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VARIATIONS IN THE CLINICAL FEATURES OF DENGUE CASES BETWEEN CHILDREN AND ADULTS IN BRUNEI DARUSSALAM.

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ABSTRACT

Background: Dengue is a common vector-borne disease in Brunei Darussalam. Early recognition of its signs and symptoms is essential for early detection and treatment. Brunei is currently using both 1997 and 2009 WHO dengue case classifications interchangeably. This study aims to describe and compare the clinical features of laboratory-confirmed cases of dengue between children (<15 years old) and adults in Brunei. **Methods:** Data on the socio-demographic, clinical symptoms and signs, presence of co-morbidities and duration of hospitalisation for laboratory-confirmed dengue cases was collected from January-December 2015. Incidence rate for dengue cases for 2015 was derived. Chi-square or Fisher's Exact tests were used to compare differences in clinical variables between children and adults. **Results:** In 2015, there was a total of 317 laboratory-confirmed dengue cases, giving an incidence rate of 76.9 per 100,000 population. Thirteen cases were excluded due to missing data and the remaining 304, consisting of 35 children (11.5%) and 269 adults (88.5%) were analysed. The median age for the children and adult cases were 10 years (IQR = 6.5) and 39 years (IQR = 25), respectively. There were proportionally more males in both children (54.3%) and adult (61.0%) groups. Higher proportions of hospitalisation were observed for both children (57.5%) and adults (66.2%). The most common clinical features among both children and adults were fever, rash, and vomiting but nausea ($p=0.037$) and headaches ($p=0.042$) were significantly more common in adults than children. The leading warning signs reported were thrombocytopenia, raised hematocrit and abdominal pain. The presence of any warning signs were significantly more in adults than in children ($p=0.011$), particularly thrombocytopenia ($p=0.008$). The proportion of respiratory symptoms recorded however was significantly more among children than adults ($p=0.005$), especially cough ($p=0.002$). **Conclusion:** There are significant differences in clinical presentation and presence of warning signs between adults and children, with adults more likely to report of headaches and nausea and have thrombocytopenia as a warning signs than children. However, children tend to present more with respiratory symptoms such as cough than adults. These differences in clinical symptoms and signs as well as warning signs could serve as a reference for general practitioners to facilitate early detection and treatment for dengue.

Keywords: Dengue, Children, Adult, Classification, Severe Dengue, Signs and symptoms.

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INTRODUCTION

Dengue is a virus from the *Flaviviridae* family with four distinct serotypes, namely DENV-1, DENV-2, DENV-3 and DENV-4.[1,2] It is trans-

mitted by infected female mosquitoes of the Aedes species, in particular, *Aedes aegypti* and *Aedes albopictus*.[3] Both DENV-1 and DENV-2 are the main circulating serotypes, however infection with different serotypes may cause nearly identical clinical syndrome.[1] This virus has emerged as a major public health threat worldwide; its incidence has risen dramatically in the recent decades and has become a leading cause of morbidity and mortality among children and adults.[4] According to World Health Organization (WHO), around 3.9 billion people globally are at risk of getting dengue. Out of the approximately 390 million dengue infections identified each year, 96 million were symptomatic (24.6%), remaining 294 million were asymptomatic (75.4%) with around 20,000 deaths (0.005%).[4] Symptomatic dengue can be broadly divided into mild and severe types. The mild form is called dengue fever (DF) and often exhibits unspecific clinical manifestations, while the severe forms include manifestations such as respiratory distress, massive bleeding or organ impairment.[4]

In Brunei Darussalam, dengue is an endemic disease and is also one of the notifiable diseases under the country's Infectious Disease Act.[5] The three known dengue serotypes that have been detected in the country are DENV-1, DENV-2 and DENV-3.[6] From 2013, the average number of notified dengue cases in Brunei was around 400 cases per year and in 2015, there were a total of 317 laboratory-confirmed dengue cases, with one patient diagnosed with dengue hemorrhagic fever (DHF).[5]

Dengue infection presents with a wide range of clinical signs and symptoms.[7] Thus, developing definitions for providing accurate case ascertainment is a challenge. Moreover, dengue-infected children may be asymptomatic or poly-symptomatic, which causes difficulty in making differential diagnosis.[8] The WHO has provided two classifications: the old 1997 and new 2009 revised dengue case classification. The WHO 1997 dengue case classification classifies dengue into DF, DHF and dengue shock syndrome.[9] However, this strict application is poorly related to disease severity.[10] In 2009, WHO proposed a re-classification of this case definition, based on broadening the spectrum of severe dengue and inclusion of warning signs. It has three categories: dengue without warning signs, dengue with warning signs and severe dengue. This new classification could improve clinical recognition and surveillance for severe illness attributable to dengue infection, thus facilitating timely patient treatment.[11] However, many countries and institutions (including Brunei) do not fully implement the revised case classifications (either still using the old 1997 only or using both classifications interchangeably).

Age at infection is one of the known risk factors of disease severity for dengue.[8] Several studies have reported clinical and laboratory differences between children and adults with dengue.[6,7] Thus, investigating any differences in clinical symptom presentations between children and adults would help to inform clinicians on the common manifestations presented by each group. Hence, this study aims to characterize and compare the differences in clinical symptoms of laboratory-confirmed dengue cases between children and adults in Brunei. The secondary objective is to classify these cases using both 1997 and 2009 WHO dengue classification schemes.

MATERIALS & METHODS

Study design, population and sample

A retrospective cross-sectional study was conducted to include all 317 recorded laboratory-confirmed dengue cases between January and December 2015 in Brunei Darussalam. Patients whose patient files were incomplete and/or inaccessible, or where the primary course of treatment was focused on

other complications were excluded from this study. These cases were identified from the Brunei Health Information Management System (Bru-HIMS) and Disease Control Division (DCD) database. The former is a centralized system that records and links patient medical data across all public hospitals and health centers in the country. While DCD (part of the Public Health Services, Ministry of Health) is responsible for collecting and responding on data pertaining to communicable diseases at the national level. A laboratory-confirmed dengue case was defined as patients who have tested positive for dengue infection using a rapid diagnostic kit that qualitatively detects NS 1 antigen as well as Ig M and Ig G antibodies to dengue virus.

Data collection

The DCD database consists of a line-list of all laboratory-confirmed dengue cases, including their demographic details and date of diagnosis. Clinical information was retrieved manually through a systematic review of each patient's clinical case notes and electronic records available from the Bru-HIMS database. Any signs and symptoms recorded from patients' electronic record and clinical case notes were matched with the clinical features based on both WHO 1997 and 2009 dengue classification schemes. The WHO classification schemes and the factors considered in the study are summarized in Appendix 1 . Any warning signs of dengue were also recorded. Based on the WHO 2009 dengue classification definition (Appendix 1), patients were classified with warning signs if they had any of the following presentations: abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, hepatomegaly, high levels of hematocrit and thrombocytopenia.

Information on the socio-demographic characteristics, hospital admission status and duration of hospitalization of each laboratory-confirmed dengue case were also collected. Comorbidity was defined as the presence of either a newly-diagnosed or pre-existing chronic medical condition (particularly for those with hypertension, diabetes mellitus, asthma, dyslipidemia and renal disorders). Hospital admission was defined as staying at the hospital for one day or longer. Accompanying respiratory symptoms, such as cough, rhinorrhea, nasal congestion and shortness of breath, were also recorded for analysis.

Statistical analysis

Data were entered and compiled using Microsoft Excel. Incidence rate per 100,000 population for dengue for year 2015 was also derived. To assess the impact of age on the clinical manifestations and outcomes, patients were categorized as children (defined as patients of ages <15 years) and adults (defined as patients of ages 15 years and above) for statistical analysis.[6,13] Groups comparison were done using chi-square or Fisher's Exact test, whenever appropriate. All statistical analyses were performed using IBM SPSS (Statistical Package for Social Sciences) Statistics Version 22.0 software . A p-value of < 0.05 is considered as statistically significant.

Ethical statement

This study was approved by the PAPRSB Institute of Health Science Ethics Committee (IHSREC), Universiti Brunei Darussalam (Reference no: UBD/IHS/B3/8), following guidelines from the Declaration of Helsinki.

RESULTS

Between January and December 2015, a total of 317 laboratory-confirmed dengue cases were reported, which gives an incidence rate of 76.9 per 100,000 population, for laboratory -confirmed dengue cases detected by the Disease Control Division. Out of these, 13 (4.1%) were excluded based on the exclusion criteria of the study. Figure 1 shows the distribution of the 304 cases included in this study, by week of symptom onset. At least one laboratory-confirmed dengue case had been report-

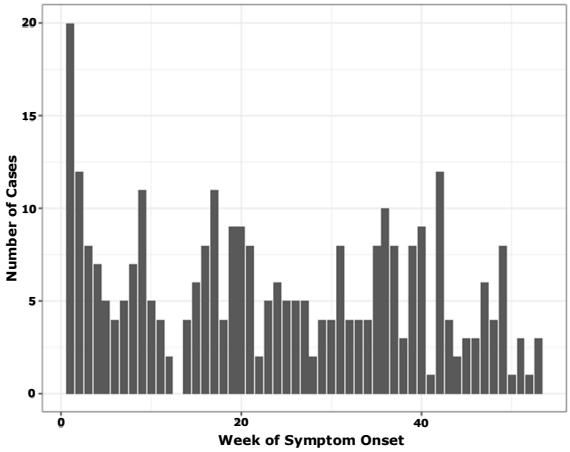

Figure 1: Distribution of laboratory-confirmed dengue case for Brunei Darussalam in 2015, according to week of symptom *onset*.

been reported in most weeks, with 20 being the maximum number. Thirty-five (11.5%) cases were children while 269 (88.4%) cases were reported in adults. The median age for the children and adult cases were 10 years (IQR = 6.5) and 39 years (IQR = 25), respectively. Gender differences were observed with more male cases reported for both children (54.3%) and adult (61.0%). No significant associations were observed for the demographic characteristics between children and adults (Table I).

The top three most common clinical features in both children and adults were fever (Table II: 97.1% and 92.2%), rashes (Table II: 60.0% and 45.4%) and vomiting (Table II: 37.1% and 37.5%). Both headache (Table II: 34.2% vs 17.1%, *p=0.042*) and nausea (Table II: 24.2% vs 8.6%, *p=0.037*) were significantly more common in Adults than in children.

The presence of any warning sign was also significantly higher among adults (77.0%) than children (Table II: 77.0% vs 57.1%, *p=0.011*). The leading three warning signs for both adults and children were thrombocytopenia, raised hematocrit, and abdominal pain but only thrombocytopenia was noted to be significantly higher in adults than children (Table II: 68.4% vs 45.7%, *p=0.008*). No differences were observed for other warning signs [Table II].

Overall, the proportion of respiratory symptoms recorded was significantly higher in children than in adults (Table II: 57.1% vs 33.1%, *p=0.005*), with cough being the predominant symptom in children than in adults

TABLE I: Characteristics of demographic and clinical features of laboratory-confirmed dengue cases between children and adults in Brunei Darussalam in 2015.

Demographic variables		Total population (n=304)	Children (n=35)	Adult (n=269)	P value
GENDER	Male	183 (60.2)	19 (54.3)	164 (61.0)	0.488[a]
	Female	121 (39.8)	16 (45.7)	105 (39.0)	
DISTRICT	Brunei-Muara	181 (59.5)	27 (77.1)	154 (57.2)	0.076[a]
	Tutong	91 (29.9)	8 (22.9)	83 (30.9)	
	Belait	16 (5.3)	0 (0.0)	16 (5.9)	
	Temburong	16 (5.3)	0 (0.0)	16 (5.9)	
HOSPITALISATION	Outpatient	142 (46.7)	15 (42.9)	91 (33.8)	0.292[a]
	Inpatient	198 (65.1)	20 (57.1)	178 (66.2)	
CO-MORBIDITIES	Any co-morbidity	145 (47.7)	13 (37.1)	132 (49.1)	0.184[a]
	Hypertension	67 (22.0)	6 (17.1)	61 (22.7)	0.458[a]
	Diabetes mellitus	34 (11.2)	1 (2.9)	33 (12.3)	0.149[b]
	Dyslipidemia	59 (19.4)	4 (11.4)	55 (20.4)	0.204[a]
	Asthma	31 (10.2)	4 (11.4)	27 (10.0)	0.768[b]
	Renal diseases	2 (0.7)	0 (0.0)	2 (0.7)	1.000[b]
	Others	40 (13.2)	2 (5.7)	38 (14.1)	0.284[b]

[a]chi squared [b]fisher's exact

TABLE II: Signs and symptoms of laboratory-confirmed dengue cases between children and adults in Brunei Darussalam in 2015.

Variables		Total population (n=304)	Children (n=35)	Adult (n=269)	P value
CLINICAL FEATURES	Fever	282 (92.7)	34 (97.1)	248 (92.2)	0.489[b]
	Rashes	143 (47.0)	21 (60.0)	122 (45.4)	0.102[a]
	Vomiting	114 (37.5)	13 (37.1)	101 (37.5)	0.963[a]
	Loss of appetite	103 (33.9)	13 (37.1)	90 (33.5)	0.665[a]
	Myalgia	102 (33.6)	8 (22.9)	94 (34.9)	0.154[a]
	Headache	98 (32.2)	6 (17.1)	92 (34.2)	**0.042[a]**
	Arthralgia	56 (18.4)	5 (14.3)	51 (19.0)	0.502[a]
	Diarrhea	61 (20.0)	4 (11.4)	57 (21.2)	0.175[a]
	Nausea	68 (22.4)	3 (8.6)	65 (24.2)	**0.037[a]**
	Weakness	40 (13.2)	1 (2.9)	39 (14.5)	0.062
WARNING SIGNS	Any warning signs	227 (74.7)	20 (57.1)	207 (77.0)	**0.011[a]**
	Thrombocytopenia	200 (65.8)	16 (45.7)	184 (68.4)	
	High Hematocrit	64 (21.0)	7 (20.0)	57 (21.2)	0.871[a]
	Abdominal pain	43 (14.1)	4 (11.4)	39 (14.5)	0.799[b]
	Lethargy	24 (7.9)	4 (11.4)	20 (7.4)	0.500[b]
	Mucosal bleeding	21 (6.9)	2 (5.7)	19 (7.1)	1.000[b]
	Clinical fluid accumulation	1 (0.3)	1 (2.9)	0 (0.0)	0.115[b]
	Persistent vomiting	1 (0.3)	1 (2.9)	0 (0.0)	0.115[b]
	Restlessness	1 (0.3)	0 (0.0)	1 (0.4)	1.000[b]
	Hepatomegaly	3 (1.0)	0 (0.0)	3 (1.1)	1.000[b]
Respiratory symptoms	Rhinorrhea	43 (14.1)	9 (25.7)	34 (12.6)	0.066[b]
	Cough	96 (31.2)	19 (54.3)	77 (28.6)	**0.002[a]**
	Nasal congestion	2 (0.7)	0 (0.0)	2 (0.7)	1.000[b]
	Sore throat	19 (6.3)	4 (11.4)	15 (5.6)	0.252[b]
	Shortness of breath	6 (2.0)	2 (5.7)	4 (1.5)	0.144[b]

[a]chi squared [b]fisher's exact

(Table II: 54.3% vs 28.6%, *p=0.002*).

Using the 1997 dengue case classification, 303 (99.7%) cases were classified as DF while 1 (0.3%) case was identified as having DHF. However based on the 2009 dengue case classification, 229 (75.3%) cases, 74 (24.3%) cases, and 1 (0.3%) case were classified respectively as dengue in the presence of warning signs, dengue without warning signs, and severe dengue.

DISCUSSION

This study reported the common signs and symptoms at presentation of laboratory-confirmed dengue cases among children and adults in Brunei Darussalam, and classified them based on both 1997 and 2009 WHO dengue classification schemes.

We observed that fever, vomiting and rash were the three most common symptoms in both children and adults. Similar findings were also reported in previous studies: Fever, generalized body ache and vomiting were the most frequently reported symptoms in Saudi Arabia,[2] while fever, arthralgia, myalgia, and headache were mainly reported in Malaysia.[12] However, the fourth most common symptom in children and adults was different (that is, loss of appetite and headache, respectively). The higher proportion of adults reporting headaches was also reported in a similar study in Brazil,[13] and the lack of reporting of

this symptom among younger children could be due to difficulty in eliciting such complaint from children. We also observed that the most common warning signs were thrombocytopenia and raised hematocrit in both children and adults. These warning signs were also similarly reported in other published studies .[14,15] In children suspected of DF, signs and symptoms such as thrombocytopenia and abdominal pain are mostly likely indicators of severity of the dengue infection.[16]

Just over a third of laboratory-confirmed dengue cases also presented with common respiratory symptoms such as cough, rhinorrhea, and sore throat, particularly in children, in addition to the common symptoms classified by WHO for dengue. Thus it is important for clinicians to take note of these respiratory symptoms, particularly so in children presenting with fever and rashes, in order to differentiate dengue from other acute febrile upper respiratory illness such as influenza.[17] Therefore, it is essential for the clinicians to understand the specific or particular nature of the clinical presentation of the acute febrile illness, including its epidemiological nature in a particular area, in order for early diagnosis, notification and response to dengue cases.[7]

Using the WHO 2009 dengue case classification, a majority of the study population was diagnosed with DF in the presence of warning signs (75.3%). Several studies have reported that that the WHO 2009 dengue classification scheme had better specificity and sensitivity for distinguishing and diagnosing dengue and severe dengue.[12,18] Therefore, the 2009 dengue case classification could help frontline clinicians to detect the early clinical warning signs, thereby ensuring timely intervention and management. This could be explained by the fact that adults with dengue infection tend to be symptomatic, as adults tend to have secondary or tertiary dengue infections, which in turn predisposes them towards symptomatic or severe disease manifestation/infection. [13,14,19,20] Brunei has a tropical climate and Aedes mosquitoes can be detected locally.[21,22] Hence, it is likely that these cases may have gotten primary dengue infection during their childhood.

Another possible explanation for the increase in the proportion of adult dengue cases could be related to demographic transition at the country level. A mathematical modeling study in Thailand have reported that both reduced birth rate and shift in population structure could explain the shift in the age distribution of the cases.[23] Though at a slow pace, we observed a slight decrease in Brunei's crude birth rate from 17.6 per 1,000 population in 2010 to 15.3 per 1,000 population in 2017.[5] Also observed is an increase in the number of people of ages 60 and above, from 19.5 thousands in 2010 to 37.8 thousands in 2017.[5] This suggests the need to revise clinical guidelines for dengue in order to anticipate such phenomenon.

There are several limitations in this study. Firstly, the retrospective nature could limit the quality of data reported in this study, as such strategy relied heavily on whether the clinician records the clinical symptoms comprehensively. Secondly, laboratory-confirmed cases from only one year were reported, which could compromise the generalizability of the results. The year 2015 was chosen because it has the most number of cases and is the most complete with epidemiological information, at the time of data collection. In subsequent years, the number of cases dropped to 84 and 75 cases (in 2016 and 2017, respectively).[5] Including more years into the study was challenging in terms of retrieving clinical information from Bru-HIMS database and sorting the information manually. Thirdly, human errors could be made during the manual data retrieval process, however efforts have been done to minimize this. Despite these limitations, it is hoped that reporting

this study results can promote further research studies on the topic and also encourage clinicians to prospectively collect data from identified cases by using a fixed data entry template. Such prospective and systematic data collection would provide a valuable source to assess clinical features of dengue in Brunei.

CONCLUSION

We reported the most common clinical features and warning signs of dengue among children and adults in Brunei Darussalam. In 2015, we observed that adults formed a majority of the reported cases, reported similar clinical features and warning signs as for children, but with some minor significant differences such as higher proportion of adults complaining of headaches and nauseas and a significantly higher proportion of adults presenting with warning signs such as thrombocytopenia. In children however, respiratory symptoms such as cough were noted to be higher in proportion. These similarities and differences in clinical signs and symptoms and warning signs could help inform outpatient doctors or general practitioners when diagnosing dengue among children and adult population in Brunei, thus allowing for prompt and effective patient management.

CONFLICT OF INTEREST

None to declare

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