

Dengue beyond the tropics: a time-series study comprising 2015-2016 versus 2019-2020 at a children's hospital in the City of Buenos Aires

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ABSTRACT

Introduction. Dengue is a public health problem worldwide. It was originally confined to tropical and subtropical areas, but it is now present in other regions, such as Argentina. Epidemic outbreaks have been observed in the City of Buenos Aires since 2008, with few reports in children.

Objective. To analyze and compare the clinical, epidemiological, laboratory, and evolutionary characteristics of the latest 2 dengue outbreaks outside the endemic area.

Population and methods. Time-series study. Patients under 18 years of age with probable or confirmed dengue and evaluated in a children's hospital of the City of Buenos Aires during the periods 2015-2016 and 2019-2020 were included.

Results. A total of 239 patients were included; 29 (12%) had a history of travel. Their median age was 132 months (interquartile range: 102-156). All had a fever. Other symptoms included headache in 170 (71%), myalgia in 129 (54%), and rash in 122 (51%). Forty patients (17%) had comorbidities. Warning signs were observed in 79 patients (33%); 14 (6%) developed severe dengue; 115 (45%) were hospitalized; none died. DENV-1 was the most common serotype. A history of travel and hospitalization prevailed in the first period; severe dengue and prior infection, in the second period.

Conclusions. No patient died due to dengue in either study period. Statistically significant differences were observed in the frequency of hospitalization; a history of travel was more common in the 2015-2016 period and severe dengue, in the 2019-2020 period.

Key words: dengue, child, mosquito-borne diseases.

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INTRODUCTION

Dengue is a viral disease transmitted by mosquitoes of the *Aedes* genus, with worldwide distribution in urban and suburban areas of tropical and subtropical regions. Dengue is caused by an arbovirus of the *Flaviviridae* family, *Flavivirus* genus, and there are 4 known serotypes: DENV-1, DENV-2, DENV-3, and DENV-4. In the last 40 years, it has re-emerged in the region of the Americas and, since then, both the vector and the viral serotypes have expanded geographically, with an increase in epidemic activity and severe clinical forms.¹

The World Health Organization (WHO) estimates that more than half of the planet is at risk of dengue, as it is the arthropod-borne viral disease with the highest morbidity and mortality in the world.²

In Argentina, dengue cases have been described in the northern provinces since the beginning of the 20th century. However, since 1997, epidemic outbreaks of increasing magnitude and the first native cases have been reported in the subtropical areas of the north of the country, such as Salta, Misiones, and Formosa.³

In 2008, epidemic outbreaks also began to occur in the central provinces of Argentina, with a greater number of cases and shorter inter-epidemic periods.⁴ There are multiple human and environmental factors that favor the development of *Aedes aegypti* (*Aa*) and dengue dissemination outside endemic areas.⁵⁻⁷

In the 2008-2009 period, 26 700 cases were reported in an outbreak that started in the northwest region of Argentina and spread to the center of the country. The number increased in successive outbreaks: 2015-2016: 41 749 cases and 2019-2020: 59 375 cases.⁸

In view of this epidemiological situation, we conducted this study to evaluate the clinical, epidemiological, laboratory, and evolutionary characteristics of the latest 2 dengue outbreaks outside the endemic area, and to compare both periods (2015-2016 and 2019-2020) in a children's hospital in the City of Buenos Aires (CABA).

POPULATION AND METHODS

This was a descriptive, analytical, time-series study. All patients under 18 years of age with a confirmed or probable diagnosis of dengue seen at Hospital de Pediatría "Prof. Dr. Juan P. Garrahan" between December 2015 and June 2020 were included. They were divided into 2 periods: period I from December 2015 to June 2016, and period II from December 2019 to June 2020. Patients diagnosed with dengue based on epidemiological criteria were excluded.

Hospital Garrahan is a tertiary care hospital that, in addition to being a referral center for highly complex pathologies, provides care by spontaneous demand in the outpatient and emergency areas.

Epidemiological, clinical, evolutionary, and laboratory characteristics were recorded.

The following variables were assessed: sex, age, comorbidities, place of origin, history of travel, presence of fever, retro-orbital pain, myalgia, arthralgia, anorexia, malaise, asthenia, nausea, vomiting, diarrhea, abdominal pain, conjunctival injection, rash, hepatomegaly, splenomegaly, petechia, epistaxis, leukopenia and/or thrombocytopenia. The presence of warning signs, hospitalization, viral classification (confirmed or probable), clinical classification (dengue or severe dengue), and course were also recorded.

For viral diagnosis, molecular techniques were used, including reverse transcription-polymerase chain reaction (RT-PCR), nonstructural protein 1 (NS1) antigen, and IgM and IgG neutralizing antibodies; the latter at the National Institute of Human Viral Diseases "Maiztegui" (Instituto Nacional de Enfermedades Virales Humanas, INEVH). The diagnostic methodology varied depending on institutional availability since, in the first period, all samples were sent to

referral centers and, in addition, NS1 was studied, whereas in the second period, RT-PCR and IgM were added to the hospital laboratory procedures. Dengue virus classification according to serotype (1 to 4) was performed by RT-PCR.

Patients positive for NS1 antigen and/or IgM were considered probable cases, and confirmed cases were those with positive RT-PCR for DENV.⁹

The guidelines of the National Ministry of Health of Argentina and the 2009 WHO recommendations were used to classify dengue: dengue with warning signs and severe dengue.^{10,11}

Statistical analysis: continuous variables were summarized into median and interquartile range (IQR), and categorical variables, into percentage and frequency. The epidemiological, clinical, and viral characteristics were compared between both periods. A χ^2 test or the rank-sum test were used depending on the variable. The Stata[®] 16 software was used for statistical analysis.

Data collection and analysis were done retrospectively, protecting the identity of both patients and their families. The study was approved by the hospital's Ethics Committee.

RESULTS

During the study period, 597 patients with suspected dengue were assessed. Of these, 239 (40%) were included and had virological confirmation, 112 (47%) during period I and 127 (53%) during period II. Two hundred and thirty-five (98%) were from the Metropolitan Area of Buenos Aires (AMBA), of which 123 (53%) were from CABA.

Two hundred and ten patients (88%) had native dengue. A history of travel was present in 29 patients (12% of the total); 22 corresponded to the first period and 7 to the second, which was statistically significant. Of those with a history of travel, 14 came from Paraguay; 7, from Misiones; 3, from Bolivia; and 5, from other places (Salta, Jujuy, Brazil, Chile, and Peru).

Male cases prevailed (n: 138, 58%). Patients' median age was 132 months (IQR: 102-156); the youngest patient was 3 months old; 4 patients were younger than 12 months (*Figure 1*). Forty patients (17%) had a comorbidity; the most common were congenital heart disease (12 children) and oncohematological diseases (10 children).

Only 3 patients had a history of dengue.

All had a fever at the time of consultation,

with a mean duration of 4 days. Headache, myalgia, and rash were the signs and symptoms that most frequently accompanied fever (Figure 2). Upon admission 111 patients (46%) had thrombocytopenia and 137 (57%), leukopenia.

Dengue with warning signs was observed in 79 patients (33%) and severe dengue, in 14 (6%). The most frequent warning sign in both periods was abdominal pain: 22 patients (20%) during period I and 15 (12%) during period II (Table 1).

A total of 115 patients (48%) were hospitalized. During period I, hospitalization was more frequent, although patients had a shorter length of stay. No patient died from dengue.

The diagnosis was confirmed by RT-PCR in 111 patients (46%). During the first period, diagnosis with NS1 antigen predominated versus RT-PCR during the second period (Table 2).

The predominant dengue serotype in both periods was DENV-1. During the second period, DENV-4 (22%) and DENV-2 (5%) were also reported.

When comparing the characteristics of both periods, it was observed that, during period I, a history of travel, the presence of warning signs, and the need for hospitalization were more frequent ($p < 0.05$). All patients who developed severe dengue and had a history of

FIGURE 1. Age group distribution by period of presentation (N: 239 patients)

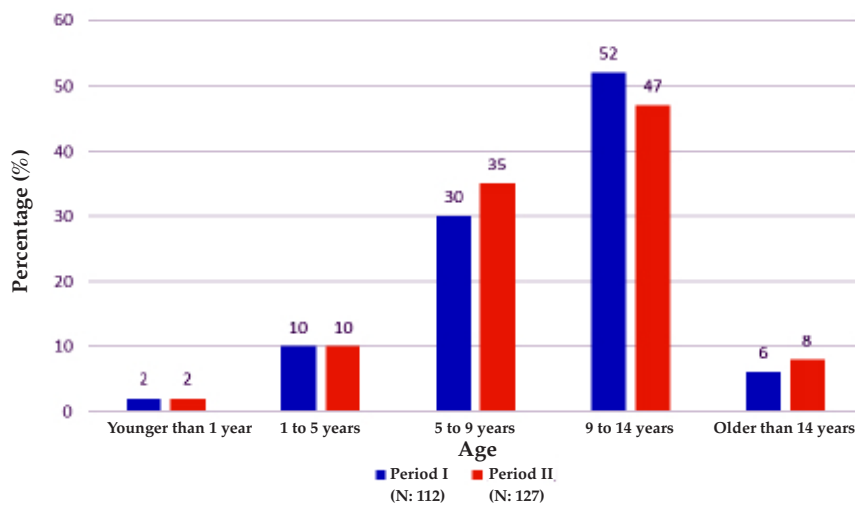
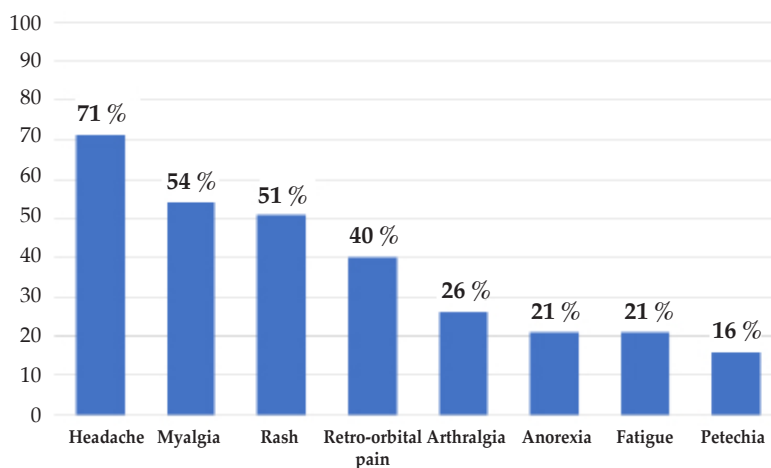


FIGURE 2. Frequency of symptoms expressed as percentage (N: 239 patients)



dengue corresponded to the second period. No statistically significant differences were observed in the rest of the comparative data.

DISCUSSION

Argentina is a country with 3700 km in length and 45 million inhabitants; almost 40% of the population is concentrated in the AMBA, which includes CABA and the suburbs of the province of Buenos Aires. Its geography encompasses a wide variety of ecosystems, climates, socioeconomic and urban conditions that make it more or less

favorable to the presence of *Aa*, a key vector for the presence and transmission of dengue.

In countries where dengue is not endemic, but there is *Aa* infestation, native cycles of infection can be established by travelers or immigrants from areas where there is viral circulation; thus, a native cycle is established outside the endemic area. This is the case in the United States, southern Europe, and the Mediterranean Sea region.¹²

Studies conducted in Argentina have exemplified the emergence of arbovirus-borne diseases out of subtropical areas into temperate

TABLE 1. Epidemiological, clinical, and evolutionary characteristics of all included patients by period of presentation

Characteristic	Total n (%)	Period I (2015-2016) n (%)	Period II (2019-2020) n (%)	p value	
Males	138 (58)	68 (61)	70 (55)	0.34	
Age (months old) (median, IQR)	132 (102-156)	137 (106-156)	128 (102-155)	0.37	
Comorbidities	40 (17)	17 (15)	23 (18)	0.54	
Place of origin	CABA	127 (53)	51 (56)	76 (60)	0.02
	PBA	108 (45)	58 (52)	50 (40)	0.05
	Other	4 (2)	3 (3)	1 (1)	0.25
Travel	29 (12)	22 (20)	7 (6)	0.001	
Prior dengue	3 (1)	0	3 (2)	-	
Duration of fever (days) (median, IQR)	4 (3-5)	5 (3-5)	4 (2-5)	0.08	
Warning signs	79 (33)	44 (39)	35 (28)	0.05	
Abdominal pain	37 (15)	22 (20)	15 (12)	0.09	
Bleeding	27 (11)	13 (12)	14 (11)	0.88	
Vomiting	8 (3)	2 (2)	6 (5)	0.21	
Sudden hematocrit increase	9 (4)	9 (8)	-	-	
Drowsiness	3 (1)	3 (3)	-	-	
Severe dengue	14 (6)	-	14 (11)	-	
Leukopenia	137 (57)	67 (60)	70 (55)	0.73	
Thrombocytopenia	111 (46)	59 (53)	52 (41)	0.07	
Hospitalization	115 (48)	64 (57)	51 (40)	0.008	
Length of stay (median, IQR)	2 (1-4)	2 (1-4)	3 (2-6)	0.01	

IQR: interquartile range; PBA: province of Buenos Aires; CABA: the City of Buenos Aires.

TABLE 2. Diagnostic methodology by period of presentation

Methodology	Total n (%)*	Period I n (%)	Period II n (%)
NS1	90 (38)	89 (79)	1 (1)
PCR	111 (46)	19 (17)	92 (72)
IgM	85 (36)	25 (22)	60 (47)

*More than 1 diagnostic methodology was used in 47 patients.

NS1: nonstructural protein 1 antigen measurement; PCR: polymerase chain reaction; IgM: immunoglobulin M.

zones, as in the case of Córdoba between 2009 and 2018¹³ and Santa Fe.¹⁴ In 2009, Seijo et al., published the first outbreak of native dengue in the AMBA, which started with imported cases in the first weeks of that year.¹⁵ Outside tropical areas, it is common for the onset of epidemics to coincide with population movements from endemic areas, especially during the period of greatest mobility coinciding with holidays and vacations. This was also reflected in our series: the first cases were related to migratory movements from neighboring countries, and then native dissemination was established. In our series, 12% of patients had a history of travel to neighboring countries, mainly Paraguay; such history was more frequent in the first epidemic period.

The study was conducted at Hospital Garrahan, where 98% of the children with dengue came from the AMBA. According to data from the National Ministry of Health, the initial cases in CABA in 2020 were concentrated in the city's working-class neighborhoods.¹⁶

Consistent with the increase in the number of dengue cases in the 3 epidemic outbreaks in Argentina corresponding to the 2008-2009, 2015-2016, and 2019-2020 seasons, Hospital Garrahan confirmed 8, 112, and 127 cases respectively; the latter period coincided with the onset of coronavirus disease 2019 (COVID-19) cases in Argentina.¹⁷

In relation to data obtained from the epidemiological surveillance conducted in CABA, dengue cases represented 15% of the country's total for the 2019-2020 outbreak and 12% for the 2015-2016 outbreak.¹⁸ Regarding age at onset, different reports show variable figures. In the region of the Americas, 70% of cases correspond to adolescents and young adults.¹⁹ In Argentina, the highest burden of disease is also registered in the adolescent and young adult population.²⁰ In 2020, in CABA, the highest incidence was observed in the 15 to 34 year-old population, and infection was less frequent in children under 5 years of age. In our series, the median age was 11 years.

Dengue is a systemic and dynamic disease. The clinical spectrum is broad and ranges from asymptomatic forms to fatal cases. The clinical form of classic dengue with fever, headache, retro-orbital pain, myalgia, arthralgia, and rash is more characteristic in older children and adolescents. The younger the age, the more non-specific the clinical picture, so a high diagnostic suspicion is required in febrile patients depending

on the local epidemiology.

In the study conducted in Cuba by Martínez et al., fever was present in all children, headache in 70%, digestive symptoms were relatively frequent, and rash was present in more than 50%, with spontaneous bleeding and skin petechiae in 20% of the cases.¹ In our series, in addition to fever, headache, myalgia, abdominal pain, rash, and malaise were the most frequent symptoms. The same is reported in a recently published study of 156 pediatric cases seen at Hospital de Niños Ricardo Gutiérrez in CABA during 2016.²¹

Dengue is generally a self-limited disease, although at the end of the febrile phase (between the third and fifth days), complications that give rise to severe dengue may occur. Complications are related to fluid extravasation, shock, and bleeding, or direct organ involvement, such as encephalitis, myocarditis or hepatitis. The presence of comorbidities and warning signs allow for the early detection of the group of patients at risk for complications. In our series, one third of the children had warning signs; these figures are consistent with those found in the bibliography, which states that 30-50% of children who consult for dengue have warning signs. The criteria for hospitalization were modified in relation to the training of health care staff in the identification and management of severe cases. In this study, patients were hospitalized less frequently in the second period, perhaps related to a better initial categorization based on greater knowledge of the disease, which led to more patients being hospitalized for observation in the first period. Previous dengue was one of the causes identified as a predisposing factor for severe forms, and no other causes were identified. It is worth noting that, despite the type of facility where the study was carried out—a high complexity, referral hospital—only 17% of the patients had associated comorbidities.

Mortality varies according to the series and depends on viral factors, such as serotype, strains, genotype, epidemic sequentiality, and history of infection, with secondary infections by a different serotype presenting greater severity due to heterotypic sensitization.²² There are also host factors associated with greater severity such as age under 1 year, diabetes, and asthma, among others. In Cuba, in 1981, 158 deaths were reported, of which 101 were children. These data do not coincide with other epidemics in which the highest mortality was reported in adults. In Argentina, in 2020, 29 patients died (0.049%). In

this series, no patient died from dengue, which is probably related to primary infections in patients with no history of exposure to dengue. The prognosis of severe forms depends greatly on early detection with the identification of warning signs that allow a timely and effective management.

Within the diagnostic triad formed by epidemiology, clinical data, and laboratory findings, viral diagnosis confirmed 40% of the cases. The method used depends on the time of disease course; direct virus search techniques are used for the initial phase, and serological techniques are used beyond the fifth day of disease course. In the initial phase, molecular techniques (e.g., RT-PCR) are the techniques of choice because of their high sensitivity and specificity and, in addition, they allow viral typing. NS1 detection is a useful diagnostic alternative applicable in low complexity laboratories and allows greater access to diagnosis. The use of serum NS1 varies according to viral serotype, time of infection, and host, and its level is highest during the early phase of infection, in primary infection, and in severe forms of dengue. NS1 detection by enzyme-linked immunosorbent assay (ELISA) has a 60-75% sensitivity and a 71-80% specificity. IgM and IgG antibody responses are useful after the fifth day of disease course and also allow differentiation between primary and secondary infections.²³ In this series on the use of direct tests, RT-PCR was most commonly used in the second period due to its availability, versus NS1 in the first period.

In relation to viral typing, findings corresponded to the serotypes circulating in Argentina and in the region; DENV-1 was the most frequent in both periods; and new serotypes DENV-4 and DENV-2 were also reported in the second period.

Early and accurate diagnosis and categorization of severity criteria are key to an adequate care and the prevention of mortality.²⁴ For this reason, it is critical to recognize dengue as an emerging disease even outside tropical areas, and to include it in the differential diagnosis of acute febrile illness, especially in densely populated urban areas such as the AMBA in Argentina.

CONCLUSION

Patients' median age was 132 months; prevailing cases were previously healthy children. All patients developed fever. No differences

were observed in the clinical and laboratory characteristics of children with dengue when comparing both periods. No patient died due to dengue in either study period. Statistically significant differences were observed in the frequency of hospitalization and the history of travel (both more common in the 2015-2016 period) and severe dengue (more common in the 2019-2020 period). ■

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