

OFFICIAL PUBLICATION OF
THE MINISTRY OF HEALTH,
BRUNEI DARUSSALAM

Brunei International Medical Journal

Volume 16

20 July 2020 (28 Zulkaedah 1441H)

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

OTHMAN NN¹, HTIKE NL², CHAW L¹.

¹PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Jalan Tungku Link Gadong, BE1410, Brunei Darussalam.

²Disease Control Division, Public Health Services, Ministry of Health, Brunei Darussalam.

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.

Brunei Int Med J. 2020;16:92-99

ISSN 1560 5876 Print
ISSN 2079 3146 Online

Online version of the journal is available at www.bimjonline.com

Brunei International Medical Journal (BIMJ)

Official Publication of the Ministry of Health, Brunei Darussalam

EDITORIAL BOARD

Editor-in-Chief	William Chee Fui CHONG
Sub-Editors	Vui Heng CHONG Ketan PANDE
Editorial Board Members	Muhd Syafiq ABDULLAH Alice Moi Ling YONG Ahmad Yazid ABDUL WAHAB Jackson Chee Seng TAN Pemasiri Upali TELISINGHE Roselina YAAKUB Pengiran Khairol Asmee PENGIRAN SABTU Dayangku Siti Nur Ashikin PENGIRAN TENGAH

INTERNATIONAL EDITORIAL BOARD MEMBERS

Lawrence HO Khek Yu (Singapore)	Surinderpal S BIRRING (United Kingdom)
Emily Felicia Jan Ee SHEN (Singapore)	Leslie GOH (United Kingdom)
John YAP (United Kingdom)	Chuen Neng LEE (Singapore)
Christopher HAYWARD (Australia)	Jimmy SO (Singapore)
Jose F LAPENA (Philippines)	Nazar LUQMAN
Dipo OLABUMUYI	

Advisor

Wilfred PEH (Singapore)

Past Editors

Nagamuttu RAVINDRANATHAN
Kenneth Yuh Yen KOK

Proof reader

John WOLSTENHOLME (CfBT Brunei Darussalam)

three relevant references should be included. Only images of high quality (at least 300dpi) will be acceptable.

Technical innovations

This section include papers looking at novel or new techniques that have been developed or introduced to the local setting. The text should not exceed 1000 words and should include not more than 10 figures illustration and references should not be more than 10.

Letters to the Editor

Letters discussing a recent article published in the BIMJ are welcome and should be sent to the Editorial Office by e-mail. The text should not exceed 250 words; have no more than one figure or table, and five references.

Criteria for manuscripts

Manuscripts submitted to the BIMJ should meet the following criteria: the content is original; the writing is clear; the study methods are appropriate; the data are valid; the conclusions are reasonable and supported by the data; the information is important; and the topic has general medical interest. Manuscripts will be accepted only if both their contents and style meet the standards required by the BIMJ.

Authorship information

Designate one corresponding author and provide a complete address, telephone and fax numbers, and e-mail address. The number of authors of each paper should not be more than twelve; a greater number requires justification. Authors may add a publishable footnote explaining order of authorship.

Group authorship

If authorship is attributed to a group (either solely or in addition to one or more individual authors), all members of the group must meet the full criteria and requirements for authorship described in the following paragraphs. One or more authors may take responsibility 'for' a group, in which case the other group members are not authors, but may be listed in an acknowledgement.

Authorship requirement

DISCLAIMER

All articles published, including editorials and letters, represent the opinion of the contributors and do not reflect the official view or policy of the Clinical Research Unit, the Ministry of Health or the institutions with which the contributors are affiliated to unless this is clearly stated. The appearance of advertisement does not necessarily constitute endorsement by the Clinical Research Unit or Ministry of Health, Brunei Darussalam. Furthermore, the publisher cannot accept responsibility for the correctness or accuracy of the advertisers' text and/or claim or any opinion expressed.

sign, and the analysis and interpretation of the data (where applicable); to have made substantial contributions to the writing or revision of the manuscript; and to have reviewed the final version of the submitted manuscript and approved it for publication. Authors will be asked to certify that their contribution represents valid work and that neither the manuscript nor one with substantially similar content under their authorship has been published or is being considered for publication elsewhere, except as described in an attachment. If requested, authors shall provide the data on which the manuscript is based for examination by the editors or their assignees.

Financial disclosure or conflict of interest

Any affiliation with or involvement in any organisation or entity with a direct financial interest in the subject matter or materials discussed in the manuscript should be disclosed in an attachment. Any financial or material support should be identified in the manuscript.

Copyright transfer

In consideration of the action of the BIMJ in reviewing and editing a submission, the author/s will transfer, assign, or otherwise convey all copyright ownership to the Clinical Research Unit, RIPAS Hospital, Ministry of Health in the event that such work is published by the BIMJ.

Acknowledgements

Only persons who have made substantial contributions but who do not fulfill the authorship criteria should be acknowledged.

Accepted manuscripts

Authors will be informed of acceptances and accepted manuscripts will be sent for copyediting. During copyediting, there may be some changes made to accommodate the style of journal format. Attempts will be made to ensure that the overall meaning of the texts are not altered. Authors will be informed by email of the estimated time of publication. Authors may be requested to provide raw data, especially those presented in graph such as bar charts or figures so that presentations can be constructed following the format and style of the journal. Proofs will be sent to authors to check for any mistakes made

Aim and Scope of Brunei International Medical Journal

The Brunei International Medical Journal (BIMJ) is a six monthly peer reviewed official publication of the Ministry of Health under the auspices of the Clinical Research Unit, Ministry of Health, Brunei Darussalam.

The BIMJ publishes articles ranging from original research papers, review articles, medical practice papers, special reports, audits, case reports, images of interest, education and technical/innovation papers, editorials, commentaries and letters to the Editor. Topics of interest include all subjects that relate to clinical practice and research in all branches of medicine, basic and clinical including topics related to allied health care fields. The BIMJ welcomes manuscripts from contributors, but usually solicits reviews articles and special reports. Proposals for review papers can be sent to the Managing Editor directly. Please refer to the contact information of the Editorial Office.

Instruction to authors

Manuscript submissions

All manuscripts should be sent to the Managing Editor, BIMJ, Ministry of Health, Brunei Darussalam; e-mail: editor-in-chief@bimjonline.com. Subsequent correspondence between the BIMJ and authors will, as far as possible via should be conducted via email quoting the reference number.

Conditions

Submission of an article for consideration for publication implies the transfer of the copyright from the authors to the BIMJ upon acceptance. The final decision of acceptance rests with the Editor-in-Chief. All accepted papers become the permanent property of the BIMJ and may not be published elsewhere without written permission from the BIMJ.

Ethics

Ethical considerations will be taken into account in the assessment of papers that have experimental investigations of human or animal subjects. Authors should state clearly in the Materials and Methods section of the manuscript that institutional review board has approved the project. Those investigators without such review boards should ensure that the principles outlined in the Declaration of Helsinki have been followed.

Manuscript categories

Original articles

These include controlled trials, interventional studies, studies of screening and diagnostic tests, outcome studies, cost-effectiveness analyses, and large-scale epidemiological studies. Manuscript should include the following; introduction, materials and methods, results and conclusion. The objective should be stated clearly in the introduction. The text should not exceed 2500 words and references not more than 30.

Review articles

These are, in general, invited papers, but unsolicited reviews, if of good quality, may be considered. Reviews are systematic critical assessments of

literature and data sources pertaining to clinical topics, emphasising factors such as cause, diagnosis, prognosis, therapy, or prevention. Reviews should be made relevant to our local setting and preferably supported by local data. The text should not exceed 3000 words and references not more than 40.

Special Reports

This section usually consist of invited reports that have significant impact on healthcare practice and usually cover disease outbreaks, management guidelines or policy statement paper.

Audits

Audits of relevant topics generally follow the same format as original article and the text should not exceed 1,500 words and references not more than 20.

Case reports

Case reports should highlight interesting rare cases or provide good learning points. The text should not exceed 1000 words; the number of tables, figures, or both should not be more than two, and references should not be more than 15.

Education section

This section includes papers (i.e. how to interpret ECG or chest radiography) with particular aim of broadening knowledge or serve as revision materials. Papers will usually be invited but well written paper on relevant topics may be accepted. The text should not exceed 1500 words and should include not more than 15 figures illustration and references

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

OTHMAN NN¹, HTIKE NL², CHAW L¹.

¹PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Jalan Tungku Link Gadong, BE1410, Brunei Darussalam.

²Disease Control Division, Public Health Services, Ministry of Health, Brunei Darussalam.

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.

Corresponding author: Liling Chaw, PhD, Lecturer, PAPRSB Institute of Health Science, Universiti Brunei Darussalam, Jalan Tungku Link Gadong, BE1410, Brunei Darussalam.
Tel: +673 2463001 Ext 2202/2206; Fax: +673 2461081
Email: liling.chaw@ubd.edu.bn

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 reclassification 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-

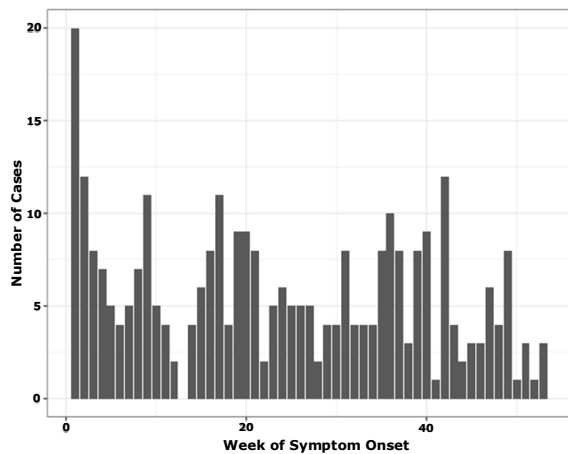


Figure 1: Distribution of laboratory-confirmed dengue case for Brunei Darussalam in 2015, according to week of symptom onset.

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

^achi squared ^bfisher'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

^achi squared ^bfisher'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 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 nausea 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

ACKNOWLEDGEMENTS

The primary author appreciates the staff members of Disease Control Division for their help in offering the resources for data collection.

REFERENCES

- 1: Yung C, Lee K, Thein T, et al. [Dengue Serotype -Specific Differences in Clinical Manifestation, Laboratory Parameters and Risk of Severe Disease in Adults, Singapore](#). *Am J Trop Med Hyg.* 2015;92(5):999–1005. [Accessed 28th June 2020].
- 2: Badreddine S, Al-dhaheri F, Al-dabbagh A, et al. [Dengue fever: Clinical features of 567 consecutive patients admitted to a tertiary care centre in Saudi Arabia](#). *Saudi Medical Journal.* 2017;38(10):1025–33. [Accessed 28th June 2020].
- 3: Rajapakse S, Rodrigo C, Rajapakse A. [Treatment of dengue fever](#). *Infection and Drug Resistance.* 2012;5(1):103–112. [Accessed 28th June 2020].
- 4: World Health Organization. [WHO | Dengue and severe dengue](#) [Internet Factsheet]. [Accessed 17th June 2017].
- 5: Ministry of Health, Brunei Darussalam. [Health Information Booklet Brunei 2017](#). [Internet]. [Accessed 16th April 2018].
- 6: Rahman ZHA, Osman O, Muharram SH, Mabruk M. [The prevalence of dengue virus in Brunei Darussalam during January–November 2010](#). *The Southeast Asian Journal of Tropical Medicine and Public Health.* 2013;44(4):594–601. [Accessed 28th June 2020].
- 7: World Health Organization. [Dengue: guidelines for diagnosis, treatment, prevention and control: New Edition 2009](#). World Health Organization. 2009:1–160. [Accessed 5th August 2019]
- 8: Wang C, Lee I, Su M, et al. [Differences in clinical and laboratory characteristics and disease severity between children and adults with dengue virus infection in Taiwan, 2002](#). *Trans R Soc Trop Med Hyg.* 2009;103:871–7. [Accessed 28th June 2020].
- 9: Tsai C, Lee I, Lee C, Yang KD, Liu J. [Comparisons of dengue illness classified based on the 1997 and 2009 World Health Organization dengue classification schemes](#). *JMII.* 2013;46(4):271–81. [Accessed 28th June 2020].
- 10: Horstick O, Jaenisch T, Martinez E, et al. [Comparing the Usefulness of the 1997 and 2009 WHO Dengue Case Classification: A Systematic Literature Review](#). *American Journal of Tropical Medicine and Hygiene.* 2014;91(3):621–634. [Accessed 28th June 2020].
- 11: World Health Organisation. [Handbook for Clinical Management of Dengue](#). WHO. 2012:1–124. [Accessed 28th June 2020].

- 12: Chen CH, Huang YC, Kuo KC, Li CC. [Clinical features and dynamic ordinary laboratory tests differentiating dengue fever from other febrile illnesses in children.](#) *Journal of Microbiology, Immunology and Infection.* 2018;51(5):614–620. [Accessed 28th June 2020].
 - 13: De Souza LJ, Bastos Pessanha L, Carvalho Mansur L, et al. [Comparison of clinical and laboratory characteristics between children and adults with dengue.](#) *Brazilian Journal of Infectious Diseases.* 2013;17(1):27–31. [Accessed 28th June 2020].
 - 14: Pone SM, Hökerberg YHM, de Oliveira RVC, et al. [Clinical and laboratory signs associated to serious dengue disease in hospitalized children.](#) *J Pediatr (Rio J).* 2016;92(5):464–471. [Accessed 28th June 2020].
 - 15: Gregory CJ, Lorenzi OD, Colón L, et al. [Utility of the tourniquet test and the white blood cell count to differentiate dengue among acute febrile illnesses in the emergency room.](#) *PLoS Negl Trop Dis.* 2011;5(12):e1400. [Accessed 28th June 2020].
 - 16: Chang C, Chen CS, Tien C, Lu M. [Epidemiological , clinical and climatic characteristics of dengue fever in Kaohsiung City , Taiwan with implication for prevention and control.](#) *PLoS One.* 2018;1–15.
 - 17: Wardhani P, Aryati A, Yohan B, et al. [Clinical and virological characteristics of dengue in Surabaya, Indonesia.](#) *PLoS ONE.* 2017;12(6):e0178443. [Accessed 28th June 2020].
 - 18: Mallhi TH, Khan AH, Adnan AS, Sarrieff A, Khan YH. [Clinico-laboratory spectrum of dengue viral infection and risk factors associated with dengue hemorrhagic fever: a retrospective study.](#) *BMC Infectious Diseases.* 2015;15:399. [Accessed 28th June 2020].
 - 19: Thai KTD, Nishiura H, Hoang PL, et al. [Age-specificity of clinical dengue during primary and secondary infection.](#) *PLoS Negl Trop Dis.* 2011;5(6):e1180. [Accessed 28th June 2020].
 - 20: Upadhyay N, Joshi H, Upadhyay C. [Thrombocytopenia and raised hematocrit-predictor in dengue hemorrhagic fever.](#) *International Journal of Contemporary Pediatrics.* 2017;4(4):1322–4. [Accessed 28th June 2020].
 - 21: Macdonald WW, Rajapaksa N. [A survey of the distribution and relative prevalence of Aedes aegypti in Sabah, Brunei and Sarawak.](#) *Bull World Health Organ.* 1972;46(2):203–209. [Accessed 28th June 2020].
 - 22: Idris FH, Usman A, Surendran SN, Ramasamy R. [Detection of Aedes albopictis preimaginal stages in brackish water habitats in Brunei Darussalam.](#) *Journal of Vector Ecology.* 2013;38(1):197–199. [Accessed 28th June 2020].
 - 23: Cummings DAT, Jamsirithaworn S, Lessler JT, et al. [The Impact of the Demographic transition of Dengue in Thailand: Insights from a Statistical Analysis and Mathematical Modelling.](#) *PLOS Medicine.* 2009;6(9):e1000139.
-

Appendix 1: Comparison between the standard criteria and those used in this study (for WHO 1997 and 2009 dengue case classification schemes)⁹

WHO 1997	Used in this study	WHO 2009	Used in this study
Fever and ≥ 2 of the following:		Fever and ≥ 2 of the following:	
Headache	Headache	Anorexia	Loss of appetite
Retro-orbital pain	-	Nausea, vomiting	Nausea, vomiting
Myalgia	Myalgia	Rash	Rash
Arthralgia	Arthralgia	Aches and pains	Myalgia
Rash	Rash		Arthralgia
Bleeding	Mucosal bleeding	Tourniquet test positive	-
Leukopenia	-		
Thrombocytopenia	Thrombocytopenia		
Rise in hematocrit	Increase in HCT		
		Warning signs:	Warning signs:
		Abdominal pain or tenderness	Abdominal pain
		Persistent vomiting	Persistent vomiting
		Clinical fluid accumulation	Fluid accumulation
		Mucosal bleeding	Mucosal bleeding
		Lethargy, restlessness	Lethargy
			Restlessness
		Liver enlargement $>2\text{cm}$	Hepatomegaly
		Laboratory: increase in HCT concurrent with rapid decrease in platelet count	Raised HCT with or without thrombocytopenia

Appendix II: List of other co-morbidities

Co-morbidity	Number of dengue cases
Anemic	3
Benign Prostatic Hyperplasia	1
Cardiovascular diseases (not specified)	3
Chronic Hepatitis B	1
Chronic Obstructive Pulmonary Diseases	1
Epilepsy	2
Gastritis	2
Gastrointestinal bleeding	1
Gout	2
Hypothyroidism	2
Ischemic Heart Disease	4
Mental Retardation	1
Mitral Valve Prolapse	1
Migraine	1
Myocardial Infarction	1
Myasthenia Gravis	1
Neuropathy	1
Obese	2
Progressive Multifocal Leukoencephalopathy	1
Pulmonary Embolism	1
Pulmonary Tuberculosis	1
Rheumatoid Arthritis	1
Schizophrenia	1
Stroke	1
Systemic Lupus Erythematosus	2
Urticaria	1
Thalassemia	1
Transient Ischemic Stroke	1
Vitamin D Deficiency	1