DEMOGRAPHIC, CLINICAL AND LABORATORY FINDINGS AMONG ADULT AND PEDIATRIC PATIENTS HOSPITALIZED WITH DENGUE IN THE PHILIPPINES

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Abstract. We evaluated the differences in demographic, clinical, and laboratory findings between adult and pediatric patients hospitalized with dengue fever. Ninety patients with dengue infection admitted at San Lazaro Hospital (SLH), Manila from September 2005 to January 2006 were included in the study. The cases were laboratory-confirmed to have dengue infection. The majority of dengue cases (92%) had secondary dengue infection (median age=18, age range: 2-37) while the remainder (8%) had a primary dengue infection (median age=12, age range: 7-22). Nearly all the patients (99%) had dengue hemorrhagic fever (DHF). Sixty-five of the cases (72%) had serotype data: 2 (3%) were dengue virus serotype 1 (DENV-1) (median age=17), 12 (18%) had DENV-2 (median age=17.5), 38 (59%) had DENV-3 (median age=16) and 13 (20%) had DENV-4 (median age=18). The initial signs, symptoms and laboratory results except hematocrit (p =0.02) and hemoglobin (p =0.02) did not differ significantly between adults and children. During the study period, half the cases were adults (≥18 years; n=45) and half were children (<18 years; n=45). The ages of cases ranged from 2 to 37 years (median=17 years) and the peak incidence was 15-19 years. Dengue is often considered as a pediatric disease. Additional studies are needed to determine if an age shift is occurring and where.

Keywords: dengue infection, adult, pediatric patient, serotype, signs, symptoms, lab results, Philippines

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INTRODUCTION

Dengue viruses (DENV) in the family Flaviviridae, genus *Flavivirus* have four antigenically-distinct serotypes (DENV-1, -2, -3, -4) (Halstead, 2008). The container-breeding mosquito *Aedes aegypti* is the primary vector responsible for DENV transmission among humans (Guzman *et al*, 2010). Female mosquitoes rely on human blood (for nutrition and reproduc-

tion) and consequently live in and around human dwellings (Scott *et al*, 1997; Halstead, 2008). There is an estimated annual incidence of 36 million cases of dengue fever (DF), 2.1 million cases of dengue hemorrhagic fever (DHF) and 21,000 DENV-related deaths occurring in over 124 countries world-wide (Beatty, 2010).

The Philippines experienced its first DHF outbreak in 1956 with DENV-3 being the predominant circulating serotype along with DENV-2 and-4 (Hayes *et al*, 1988). The Philippines has frequent DENV outbreaks superimposed on year-round transmission (Hayes *et al*, 1988; Arima *et al*, 2013). Cases are usually diagnosed clinically rather than laboratory confirmation. Only those who seek medical attention are included in the national statistics. There is a paucity of published data on the impact of dengue infections in the Philippines. Although dengue infections consistently rank among the top-ten causes of morbidity in the Philippines, vector control programs are devolved and limited (Espino *et al*, 2012). Studies are needed to better understand the true impact of dengue infections in the Philippines.

Dengue primarily affects pediatric populations in endemic countries (Halstead and Yamarat, 1965). However, a number of studies have described dengue in adults (Sharma *et al*, 1998; Tripathi *et al*, 1998; Wali *et al*, 1999; Torres *et al*, 2004; Hammond *et al*, 2005; Low *et al*, 2011). Other studies have compared the clinical presentation of dengue infection between adults and children (Zagne *et al*, 1994; Richards *et al*, 1997; Garcia-Rivera and Rigau-Perez, 2003; Wichmann *et al*, 2004; Hammond *et al*, 2005; Hanafusa *et al*, 2008). A shift in the peak age of patients infected towards older age groups has been observed in some countries (Guha-Sapir and Schimmer 2005; Witayathawornwong, 2005; Cummings *et al*, 2009). In some studies the authors report the age for dengue mortality has shifted from children to adults (Goh, 1997; Garcia-Rivera and Rigau-Perez, 2003). One study (Anders *et al*, 2011) found an increase in the proportion of adults being admitted to the hospital with dengue infection with an increase in the mean age of patients over the previous 10 years. It is unclear whether this represents a significant change in the epidemiology of dengue or some other fact, such as reporting bias. Accurate epidemiologic data is important to inform dengue control policies. The demographic characteristics of patients at highest risk for severe dengue infection are needed to determine where public health care resources should be spent (Suaya *et al*, 2009).

MATERIALS AND METHODS

Study site

The study was conducted at San Lazaro Hospital (SLH), a 500-bed, tertiary care, government-owned referral facility for infectious and communicable diseases in Metro Manila, Philippines. Of its 11 pavilions, one has been designated for the care of both pediatric and adult patients with suspected dengue infection and other vector-borne diseases.

Ethical review

The protocol and consent/assent forms were approved by the ethics review committees of SLH and the Walter Reed Army Institute of Research (WRAIR).

Study design

This study was a prospective, hospital-based surveillance of patients admitted to the vector-borne pavilion of SLH with dengue-like illness (DLI) from September 2005 to January 2006. Inclusion criteria were: of age ≥ 2 years with

fever (temperature ≥ 38°C on admission or history of subjective fever within the previous 7 days) and with one of the following: positive tourniquet test, eschar, migratory polyarthritis, or any two of the following: headache, generalized rash, myalgias, arthralgias, retro-orbital pain. Pregnant patients were excluded. The primary analysis was done on all patients with laboratory-confirmed dengue (as defined below). Dengue cases were clinically graded according to World Health Organization (WHO) guidelines (WHO 1997).

Clinical evaluations

The investigators used case report forms to record the demographic, clinical and laboratory data on admission, as well as subsequent daily clinical assessments and routine laboratory and radiologic examinations (*eg*, complete blood counts, blood chemistry, hematocrit estimations, platelet counts, chest X-ray, ultrasound, etc) or other investigations requested by the attending physician until the patient was discharged.

Specimen collection

Patients who satisfied inclusion criteria and without any of the exclusion criteria were requested to provide both acute and convalescent blood samples. A convalescent serum was drawn: 1) ≥ 5 days after the acute illness sample, 2) ≥ 7 days after onset of illness, or 3) ≥ 3 days after fever defervescence, with the priority of convalescent serum collection based on this order.

Laboratory testing

The Armed Forces Research Institute of Medical Sciences (AFRIMS) provided technical training to SLH laboratory technicians to perform on-site the AFRIMS in-house dengue/Japanese encephalitis enzyme linked immunoassay (EIA) (Innis *et al*, 1989). This EIA was subsequently used to classify subjects as dengue-positive based on seroconversion between acute and convalescent sera. Dengue serotype determinations using semi-nested reverse transcriptase polymerase chain reaction (RT-PCR) for detection of DENV RNA (Klungthong *et al*, 2007) were performed on acute samples. When convalescent serum specimens were not available, the diagnosis of dengue was based solely on dengue RT-PCR testing of the acute specimen. A definitive diagnosis was determined retrospectively once all clinical and laboratory data were available.

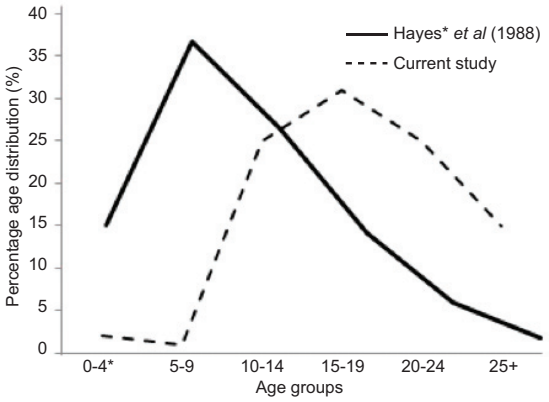
Statistical analysis

Data were analyzed using STATA version 6.0. Age distribution was explored numerically using measures of central tendencies and dispersion. The means (for quantitative variables) and proportions (for categorical variables) were also calculated to describe the characteristics of patients. Clinical and laboratory profiles of pediatric and adult patients were compared using independent sample *t*-test and chi-square test for quantitative and categorical variables, respectively. Associations among categorical variables were estimated and tested for significance using the chi-square or Fisher's exact test where appropriate. A p-value <0.05 was considered statistically significant.

RESULTS

Subject demographics

Of the 104 febrile subjects enrolled during the study period, 90 were laboratory-confirmed to have dengue infection. The dengue cases per month from September 2005 to January 2006 were 29, 8, 11, 22 and 20, respectively. The burden of disease was distributed equally between pediatric subjects (<18 years of age, n=45)



*Age group 2-4 old for current study.

Fig 1–Comparison of percentage age and gender distribution and age groups in the Hayes *et al* (1998) and the current study.

and adult subjects (≥ 18 years of age, *n*=45) with majority 28/90 (31%) of cases belonging to the 15-19 year age group (Fig 1). The male to female ratio was 1.5:1 and the age range was 2 to 37 years (mean = 18.2, SD=6.3). The majority were urban poor, with 77/ 90 (86%), living in Metro Manila and 83/ 90 (92%) had a monthly household income of USD 200 or less.

Clinical data

Of the 90 laboratory-confirmed dengue cases, the majority, 49/ 90 (54%) were classified as DHF grade 2 (Table 1). The most common symptoms were fever, loss of appetite, abdominal pain and headache (Table 2). The most common hemorrhagic manifestations were skin hemorrhage (petechiae, hematoma) (*n*=37), epistaxis (*n*=19), gingival bleeding (*n*=17), hematemesis (*n*=15) and melena (*n*=7). When comparing the pediatric and adult patients, there were no significant differences in the number of days of illness prior to hospitalization (p=0.24), number of days of hospitalization (p=0.48), number of days of fever (p=0.61) and maximum recorded temperatures (p=0.61) (Table 3). There were no significant differences between pediatric and adult age groups in the presence of hemorrhages (82% and 89%, respectively, p=1.0) or plasma leakage (47% and 56%, respectively, p=0.20). Two patients died but they tested negative for dengue and were excluded from the primary analysis.

Laboratory data

Of the 90 patients with laboratory-confirmed dengue, the diagnosis in 87 (97%) was based on seroconversion between acute and convalescent specimens and the remainder were diagnosed with dengue RT-PCR on the acute specimen alone. The majority (92%) of dengue cases was due to secondary DENV infections. There were 6 cases of primary DENV infections (median age=12, age range: 7-22). Sixty-five (72%) of the confirmed dengue cases had serotype data: 2 (3%) had DENV-1 infection (median age=17), 12 (18%) DENV-2 (median age=17.5), 38 (59%) DENV-3 (median age=16) and 13 (20%) DENV-4 (median age=18) (Table 1). There were no significant differences (p=0.77) by serotype with respect to median age.

Comparison of clinical laboratory data between pediatric and adult groups revealed no significant differences except for baseline (p<0.01), maximum (p=0.02) and minimum hematocrit (p=0.02) levels and minimum hemoglobin levels (p=0.02) (Table 3).

DISCUSSION

When comparing the clinical presentations of adults and children, the five most common presenting signs and symptoms (in order of frequency) were similar. The occurrence of hemorrhage and plasma leakage was also similar in

Table 1
Clinical and laboratory characterization of dengue infections by serotype.

Clinical diagnosis	Acute primary (*n*=6)				Acute/Recent secondary (*n*=83)					Indeterminate (*n*=1)	Total
	DEN1	DEN2	DEN3	NS*	DEN1	DEN2	DEN3	DEN4	NS*	DEN4	
DF		1									1
DHF gr 1	1		1			2	10	3	7	1	25
DHF gr 2			2			7	21	5	14		49
DHF/DSS				1	1	2	4	4	3		15
Total	1	1	3	1	1	11	35	12	24	1	90

*NS, no serotype data.

Table 2
Presenting symptoms and signs among pediatric and adult dengue infected patients.

Symptoms/Signs	Pediatrics (*N*=45) No. (%)	Adults (*N*=45) No. (%)	*p*-value
Fever	45 (100)	45 (100)	1.0
Anorexia	32 (71)	27 (60)	0.19
Abdominal pain	25 (56)	23 (51)	0.42
Headache	20 (44)	22 (49)	0.42
Flushed face	17 (38)	15 (33)	0.41
Bleeding	11 (24)	11 (24)	0.40
Hepatomegaly	11 (24)	7 (16)	0.21
Petechiae	8 (18)	10 (22)	0.40
Vomiting	7 (16)	3 (7)	0.16
Rash	5 (11)	5 (11)	0.37
Myalgia	5 (11)	9 (20)	0.19
Diarrhea	4 (9)	2 (4)	0.34
Retro-orbital pain	0 (0)	4 (9)	0.06

presentation between adults and pediatric patients. Among the clinical parameters, the only significant difference between adults and children was the tourniquet test on admission, although this was not consistently performed during the hospitalization. The only laboratory differences were the hematocrit and hemoglobin between adults and children, but this finding could be due to age related differences in normal values.

The majority of the study population lived in urban areas (86%) where population density and short flying distances for the vector are conducive to virus transmission. Differences in health seeking behavior, traditional practices, and socio-economic factors among people in the urban and rural areas may also substantially influence the differences in reported incidence between the two areas.

Table 3
Clinical and laboratory findings among pediatric and adult dengue infected patients.

Parameters	Pediatric		Adult		
	n	Mean	*n*	Mean	*p*-value
Days of hospitalization	45	5.2	45	5.3	0.48
Illness prior to admission (IPA) in days	45	4.0	45	3.8	0.24
Fever duration from onset to defervescence	45	5.4	45	5.5	0.61
Days of fever in hospital	45	1.4	45	1.7	0.18
Baseline platelet count	45	71.5	45	74.6	0.68
Minimum platelet count	45	42.1	45	38.0	0.46
Maximum platelet count	45	187.4	45	167.7	0.19
Baseline hematocrit	45	41.8	45	45.4	<.01
Minimum hematocrit	45	36.1	45	38.9	0.02
Maximum hematocrit	45	44.2	45	46.7	0.02
Minimum WBC	45	3.1	45	3.6	0.12
Maximum WBC	45	6.7	45	7.2	0.53
Minimum hemoglobin	45	120.7	45	129.7	0.02
AST	5	245.4	6	200.5	0.66
ALT	5	95.8	5	185.0	0.33
PT	21	12.2	24	17.5	0.15
aPTT	22	46.9	25	57.1	0.32
Minimum SBP	44	94.8	44	98.9	0.10
Minimum pulse pressure	45	30.7	45	30.4	0.84
Maximum temperature	45	38.2	45	38.1	0.61

Our study showed equal frequencies of hospitalized patients with dengue infection in both pediatric and younger adult patients. This may reflect the more severe presentation of dengue infections among older age groups requiring hospitalization as reported in several studies within the region (Sumarmo, 1987; Guzman *et al*, 1990; Goh, 1997; Muto, 2000; Rigau-Pérez *et al*, 2001; Rahman *et al*, 2002) and higher infection rates among adults (Chareonsook *et al*, 1999; Wali *et al*, 1999). Caution is advised as this apparent age shift in hospitalizations may not necessarily reflect the actual age distribution of dengue cases in the community. While we found the peak number of cases among those aged 15-19 years, Hayes *et al* (1988), observed a peak incidence in those aged 5-9 years (188/517 or 36% of cases) at the same hospital more than two decades ago (Fig 1). Some caution should be applied to retrospective comparisons given potential confounding factors in addition to the slightly different inclusion and exclusion criteria used between the 2 studies and as such limits direct comparison. First, population demographics in Manila have changed over the past 20 years including a reduction in birth rate. This may have impacted the underlying structure of the population from which these cases were drawn and may have altered transmission dynamics. Second, with the increase of internal migration from rural areas to Manila since the mid-1980's (Ooi, 2008), if

migrants came from areas of lower dengue incidence, this could render them more susceptible to adult dengue. The total fertility rate (number of children each woman is expected to have over her lifetime if fertility remains constant) has fallen from 5 in 1980 to 3.4 in 2000 (US Census Bureau, 1996). This reduction reduces the flow of dengue susceptible people into the population, and increases the relative abundance of older, typically immune, adults compared to younger, typically susceptible people. The change in relative abundance of susceptible people reduces the probability that an infected mosquito will bite a susceptible person, and thus reduces the force of infection that any susceptible person encounters. This could delay infection for susceptible people and increase the average age of both first and second infections.

Recognizing that dengue causes a wide spectrum of clinical disease ranging from asymptomatic infection to undifferentiated fever to DF and DHF, epidemiologic studies confirm that majority of infections are inapparent and most illnesses do not require hospitalization (Endy *et al*, 2002). Vaccine policy in dengue-endemic countries will be predicated on reducing, if not eliminating, the human impact of dengue while diverting the costs of dengue hospitalizations towards vaccine implementation. Once a dengue vaccine is introduced, it will likely become a childhood vaccine. If additional investigations corroborate our findings of comparable impact of severe dengue between children and young adults, vaccine introduction may need to include "catch-up" vaccinations targeting select adult age groups.

In summary, comparison of adult and pediatric hospitalized patients with laboratory confirmed dengue virus infection showed that there were no significant differences in the frequency of presenting clinical signs and symptoms. Only hematocrit and hemoglobin levels differed significantly among the laboratory parameters but these may be attributed to age related differences in normal values. The majority of patients in our study had secondary infections, presenting as DHF and with DENV-3 as the prevailing serotype. Although dengue has been considered as a pediatric disease, equal numbers of adults and children were diagnosed with dengue with a peak incidence observed in the 15-19 year age group. This apparent shift in age-related susceptibility to severe dengue is worth noting, given its potential impact on defining target populations for possible dengue vaccines. Additional studies are needed to determine if there is an age shift among hospitalized patients presenting with severe dengue infection. This information is essential to appropriately inform vaccine policy to maximize public health and economic benefits from future vaccine introduction which may need to be supplemented with an adult "catch-up" vaccination program targeting young adults.

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