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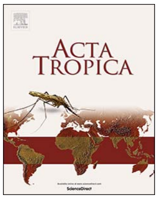

The reintroduction of DENV-2 in 2011 in Panama and subsequent outbreak characteristic

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ABSTRACT

The circulation of the South-east Asian/American (AS/AM) dengue 2 virus (DENV-2) genotype in the Americas has been associated with a high rate of severe disease. From 1993, the year DENV was reintroduced in Panama, until 2011 there were 29 dengue-associated deaths, 17 of which occurred in 2011, the most severe outbreak with a case fatality rate (CFR) of 44% (17 deaths out of 38 severe dengue cases). During this outbreak DENV-2 was reintroduced into the country, whereas over the prior five years DENV-1 and −3 were predominant. Herein, we describe the 2011 Panama outbreak and genetically characterize the Panamanian DENV-2 strains, which were associated with severe dengue disease in Panama. Our results suggest that the DENV-2 isolates from this outbreak belonged to the AS/AM genotype sub-clade 2BI and were genetically close to viruses described in the outbreaks in Nicaragua, Honduras, Guatemala and Mexico from 2006-2011. Sub-clade 2BI has previously been associated with severe disease in Nicaragua during outbreaks from 2005-2007.

1. Introduction

Dengue viruses (DENV) are the most common mosquito-borne arbovirus in the world with approximately 390 million cases annually (Bhatt et al., 2013). It is an enormous world wide economic burden (Bhatt et al., 2013) costing the Americas 1.9-2.2 billion dollars annually (Shepard et al., 2011). DENV belong to the genus *Flavivirus*, family *Flaviviridae* (Chambers et al., 1990) and there are currently four recognized serotypes (DENV-1-4). It is transmitted by the mosquitoes *Aedes aegypti* and *Ae. albopictus* as primary and secondary vectors respectively (WHO, 2009). Clinical disease caused by DENV is classified as dengue, dengue with warning signs and severe dengue base on the patients clinical presentation (WHO, 2009). The underlying mechanisms for progressing to severe disease have not been fully elucidated. However these are likely influenced by both specific host and viral factors that act in concert (Yacoub and Wills, 2014). Severe disease has been associated with: secondary infection with a different serotype (Mongkolsapaya et al., 2003; Halstead, 1988; Balmaseda et al., 2006),

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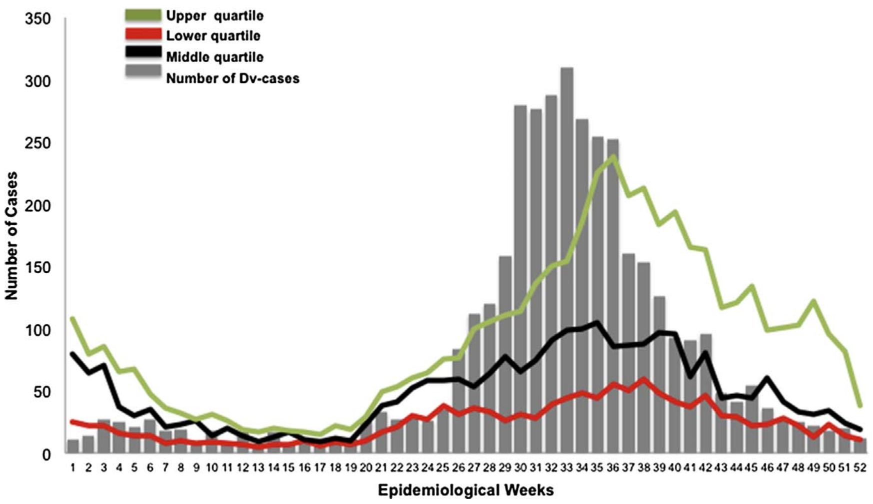

Fig. 1. Endemic channel of Dengue cases during 2011 outbreak. In grey bars, number of dengue cases per epidemiological week: lines show the endemic channel with green representing the upper quartile, red the lower quartile, black the middle quartile. Since epidemiological week 26, an increase of cases is shown; which is maintained for 11 weeks, with a sustained increase during epidemiological weeks 30 to 33. The endemic channel was constructed using 7 years of data, which included two Dengue epidemic years 2005 and 2009.

Table 1

Dengue confirmed cases by laboratory and epidemiological link, and total incidence rate by province during 2011.

Province	Percentage of Dengue cases confirmed by epidemiological link %(n)	Percentage of Dengue confirmed cases by Laboratory tests %(n)	Total of Dengue cases	Incidence rate* (x10 [5] inhabitants, July 1st, 2011)
Total	18.7 (721)	81.3 (3129)	3850	103.4
Bocas del Toro	45.3 (170)	54.7 (205)	375	269.8
Cocle	27.8 (35)	72.2 (91)	126	50.9
Colon	0.6 (2)	99.4 (314)	316	121.8
Chiriqui	1 (1)	99 (99)	100	22.8
Darien	35.9(14)	64.1 (25)	39	75.4
Herrera	0 (0)	100 (97)	97	83.0
Los Santos	12.1 (19)	87.9 (138)	157	166.5
Panama city	24.5 (286)	75.5 (879)	1165	114.4
West Panama	45.3 (139)	54.7 (168)	307	61.4
East Panama	2 (1)	98% (48)	49	96.8
San Miguelito	5.3 (50)	94.7 (899)	949	279.9
Veraguas	0 (0)	100% (154)	154	64.0
Guna Yala	25 (4)	75 (12)	16	40.8
Embera	0 (0)	0 (0)	0	0
Ngäbe-Bugle	0 (0)	0% (0)	0	0

host genetic susceptibility (Stephens, 2010), patient co-morbidities (Saqib et al., 2014; Toledo et al., 2016), specific DENV serotypes and genotypes (Balmaseda et al., 2006; Fried et al., 2010; Yung et al., 2015; Halsey et al., 2012), viral load (Longdon et al., 2015) and the immune response induced by the DENV-NS1 protein (Halstead and Cohen, 2015; Libraty et al., 2002; Chen et al., 2016; Modhiran et al., 2015).

Phylogenetic and molecular analyses have revealed extensive genetic diversity among DENVs, leading to the recognition of different genotypes within each serotype (Rico-Hesse, 1990; Weaver and Vasilakis, 2009). DENV-2 has 5 genotypes (Asian I, Asian II, Cosmopolitan, American and South-east Asian/American). The initial introduction of DENV-2 in Americas was caused by American genotype, then in 1975, it was replaced by the Asian/American (AS/AM) genotype in the Caribbean, with dissemination to Central and South America in the 1980-90s (Allicock et al., 2012). Its reintroduction in Nicaragua, Peru and Brazil since 2000's has been associated with more severe outbreaks (Dick et al., 2012; OhAinle et al., 2011; Nogueira et al., 1993).

Recent analysis of DENV-2 strains from Nicaragua, Honduras and Guatemala showed that the AS/AM circulating in Central America is divided into 2 clades; clade 2 is further divided in 2 sub-clades: 2A and 2B (Añez et al., 2011). Sub-clade 2 B has been implicated in severe cases in patients with primary exposure to DENV-1 in Nicaragua (OhAinle et al., 2011).

Dengue was responsible for outbreaks in Panama in 1904 (Carpenter Dudley and Sutton, 1903), 1912 (Rosen, 1958) and 1941–1942 (Laurence Fairchild, 1945). In 1958 Panama was declared *Ae. aegypti*-free after an intense vector control campaign. Panama was re-infested by *Aedes aegypti* in 1985 (Quiroz et al., 1997), and in 1993, a limited outbreak of dengue occurred in Panama City, confirming the return of autochthonous circulation of DENV-2 (Quiroz et al., 1997; Ministerio de Salud de Panama, 1994). Since then, the four DENV serotypes have circulated in Panama and continue to be a substantial public health burden (Armien et al., 2008).

In Panama, during the first half of 2011, DENV-1 and DENV-3 comprised the majority of circulating DENV. However, during the second half of the year, DENV-2 was detected and became the predominant circulating serotype and a corresponding increase in dengue deaths was observed. DENV-2 previously circulated in Panama in 1993–1994 and 1999–2004 (www.paho.org) and each reintroduction was associated with outbreaks but none were apparently associated with an increase in mortality. A retrospective analysis of data available through the National Dengue Epidemiologic Surveillance System was performed to characterize the 2011 DENV-2 outbreak in Panama. Herein, we report the results of the outbreak investigation as well as the genetic analysis of the viral strains detected during the outbreak.

2. Materials and Methods

2.1. *Ethical considerations*

The permit to study arboviral outbreaks was approved by The National Committee of Bioethics in Panama, IRB number: 0277/CBI/ICGES/15. Patient information was de-identified in order to protect the confidentially of individuals involved.

2.2. *Case definition*

The Dengue case definition used during 2011 Dengue outbreak in Panama, was based on the 1997-World Health Organization (WHO) classification system which includes: Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) (WHO, 2009). The epidemiological link criterion was defined as a case in close contact with a confirmed case within 30 days of symptoms onset.

2.3. *Dengue surveillance program and Epidemiological Data Collection*

Using the WHO's Dengue case definition(WHO, 2009; WHO, 1997)