

Features of Dengue and Chikungunya Infections of Colombian Children under 24 Months of Age Admitted to the Emergency Department

by Angel Paternina-Caicedo,¹ Fernando De la Hoz-Restrepo,²
Fredy Díaz-Quijano,³ William Caicedo-Torres,⁴
María Auxiliadora Badillo-Viloria,⁵ Doris Bula-Anichiarico,¹
Nelson Alvis-Guzmán,^{1,6} Salim Mattar,⁷ Dagna Constenla,⁸
and Hernando Pinzón-Redondo^{1,6}

¹Departamento de Epidemiología, Hospital Infantil Napoleón Franco Pareja—La Casa del Niño, Cartagena, Colombia

²Facultad de Medicina, Universidad Nacional de Colombia, Bogotá, Colombia

³Departamento de Epidemiología, Faculdade de Saúde Pública, Universidade de São Paulo, São Paulo, Brazil

⁴Facultad de Ingeniería, Universidad Tecnológica de Bolívar, Cartagena, Colombia

⁵Facultad Ciencias Básicas y Biomédicas, Universidad Simón Bolívar, Barranquilla, Colombia

⁶Facultad de Medicina, Universidad de Cartagena, Cartagena, Colombia

⁷Instituto de Investigaciones Biológicas del Tropico, Universidad de Córdoba, Montería, Colombia

⁸Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA

Correspondence: Angel Paternina-Caicedo, Hospital Infantil Napoleón Franco Pareja—La Casa del Niño, Bruselas Transversal 36 N. 36-33, Cartagena, Bolívar, Colombia. Tel: +1-412-3267809. E-mail <angel.paternina@gmail.com> or <ajpaterninac@unal.edu.co>.

ABSTRACT

We aimed to assess clinical and laboratory differences between dengue and chikungunya in children <24 months of age in a comparative study. We collected retrospective clinical and laboratory data confirmed by NS1/IgM for dengue for 19 months (1 January 2013 to 17 August 2014). Prospective data for chikungunya confirmed by real-time polymerase chain reaction were collected for 4 months (22 September 2014–14 December 2014). Sensitivity and specificity [with 95% confidence interval (CI)] were reported for each disease diagnosis. A platelet count <150 000 cells/ml at emergency admission best characterized dengue, with a sensitivity of 67% (95% CI, 53–79) and specificity of 95% (95% CI, 82–99). The algorithm developed with classification and regression tree analysis showed a sensitivity of 93% (95% CI, 68–100) and specificity of 38% (95% CI, 9–76) to diagnose dengue. Our study provides potential differential characteristics between chikungunya and dengue in young children, especially low platelet counts.

KEYWORDS: dengue, chikungunya, severe dengue, complications, children

INTRODUCTION

Dengue and chikungunya are viruses most commonly transmitted by the mosquito vectors *Aedes aegypti* and *Aedes albopictus*, disseminating both diseases in tropical settings worldwide [1]. Some patients infected with dengue may develop life-threatening consequences and require hospitalization, while the acute symptoms of patients infected with chikungunya may resolve within 7–14 days. Dengue is an emerging tropical disease that caused 96 million apparent new infections worldwide in 2010 [2], and a third of these infections required health-care attention [2]. The co-circulation of dengue and chikungunya has been confirmed in at least 98 countries/territories worldwide [1]. In Colombia, the co-circulation started in 2014 when chikungunya arrived to the country in a town near Cartagena [3].

Chikungunya fever can be indistinguishable at early ages from dengue and other viruses (e.g. Zika, Mayaro and Oropouche) [4], hence the need for proper diagnosis in children. In tropical settings, where both dengue and chikungunya are endemic, the laboratory confirmation of chikungunya is problematic, as virological/serological tests needed to make proper diagnosis may not be readily available. The differentiation between dengue and chikungunya in rural and low-income settings is of special importance because dengue may rapidly worsen clinical condition, leading to dengue shock and potentially death, while chikungunya rarely produces severe disease.

Colombia is 1 of 10 countries with most reported dengue cases, according to different estimations [2, 5]. Chikungunya was introduced by mid-2014 in the country, with no confirmed case before September 2014 [6]. In the present study, we assess the key clinical and laboratory differences between hospitalized chikungunya and dengue in children <24 months of age from Colombia.

PATIENTS AND METHODS

We carried out a comparative study to assess clinical and laboratory differences between chikungunya and dengue. We collected data from Hospital Infantil

Napoleón Franco Pareja—La Casa del Niño (HINFP), a pediatric university hospital from Cartagena (a city of around 1 million people located in northern tropical Colombia, South America), which serves lower-middle-income and low-income population, with around-the-clock physicians, including residents, intensivists and infectious disease pediatricians.

Co-circulation of dengue and chikungunya began in Colombia in September 2014.

We conducted a retrospective study of confirmed cases of dengue between 1 January 2013 and 17 August 2014 [7], when chikungunya was not circulating in the country. Then, as chikungunya was entering Latin America and the Caribbean, and circulation was confirmed in Colombia, we had a unique opportunity to highlight differences in clinical manifestation and management between chikungunya and dengue in infants and children of our setting, an upper-middle-income country with a gross domestic product per capita of US\$13.357 Power Purchasing Parity in 2014 [8].

We designed an analysis to compare our retrospective cohort of confirmed dengue cases before September 2014 (our dengue patients) with the prospective cohort of confirmed chikungunya cases after September 2014 (our chikungunya patients). We did not assess co-infection with dengue and chikungunya. The analyses included patients between 0 and 24 months of age. These patients were excluded because an analysis of our chikungunya patients [4] showed that neonates and infants of lower age had more severe disease, making more likely the need for hospitalization. This highlights the need in these patients of a clearer diagnostic pathway to differentiate dengue and chikungunya in countries with co-circulation. All patients included in the sample were admitted to the emergency department, after which they may or may have not needed hospitalization at HINFP. Hospitalization was defined as at least an overnight stay at the health institution. The ethics committee of HINFP approved both data collections.

The Supplementary Material describes our data collection methods for both dengue and chikungunya patients. The flowchart of the sample size is shown in Fig. 1.

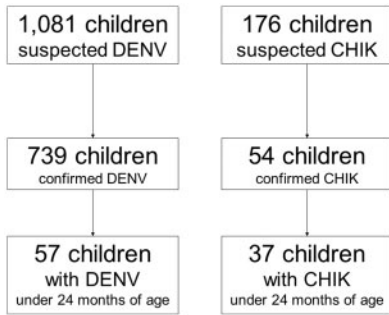


Fig. 1. Flowchart for patient inclusion in the study.

Study variables and data analysis

For both children with dengue and chikungunya, we collected information about age, gender, time of onset of symptoms, clinical signs at admission (ascites, pleural effusion and vomit), vital signs at admission (temperature, systolic blood pressure and diastolic blood pressure), laboratory values at admission (platelets, hemoglobin, hematocrit and white blood cell count) and need of critical care or not during hospital stay.

For variable description, categorical variables were reported in percentages and continuous variables in median with interquartile range (IQR) as dispersion measure. Analyses were made in Stata (Stata v. 13 for Windows; StataCorp; TX, USA) and R statistical software.

The Supplementary Material also expands our data analysis section.

RESULTS

Characteristics of the sample

A total of 57 children with dengue and 37 children with chikungunya were admitted to the emergency department (Fig. 1). Age differed between cases of dengue and chikungunya ($p < 0.001$). Median age was 12 months (IQR, 8.4–13.2) in patients with dengue, and 1.2 months (IQR, 1.2–3.6) in patients with chikungunya. We collected 11 of 37 (30%) neonates with chikungunya; no cases of neonatal dengue were reported. A total of 34 males (60%) with dengue and 22 males (59%) with chikungunya presented to the emergency department ($p = 0.985$).

Median time with symptoms before emergency admission was 5.0 days (IQR, 4.0–6.0) in dengue

patients and 1.0 days (IQR, 1.0–3.0) in patients with chikungunya. The time with symptoms before emergency admission was different between children with dengue and chikungunya ($p < 0.001$).

Figure 1 shows the median and IQR of children with dengue or chikungunya by days with symptoms before emergency department admission. Figure 2 and Table 1 show that platelet count increased significantly. In the crude analysis, we found differences in the presence of diarrhea, hemoglobin decreased for age, white blood cells decrease for age and platelets, between cases with dengue and controls with chikungunya (Table 1).

In multivariable logistic regression (adjusted by age, sex and time with symptoms previous to admission), only platelet count was significantly different between dengue and chikungunya (Table 1). Clinical characteristics were found to not be significantly different.

Diagnosis of dengue

An assessment of cutoff values for these variables with the greatest AUC is reported in Table 2. The characteristic that best diagnosed dengue was a platelet count $< 150\,000$ cells per mm^3 at emergency admission, with an AUC of 0.81 [95% confidence interval (CI), 0.73–0.88], a sensitivity of 67% (95% CI, 53–79) and specificity of 95% (95% CI, 82–99).

Algorithm to differentiate dengue and chikungunya

Data were randomly split into two data sets. The training data set was composed of 56 children and the testing data set composed of 23 children. The model used values of hematocrit, platelet and white blood cells collected at emergency admission to predict dengue in the sample.

The model that used 10 observations as minimum in each split had an AUC of 0.75 (95% CI, 55–96), with 15 minimum observations in each split, the AUC was 0.77 (95% CI, 57–97) and with 20 minimum observations in each split, the AUC was 0.74 (95% CI, 0.54–0.94).

The final model used 15 minimum observations in each split because of its higher AUC. The resulting model is shown in Fig. 3. In summary, two groups of children were classified as having dengue:

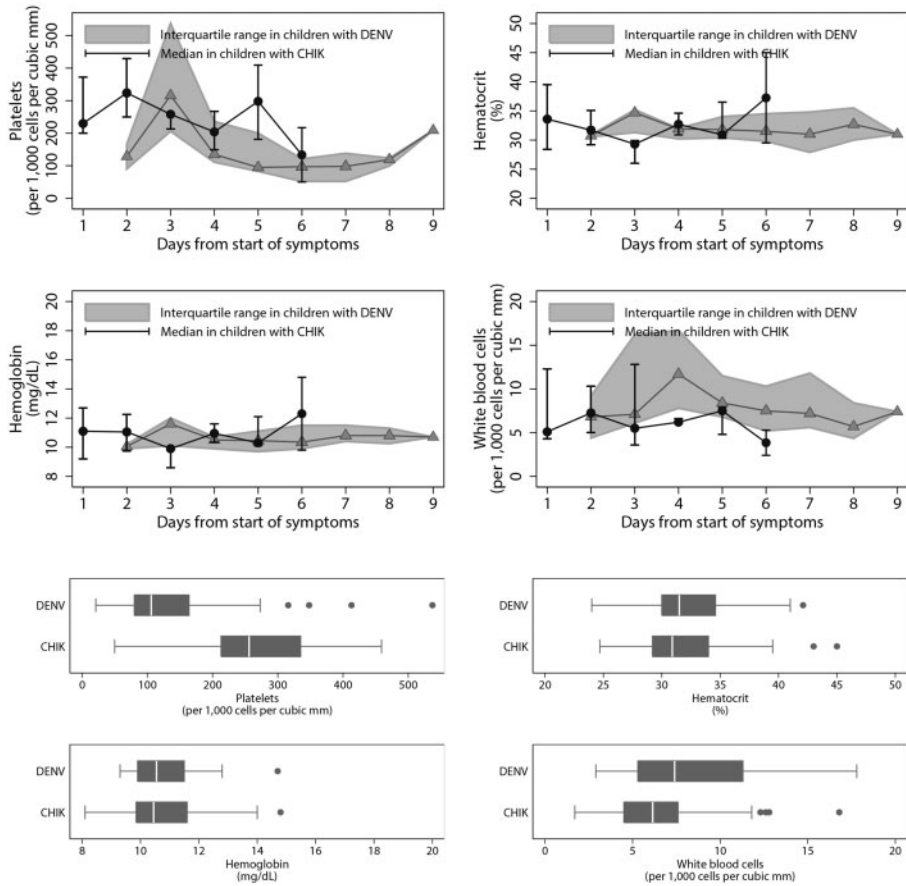


Fig. 2. Median and IQR of children with dengue or chikungunya by duration of symptoms.

1. Platelets <168 000 cells/ml.
2. Platelets \geq 168 000 cells/ml, and white blood cell count between 5300 and 12 000 cells/ml.

The diagnostic assessment of the final tree showed a sensitivity of 93% (95% CI, 68–100) and specificity of 38% (95% CI, 9–76) to diagnose dengue, a positive predictive value of 74% (95% CI, 49–91) and a negative predictive value of 75% (95% CI, 19–99).

DISCUSSION

Our analyses suggest that a few key simple laboratory variables may be valuable for differential diagnosis between chikungunya and dengue in infants and children that need admission to the emergency

department, evidencing that platelets <150 000 cells per ml would only miss one of three cases with dengue, and the algorithm including platelets and white blood cell count would miss only 7 in 100 cases with dengue. This is important to the health-care worker in low-income or rural settings without access to rapid tests/laboratory confirmation of dengue because these low-level health-care facilities may avert deaths and disability by safely remitting patients with high index of dengue suspicion to higher levels of care.

Our study also highlights that for conclusive differentiation between dengue and chikungunya that needs hospitalization, clinical/laboratory variables alone may not be as useful, and confirmation through rapid tests or other methods may be needed for a better clinical management.

Table 1. Clinical and laboratory characteristics of chikungunya and dengue and their relative adjusted risks among children <24 months of age in Colombia

Characteristics	Crude analysis Chikungunya	Risks for dengue		
		Dengue	<i>p</i> -value	Adjusted odds ratio (95% CI)*
Clinical				
Diarrhea, <i>n</i> (%)	3/37 (8)	13/57 (23)	0.064	2.13 (0.29–15.66)
Ascites, <i>n</i> (%)	0/37 (0)	1/57 (2)	1.000**	N.E.
Pleural effusion, <i>n</i> (%)	0/37 (0)	2/56 (4)	0.516	N.E.
Laboratory				
Hemoglobin (mg/dl) median (IQR) [<i>n</i>]	10.5 (10–12) [36]	10.5 (10–12) [53]	0.910	
Decrease for age, <i>n</i> (%)	26/36 (72)	25/53 (47)	0.019	1.33 (0.26–6.87)
Increase for age, <i>n</i> (%)	0/36 (0)	1/53 (2)	1.000**	N.E.
Hematocrit (%) median (IQR) [<i>n</i>]	30.9 (29–34) [33]	31.5 (30–35) [52]	a. 0.510	
Decrease for age, <i>n</i> (%)	24/33 (73)	30/52 (58)	0.160	1.04 (0.26–4.19)
Increase for age, <i>n</i> (%)	0/33 (0)	1/52 (2)	1.000**	N.E.
White blood cells (1000 cells/ml) median (IQR) [<i>n</i>]	6.4 (5–10) [33]	7.4 (5–12) [53]	0.220	
Decrease for age, <i>n</i> (%)	17/33 (52)	16/53 (30)	0.048	0.28 (0.07–1.08)
Increase for age, <i>n</i> (%)	4/33 (12)	5/53 (9)	0.728	1.97 (0.27–14.17)
Platelets (1000 cells/ml) median (IQR) [<i>n</i>]	256.0 (213–335) [34]	106.0 (80–164) [53]	<0.001	0.22 (0.05–0.87)***

Note: N.E.: Not estimable.

*Adjusted by age, days with symptoms and sex.

**Fisher's exact test.

***Best fit was natural logarithm of the exposure variable.

Table 2. Prognostic value of parameters for dengue diagnosis of children <24 months old

Parameters at emergency admission	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	AUC (95% CI)
Platelets (cells/ml)			
<100 000	40 (28–54)	97 (86–100)	0.69 (0.62–0.76)
<150 000	67 (53–79)	95 (82–99)	0.81 (0.73–0.88)
<200 000	74 (60–84)	84 (68–94)	0.79 (0.70–0.87)
White blood cell count			
High for age	91 (79–97)	12 (3–28)	0.51 (0.44–0.58)
Low for age	70 (56–82)	52 (34–69)	0.61 (0.50–0.71)
Hematocrit			
High for age	2 (0–10)	100 (89–100)	0.51 (0.49–0.53)
Low for age	42 (29–57)	73 (54–87)	0.58 (0.47–0.68)

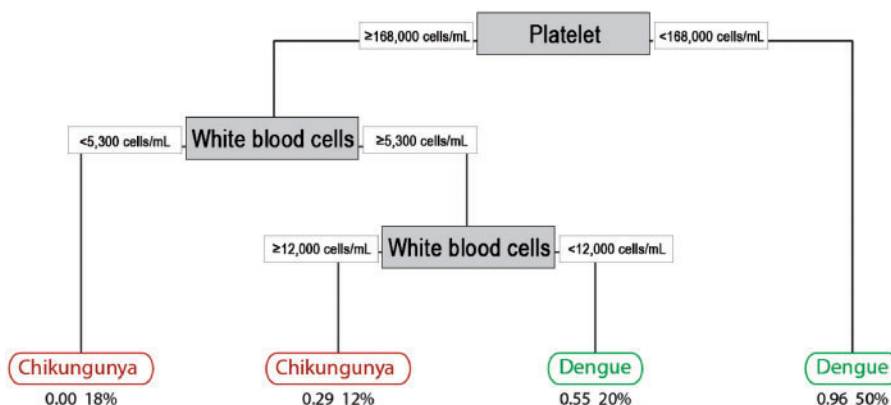


Fig. 3. Algorithm for differential diagnosis of chikungunya and dengue in children under 24 months old in Colombia.

The arrival of Zika in 2015 to the region may complicate differential diagnosis of fever of unknown origin. In pediatric chikungunya, and especially at younger ages, arthralgia and arthritis cannot be properly assessed despite being hallmarks of chikungunya [4], and the laboratory diagnosis of chikungunya or Zika is still uncommon in our region. The clear differentiation between dengue, chikungunya and Zika in their acute clinical presentation is important for health-care clinical workers and decision-makers; currently, a patient must undergo several tests to differentiate between these three diseases in a burdensome and costly process.

A call is warranted for a rapid test or cheap laboratory tests with adequate sensitivity and specificity to diagnose dengue, chikungunya and/or Zika, including tools to detect co-infection of patients.

The highest burden of these three diseases is set in low- and lower-middle-income regions throughout tropical climates [9]. Adequate identification of acute disease will lead to better knowledge on the specific burden of each disease, helping decision-makers to redirect policies to lower the mortality and disability in regions that need this the most.

A recent case series from Colombia showed that vertical transmission of chikungunya can lead to severe disease in the neonate [10]. Although in the present study chikungunya vertical transmission was not confirmed, we cannot rule it out in some patients, given the age of diagnosis. The age difference between the two cohorts can alter physiologic normal values for some variables. For platelets,

previous literature does not suggest that normal values change throughout life [11]. We adjusted all other parameters for age to account for these differences.

Our main limitation is that patients with dengue and chikungunya were not ascertained in the same timeframe, allowing for some source of information bias and selection bias. Laboratory tests, like platelet counts, were conducted at different time points for dengue and chikungunya patients, and by different technicians and using different equipment. It could lead, up to some point, to differences in results between the two groups explained by procedural differences. Though this source of bias is potentially present, it is unlikely to fully explain the large differences in platelet accounts that we found in the study. Also, we were not able to select patients with co-infection. Despite this, we confirmed all patients through laboratory test, and we think it is unlikely that the severity profiles of the diseases would change in our analyzed timeframes. Our sample of children with dengue did not include patients with chikungunya because in that timeframe, chikungunya was not circulating in Colombia. For the timeframe of the chikungunya data collection, the high specificity in the literature of the dengue tests (>94%) (10–14) makes false positives unlikely, but the relative low sensitivity of rapid methods for dengue may mask some dengue/chikungunya co-infections among the chikungunya group. This potential information bias would decrease the magnitude of the relationship between platelet counts and dengue;

thus, it would not explain the differences we found. If something, the difference may well be larger if better dengue diagnosis tests had been available. Other limitations are related to selection, information and misclassification bias, especially for the children with dengue. Selection bias may be possible for dengue because confirmation was made with rapid tests. However, the rapid tests we used have a good sensitivity and high specificity. Information bias may be also possible for the dengue patients because data collection was retrospective; however, trained health personal (who usually care for dengue patients) systematically gathered data for all patients in our research. The chikungunya data are prospective, and so, information bias is unlikely.

Chikungunya and dengue are two under-researched emerging diseases. Further, evidence-based medicine and translation research are needed to curve down endemicity and disease burden worldwide. The uncertainty in the differential diagnosis of Chikungunya and dengue and the emergency of Zika as a disease with increased disability renew calls for proper diagnostic tests for these diseases.

SUPPLEMENTARY DATA

Supplementary data are available at *Journal of Tropical Pediatrics* online.

ACKNOWLEDGEMENTS

The authors are deeply thankful to Katherine Barrios-Redondo, Andrea Zarate-Vergara, Irina Tirado-Pérez and Rossana Fortich for their contributions in gathering data.

FUNDING

Hospital Infantil Napoleón Franco Pareja—La Casa del Niño provided funding for chikungunya confirmation tests.

REFERENCES

1. Furuya-Kanamori L, Liang S, Milinovich G, *et al.* Co-distribution and co-infection of chikungunya and dengue

- viruses. *BMC Infect Dis* 2016;16:84. [cited 12 December 2016] <http://www.ncbi.nlm.nih.gov/pubmed/26936191>.
2. Bhatt S, Gething PW, Brady OJ, *et al.* The global distribution and burden of dengue. *Nature* 2013;496:504–7. [cited 12 December 2016] <http://www.ncbi.nlm.nih.gov/pubmed/23563266>.
3. Mattar S, Miranda J, Pinzon H, *et al.* Outbreak of chikungunya virus in the North Caribbean area of Colombia: clinical presentation and phylogenetic analysis. *J Infect Dev Ctries* 2015;9:1126–32. [cited 12 December 2016] <http://www.jidc.org/index.php/journal/article/view/6670>.
4. Pinzón-Redondo H, Paternina-Caicedo A, Barrios-Redondo K, *et al.* Risk Factors for Severity of Chikungunya in Children: A Prospective Assessment. *Pediatr Infect Dis J* 2016;35:702–4. [cited 12 December 2016] http://content.wkhealth.com/linkback/openurl?sid=WKP_TLP:landingpage&an=00006454-201606000-00024.
5. Fullerton LM, Dickin SK, Schuster-Wallace CJ. Mapping global vulnerability to dengue using the water associated disease index, 2012. Hamilton, Canada: United Nations University.
6. Instituto Nacional de Salud. Comportamiento de los eventos de vigilancia en salud pública. *Boletín Epidemiológico Semana*. 2014, 17–19. [cited 12 December 2016] <http://www.ins.gov.co/boletin-epidemiologico/BoletinEpidemiologico/2014BoletinEpidemiologicoSemana53.pdf>.
7. Pinzón-Redondo H, Paternina-Caicedo A, Alvis-Guzman N, *et al.* Performance of two World Health Organization Dengue classifications in a pediatric cohort from Colombia. *Value Heal* 2015;18:A248–9. [cited 12 December 2016] <http://linkinghub.elsevier.com/retrieve/pii/S1098301515015041>.
8. World Bank Group. 2016. [cited 1 May 2016] <http://www.worldbank.org/>.
9. Oviedo M, Mendez N, Mattar S, *et al.* Epidemic outbreak of chikungunya in two neighboring towns in the Colombian Caribbean: a survival analysis. *Arch Public Heal* 2017;75:1.
10. Villamil-Gómez W, Alba-Silvera L, Menco-Ramos A, *et al.* Congenital chikungunya virus infection in Sincelejo, Colombia: a case series. *J Trop Pediatr* 2015;61:386–92. [cited 12 December 2016] <http://www.ncbi.nlm.nih.gov/pubmed/26246086>.
11. Kliegman R, Nelson WE. *Nelson Textbook of Pediatrics*. 19th edn. Philadelphia, PA: Elsevier/Saunders, 2011, 2610.