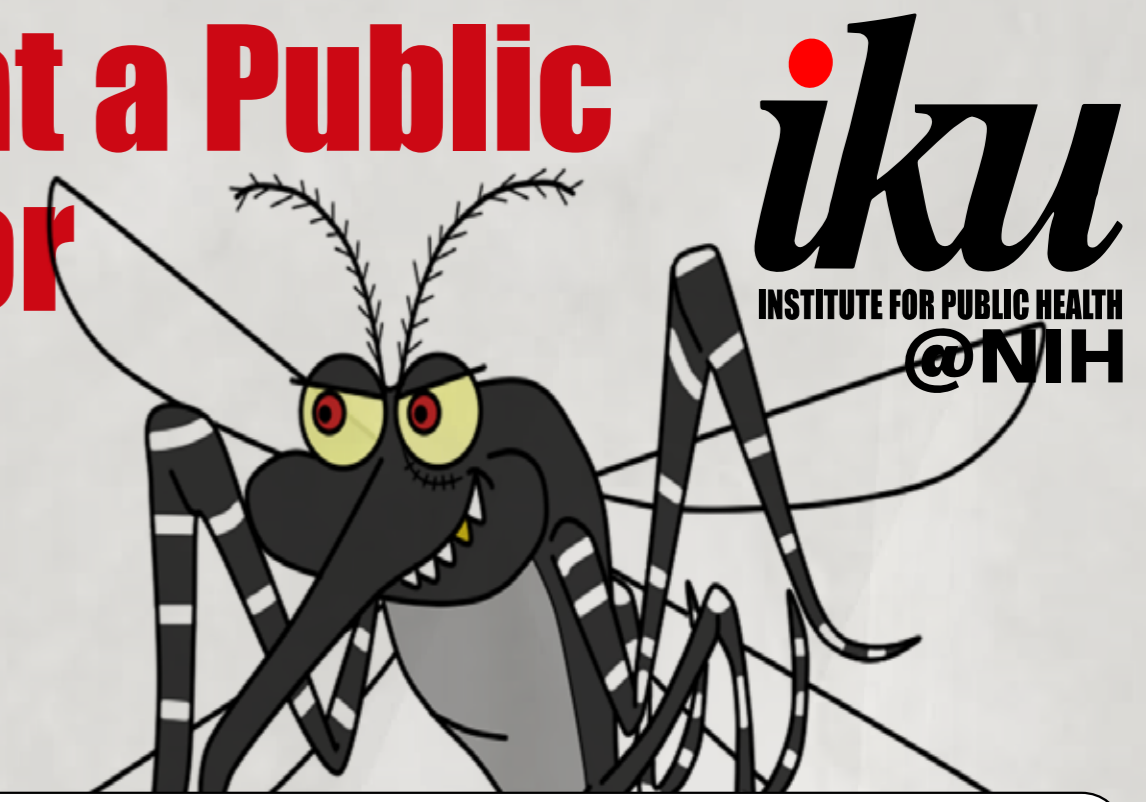
Background

Dengue fever can present with mild and non-specific symptoms [1]. Physicians regularly face uncertainties in its diagnosis or exclusion. Knowing the socioeconomic, clinical, and epidemiological predictors of the final diagnosis among patients with dengue-like symptoms can reduce misdiagnosis, especially a missed dengue diagnosis that could lead to complications and death. This study aims to identify these predictors at a public clinic in Selangor.

Methods

Febrile patients with suspected dengue, who presented to Klinik Kesihatan Seksyen 7, Shah Alam, a clinic with the highest dengue burden in Selangor, between November 2017 to March 2018 during normal working hours over weekdays, were recruited consecutively. Structured questionnaire was used by medically trained research assistants to capture potential predictor variables, i.e. socio-demography, signs and symptoms upon first presentation, and history of previous and current diseases. Venous blood samples were collected and processed. Serum specimens were stored at -80˚c for further testing in batches in a virology laboratory at the Faculty of Medicine, University of Malaya.

Dengue diagnosis was confirmed if tested positive on either dengue reverse-transcriptase polymerase chain reaction (RT-PCR), non-structural protein-1 (NS1) or immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA). Dengue immunoglobulin G (IgG) ELISA was also performed to determine dengue patient's previous exposure using a combination of "Recife" method and IgM/IgG ratio [1, 2] (Figure 1). STATA v12 was used to perform descriptive and subgroup analyses, Mann-Whitney test to compare continuous variables, and two-proportions z-test to compare categorical variables. Predictors were variables with significant association (p<0.05) with any diagnosis of interest.
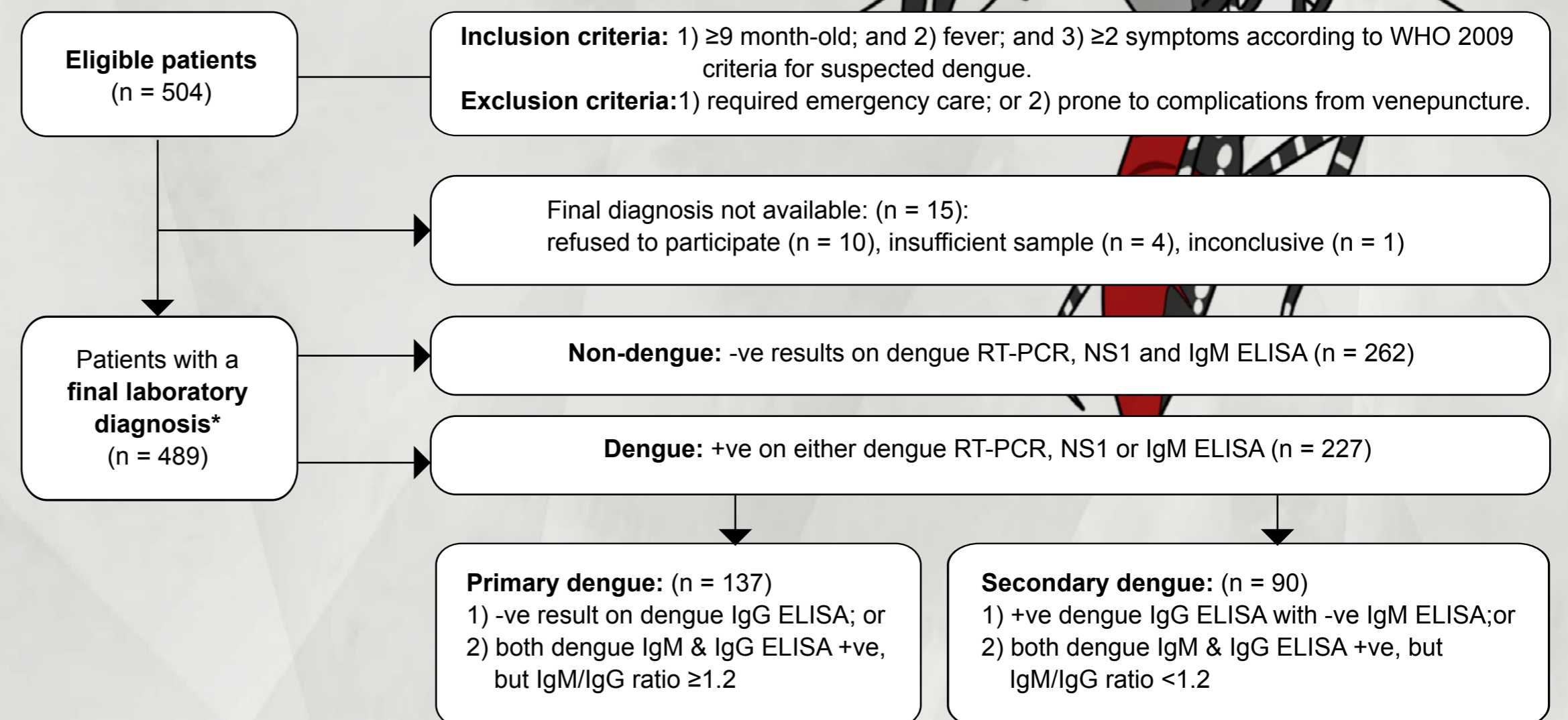

Eligible patients (n = 504)

Inclusion criteria: 1) ≥9 month-old; and 2) fever; and 3) ≥2 symptoms according to WHO 2009 criteria for suspected dengue.
Exclusion criteria: 1) required emergency care; or 2) prone to complications from venepuncture.

Final diagnosis not available: (n = 15): refused to participate (n = 10), insufficient sample (n = 4), inconclusive (n = 1)

Patients with a final laboratory diagnosis* (n = 489)

Non-dengue: -ve results on dengue RT-PCR, NS1 and IgM ELISA (n = 262)

Dengue: +ve on either dengue RT-PCR, NS1 or IgM ELISA (n = 227)

Primary dengue: (n = 137) 1) -ve result on dengue IgG ELISA; or 2) both dengue IgM & IgG ELISA +ve, but IgM/IgG ratio ≥1.2

Secondary dengue: (n = 90) 1) +ve dengue IgG ELISA with -ve IgM ELISA; or 2) both dengue IgM & IgG ELISA +ve, but IgM/IgG ratio <1.2

Figure 1 Study Flow Diagram
*Laboratory tests used were iTaq Universal SYBR Green One-Step real-time RT-PCR (Bio-Rad Laboratories, Hercules, CA), Panbio Dengue Early (NS1) ELISA, and SD Dengue IgM and IgG capture ELISA (Standard Diagnostics, Korea).

Results

The final analysis included 489 patients, who participated and had a final laboratory diagnosis, out of a total of 504 eligible patients (response rate = 97.0%). The mean age of the patients was 27.2 (standard deviation, s.d. 11.8) years. Majority of them were male (282, 57.7%) and Malay (391, 80.0%). Most of them completed secondary school (200, 40.9%) and had a monthly household income of RM 3000 and above (175, 35.8%) (Table 1).

On average, they first presented to a healthcare facility on 2.6 (s.d. 1.5) days of fever. Majority complained of nausea, vomiting or anorexia (480, 98.2%), aches and pain (470, 96.1%), and at least one symptom resembling dengue warning sign (466, 95.3%), of which the most commonly reported were lethargy (446, 91.2%), abdominal pain (112, 22.9%), persistent vomiting (76, 15.5%), and persistent diarrhoea (66, 13.5%) (Table 2). About the current disease, majority reported a reduction in daily activities (351, 71.8%) (Table 2) and previous health seeking (330, 67.5%). There were also 147 (30.1%) reports of fever among family members, 85 (17.4%) previous dengue infections, and 53 (10.8%) recent visits to the wild (Table 3).

Table 1 Socio-demographic characteristics of patients with dengue-like symptoms

Characteristics	Mean (s.d.) or n (%)*			p-value~	Mean (s.d.) or n (%)*		p-value~
	Total 489	Dengue 227	Non-dengue 262		Primary 137	Secondary 90	
Age (years)	27.2 (11.8)	28.4 (10.6)	26.1 (12.6)	**0.01**	26.6 (9.7)	31.1 (11.3)	**<0.001**
Gender							
Male	282 (57.7)	135 (59.5)	147 (56.1)	0.45	83 (60.6)	52 (57.8)	0.67
Female	207 (42.3)	92 (40.5)	115 (43.9)	0.45	54 (39.4)	38 (42.2)	0.67
Ethnicity							
Malay	391 (80.0)	179 (78.9)	212 (80.9)	0.57	108 (78.8)	71 (78.9)	0.99
Chinese	4 (0.8)	3 (1.3)	1 (0.4)	0.25	1 (0.7)	2 (2.2)	0.34
Indian	46 (9.4)	15 (6.6)	31 (11.8)	**<0.05**	10 (7.3)	5 (5.6)	0.60
Sabahan & Sarawakian	12 (2.4)	7 (3.1)	5 (1.9)	0.40	4 (2.9)	3 (3.3)	0.86
Foreigner	36 (7.4)	23 (10.1)	13 (5.0)	**0.03**	14 (10.2)	9 (10.0)	0.96
Education							
Pre-school	21 (4.3)	3 (1.3)	18 (6.9)	**<0.01**	2 (1.5)	1 (1.1)	0.82
Up to primary	45 (9.2)	20 (8.8)	25 (9.5)	0.76	15 (10.9)	5 (5.6)	0.16
Up to secondary	200 (40.9)	92 (40.5)	108 (41.2)	0.82	50 (36.5)	42 (46.7)	0.13
Up to diploma	136 (27.8)	69 (30.4)	67 (25.6)	0.26	39 (28.5)	30 (33.3)	0.44
Completed tertiary	85 (17.4)	43 (19.0)	42 (16.0)	0.42	31 (22.6)	12 (13.3)	0.08
Missing	2	-	2		-	-	
Monthly household income							
Less than RM 1500	156 (31.9)	71 (31.3)	85 (32.4)	0.74	46 (33.8)	25 (27.8)	0.34
RM 1500-2999	154 (31.5)	74 (32.6)	80 (30.5)	0.66	45 (33.1)	29 (32.2)	0.89
RM 3000 and above	175 (35.8)	81 (35.7)	94 (35.9)	0.92	45 (33.1)	36 (40.0)	0.29
Missing	4	1	3		1		

*Column % (missing included in the calculation but % not shown, rounding error may be present)
~p-value computed using Mann-Whitney test for continuous variables and two-proportions z-test for categorical variables
Notes: s.d.: standard deviation

Table 2 Clinical characteristics of patients with dengue-like symptoms upon first presentation

Characteristics	Mean (s.d.) or n (%)*			p-value~	Mean (s.d.) or n (%)*		p-value~
	Total 489	Dengue 227	Non-dengue 262		Primary 137	Secondary 90	
Day of fever	2.6 (1.5)	2.6 (1.7)	2.6 (1.4)	0.82	2.6 (1.6)	2.7 (1.7)	0.90
Presence of symptom							
i) Nausea, vomiting or anorexia	480 (98.2)	223 (98.2)	257 (98.1)	0.90	135 (98.5)	88 (97.8)	0.67
ii) Rash	96 (19.6)	64 (28.2)	32 (12.2)	**<0.001**	43 (31.4)	21 (23.3)	0.19
iii) Aches and pain^	470 (96.1)	221 (97.4)	249 (95.0)	0.19	132 (96.4)	89 (98.9)	0.24
Presence of warning sign							
i) Presence of at least one	466 (95.3)	218 (96.0)	248 (94.7)	0.47	130 (94.9)	88 (97.8)	0.28
ii) Abdominal pain	112 (22.9)	41 (18.1)	71 (27.1)	**0.02**	18 (13.1)	23 (25.6)	**0.02**
iii) Persistent vomiting	76 (15.5)	32 (14.1)	44 (16.8)	0.41	21 (15.3)	11 (12.2)	0.51
iv) Persistent diarrhoea	66 (13.5)	27 (11.9)	39 (14.9)	0.33	18 (13.1)	9 (10.0)	0.47
v) Bleeding	17 (3.5)	11 (4.8)	6 (2.3)	0.12	7 (5.1)	4 (4.4)	0.82
vi) Lethargy	446 (91.2)	211 (93.0)	235 (89.7)	0.20	129 (94.2)	82 (91.1)	0.38
vii) Fluid accumulation	1 (0.2)	1 (0.4)	0 (0.0)	0.28	0 (0.0)	1 (1.1)	0.22
viii) Liver tenderness	2 (0.4)	2 (0.9)	0 (0.0)	0.13	0 (0.0)	2 (2.2)	0.08
Other signs							
i) Reduced fluid intake	118 (24.1)	52 (22.9)	66 (25.2)	0.56	34 (24.8)	18 (20.0)	0.40
ii) Reduced urine volume	81 (16.6)	37 (16.3)	44 (16.8)	0.88	19 (13.9)	18 (20.0)	0.22
iii) Reduced activities	351 (71.8)	165 (72.7)	186 (71.0)	0.68	100 (73.0)	65 (72.2)	0.90

*Denominator for % was corresponding total number of included patients within each column (negative responses not shown)
^Aches and pain included retro-orbital pain, headache, body ache, and muscle and joint pain
~p-value computed using Mann-Whitney test for continuous variables and two-proportions z-test for categorical variables
Notes: s.d.: standard deviation

Table 3 History of current and previous disease among patients with suspected dengue

Characteristics	n (%)*			p-value~	n (%)*		p-value~
	Total 489	Dengue 227	Non-dengue 262		Primary 137	Secondary 90	
Previous consultation for current disease	330 (67.5)	183 (80.6)	147 (56.1)	**<0.001**	106 (77.4)	77 (85.6)	0.13
Had history of fever among family members	147 (30.1)	75 (33.0)	72 (27.5)	0.18	54 (39.4)	21 (23.3)	**0.01**
Had recent travelling/jungle trekking/waterfall swimming	53 (10.8)	16 (7.0)	37 (14.1)	**0.01**	10 (7.3)	1796 (6.7)	0.86
Had history of previous dengue	85 (17.4)	33 (14.5)	52 (19.8)	0.12	12 (8.8)	21 (23.3)	**<0.01**

*Denominator for % was corresponding total number of included patients within each column (negative responses not shown)
~p-value computed using two-proportions z-test (for categorical variables)

Discussion

Our study found that age was positively associated with dengue, especially a secondary dengue, while younger pre-schoolers with dengue-like symptoms were less likely to have dengue. This is explainable as cumulative time of exposure to Aedes bites increases the likelihood of contracting dengue [3], and second dengue infection is usually more serious compared to milder or asymptomatic primary dengue [1].

Foreigners were more likely to have dengue. The foreigners who participated in our study came from lower income countries to work in industries surrounding the clinic, often living in conditions favourable to dengue transmission [1, 4]. They were incentivised to put more time to work as time off work usually equals to loss of income. As such, they had higher threshold for health-seeking, so practitioners should be more vigilant with foreigners with dengue-like symptoms in view of association with a dengue diagnosis. However, the association of ethnicity to non-dengue diagnosis requires further study or more advance analysis to better explain and cannot be applied directly.

Having rash was the only symptom that was associated with dengue. The lack of association for other symptoms signifies the non-specificity of dengue symptoms [1], and/or the subjective nature of these symptoms as opposed to rash. Afterall, subjective signs and symptoms even those resembling warning signs were reported more frequently and could be over-reported by study participants. This highlights the importance of physician's clerking and assessment to correctly identify patients with actual warning signs only after reaching a dengue diagnosis to avoid crowding of health facilities due to overdiagnosis.

It is interesting to note that while abdominal pain was associated with a non-dengue diagnosis, it was more likely to be observed among patients with secondary dengue. This could be the result of patients presenting with acute gastroenteritis and a complain that faintly meant fever being screened for dengue even without a raised temperature on the thermometer, which reflected the vigilance of the health personnel staffing a clinic in a dengue-endemic neighbourhood. On the other hand, although more likely in secondary dengue, abdominal pain as a warning sign can be observed also in primary dengue, just like any other warning signs [1]. Further management should be administered once any warning sign is identified after a dengue diagnosis is made [1].

Finally, patients who had previous consultation for the current disease were more likely to have dengue, while those who recently travelled to the wild were less likely to have dengue. These findings highlight the need to suspect dengue among patients who repeat healthcare seeking for the same illness and the importance of epidemiological history in establishing differential diagnosis of dengue fever [5]. On the other hand, more studies are required to explain the association of primary dengue with fever among family members, but the higher likelihood of secondary dengue among patients with history of previous dengue were self-explanatory.

Conclusion

Age, ethnicity or origin, certain symptoms, history of current and past diseases were predictive of the final diagnosis among patients with suspected dengue in Selangor. Similar studies can be conducted in different clinics in Malaysia to identify the predictors of diagnosis there. These predictors, especially those of dengue can help physicians practising in dengue-endemic areas in their routine consultation to better diagnose it to reduce case fatality rate.

References

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