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Epidemiological behavior and risk factors of dengue in pediatric cohort of District II in Managua-Nicaragua, period 2004 to 2021.

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ABSTRACT

Dengue is a vector-borne disease that has presented an increase in cases worldwide. In Nicaragua, as in other countries of the region, dengue epidemics continue to increase. Therefore, the objectives of this study were to determine

the seroprevalence, to demonstrate dengue cases in children in a pediatric dengue cohort from 2004 to 2021, to recognize the factors associated with dengue cases for the year 2019, and to identify these epidemiological indicators with geographic information system tools.

Methodology: A retrospective cohort study was conducted using databases of a sample of participants aged 2 to 18 years who received care at the Socrates Flores Health Center in District II of Managua, Nicaragua. The laboratory results and the answers provided in the surveys by the participants were analyzed to analyze and process the variables of interest.

Results: Dengue seroprevalence decreased from 60% in the first years (2004-2008), to 26% by 2016 and an increase of 49% by 2021. The highest number of dengue cases was in 2019 with 368. In this same year, age group and neighborhood of origin were associated with dengue cases. The geospatial representation of the epidemiological indicators allowed the identification of the neighborhoods with the highest number of dengue cases, and the increase in the number of participants who presented antibodies for this virus.

Conclusions: The analysis of the pediatric dengue cohort showed that dengue fever has presented variations regarding the number of participants with antibodies for dengue, as well as the different years of outbreaks that have occurred in district II, with age and geospatial location being factors associated with dengue cases.

INTRODUCTION

Dengue virus disease (DENV) continues to be one of the global priority diseases for public health in tropical regions (Srisawat et al., 2022). In the Americas region, the increase in cases has doubled in recent years (2021= 1.2 million; 2022= 2.8 million) (World Health Organization, 2023), and cases have expanded beyond the tropics generating outbreaks as far as Europe (European Centre for Disease Prevention and Control, 2023). To recognize the impact of dengue disease, some variables should be evaluated such as the seroprevalence of total antibodies, the number of new cases per year, in addition to socio-clinical factors that are associated with the infection (WHO, 2010). With the analysis of seroprevalence, incidence, and geographical distribution of dengue cases it is possible to efficiently plan control measures against dengue disease (Ganeshkumar et al., 2018). This is why seroprevalence studies are of vital need for the health authorities of a country or region to determine the magnitude of infection caused (Aballay et al., 2022).

In the Americas region, dengue has been endemic since the 18th century; the first dengue epidemic occurred in Cuba in 1981 (Pan American Health Organization, 1997). In Nicaragua, the first documented epidemic of dengue occurred in 1985 (Guzman et al., 1996). Dengue has persisted until the present time with endemic behavior and outbreaks in different departments

of the country (Balmaseda et al., 2010). Dengue control in Nicaragua has focused on outbreak control actions and mobilization of human and financial resources (MINSA, 2015). However, despite these multiple efforts, control of the disease and more importantly sustainability in its control has not been achieved. Being able to determine which factors may be a risk for dengue transmission is important to be able to guide control actions and better understand the dynamics of transmission.

In Nicaragua, a pediatric dengue cohort has been established since 2004 in District II of Managua, in which the epidemiological behavior of the disease, the immune history, and the socio-clinical characteristics of the participants have been recorded (Kuan et al., 2009). The objective of this study is to describe the seroprevalence and cases of dengue in this cohort in the period 2004-2021, to support the community family health model (MINSA, 2008), and to identify the epidemic cycles of dengue in the region.

METHODOLOGY

Informed consent

Parents or legal guardians of all pediatric subjects gave written informed consent. Participants aged 6 to 14 years gave oral consent and participants aged 15 to 18 years gave written consent (CIRE protocol:2010-09-2245).

Experimental design and sample size

The study has a pediatric cohort design for a population aged 2 to 18 years to study the epidemiological conditions of dengue disease such as seroprevalence, incidence, and demographic factors, a detailed description of the design, methods, and population can be found in Kuan et al., (2009).

Briefly, data from approximately 3,800 children in Managua, Nicaragua, were reviewed from 2004 to 2021, recruitment for the study began in August 2004 through house-to-house visits, inviting all children aged 2 to 18 years residing in the study area to participate. Upon enrollment, families agreed to take their children to the Socrates Flores Vivas Health Center (CSSFV as in Spanish) at the first sign of illness. Annually, every February or March, staff from the Institute of Sustainable Sciences (ICS), collect a blood sample to assess for DENV infection, similarly, staff conduct socioeconomic and risk factor surveys to obtain data related to DENV infection (Gordon et al., 2013).

New 2-year-old children are enrolled each year and children are withdrawn when they turn 18 years old. The study excludes only those participants who change address before the first sample collection, those who do not attend during the annual sample collection, and those who decide not to participate in the study.

Study area

This project was carried out in District II of Managua, which is one of the seven districts that make up the capital city of Managua, Nicaragua. District II is made up of 32 neighborhoods and is located in the northwestern part of Managua, bordering Lake Xolotlán to the north, west, and northeast. In 2011, District II had a population of 160,048 inhabitants and a population density of 9,415 people per km^2 (INIDE, 2008). The specific area is the area of influence of the CSSFV, which is the primary care center serving all neighborhoods in District II (Balmaseda et al., 2010). Children in the study who require additional medical attention are transferred to the study hospital, the Hospital Nacional de Referencia Pediátrica, Hospital Infantil Manuel de Jesús Rivera (HIMJR). Clinical laboratory tests are performed at the CSSFV, while all virological and serological tests are performed at the National Virology Laboratory of the National Diagnostic and Reference Center (CNDR).

Case definition

A possible dengue case was considered positive when DENV RNA was demonstrated by reverse transcriptase polymerase chain reaction (RT-PCR), DENV was isolated, or DENV-specific immunoglobulin M (IgM) seroconversion was observed by enzyme-linked immunosorbent assay (MAC-ELISA) or a >4-fold increase in anti-DENV antibody titer was measured using inhibition ELISA in acute and convalescent samples (Balmaseda et al., 2010).

Pediatric cohort data

To manage the large amounts of data collected, the information technology staff developed a series of interrelated databases. The data are from a secondary source that came from the socioeconomic and risk factor surveys conducted during the annual pediatric cohort sampling. Data were collected on the demographics of the participants, as well as variables useful for identifying household and personal risk factors for dengue infection. Review, analysis, and database cleaning of laboratory results, and socioeconomic and risk factor surveys of the study participants were performed to obtain a consolidated database to perform the analyses corresponding to the objectives of the study.

To ensure data quality, the databases were designed with restricted value fields whenever possible. As much data as possible, such as study code, date, and time, were automatically entered through barcode scanning. In addition, many laboratory results are electronically transferred to the study databases, finally, a series of quality control queries are run daily on all databases to detect and allow real-time correction of errors that occur.

Statistical analysis

Descriptive estimates of seroprevalence, incidence, and number of dengue cases between 2004 and 2021 were performed. The normality of the data was then verified (Shapiro test = 0.55906, p= <0.005.), so we decided to perform nonparametric tests. Variables of interest (sex, age group, neighborhood, water storage, asthma, heart disease, diabetes, education level, other diseases, and high blood pressure) were evaluated for the 2019 epidemic using Chi-square tests and Fisher's exact test (Marín, J.M., 2000). A Mantel-Haenszel test was performed to verify collinearity between the variable's age group and level of schooling. A logistic regression model for categorical variables was used to identify the age group most associated with dengue cases. The variables with statistical significance (age group and neighborhood) and without collinearity between them were selected to generate a simple linear regression model and determine associations concerning dengue virus disease. Finally, the epidemiological indicators for 2019 (dengue seroprevalence and dengue cases) were represented in maps using the QGIS 3.26 map development program (QGIS Development Team, 2023). All analyses and figures were performed using R 3.3.0+ and R Studio 2023.06.2+561 software (RStudio Team., 2022).

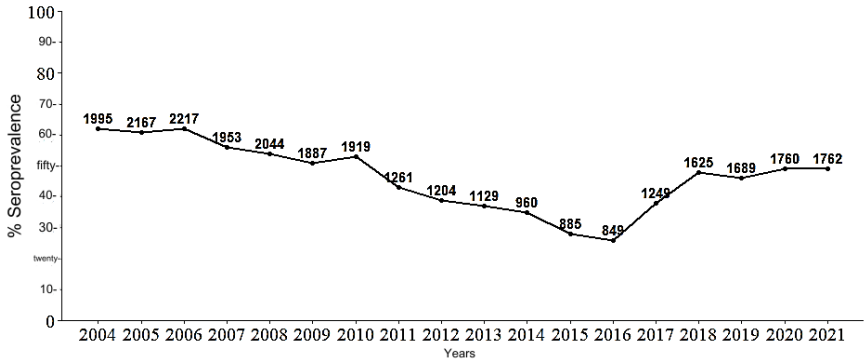
RESULTS

Behavior of dengue 2004-2021

During the period from 2004 to 2006, a constant seroprevalence of over 60% was maintained, marking an initial trend in the pediatric cohort study. However, starting in 2007, a gradual decline in seroprevalence was identified; this decline continued until 2010 when a sudden peak of 53% was recorded. Thereafter, seroprevalence showed a steady downward trend until 2016, when it reached its lowest point at 30%. However, in 2021 it showed a marked increase to 55%. These marked changes in seroprevalence over the years highlight the key moments in this study, where the highest and lowest levels of dengue seroprevalence were observed in the Nicaraguan pediatric cohort (Figure 1).

Figure 1

Dengue seroprevalence in the pediatric cohort of Managua district II 2004-2021. The figure shows the % seroprevalence for dengue virus by year and at each point corresponding to the year, the cases that presented antibodies for dengue are represented.



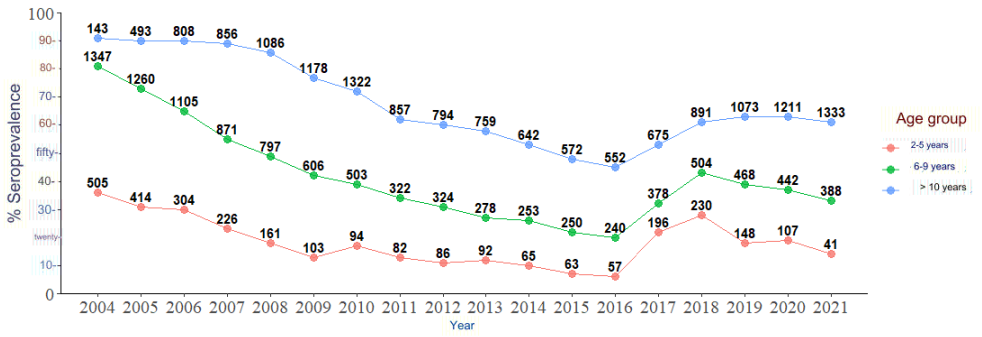
Overall seroprevalence was evaluated in three age groups, and similar patterns of behavior were observed throughout the study. In 2004, there were notable differences between age groups. The 2-5 age group had a seroprevalence of 42%, while the 6-9 age group had a seroprevalence of 84%. However, in 2005, both groups showed a downward trend, with a seroprevalence of 35% and 78%, respectively.

In subsequent years, a gradual and uniform decrease in seroprevalence was maintained in all age groups until 2016. Between 2016 and 2021, a progressive increase in the percentage of dengue virus seroprevalence was observed in the different age groups (Figure 2).

Following the same analysis of seroprevalence in general when we analyze seroprevalence concerning gender, the seroprevalence pattern remained constant in both genders from 2004 to 2010, with levels of 53%. From 2011, a slight decrease was observed, with 41%, and 42%. Since 2016, both genders experienced an increase in seroprevalence, reaching 50% in females and 48% in males in 2021.

Figure 2

Percentage of seroprevalence by age group and year from 2004 to 2021.

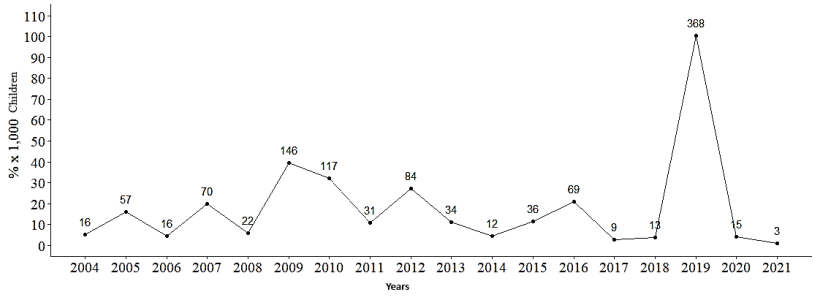


* The 2004 value for the age group >10 years is due to the first collection of data for this age group only.

After analyzing the serological behavior of dengue, we examined the record of dengue cases from 2004 to 2021 (Figure 3). It was observed that the year with the highest number of dengue cases was 2019, with 368 reported cases. Similarly, 146 cases were reported in 2009. These years stood out for the number of cases and were considered years of dengue outbreaks in the pediatric cohort.

Figure 3

Number of dengue cases in the pediatric cohort in District II of Managua 2019.



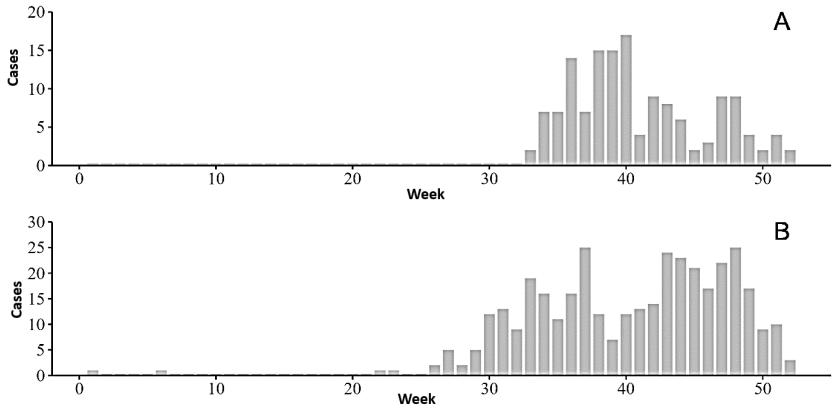
From the data obtained from the analysis of dengue cases in the pediatric cohort over the years, we were able to create epidemic curves to visualize the number of cases by epidemiological weeks for the years 2009 and 2019 (Figure 4).

In 2009, no cases of dengue were recorded from weeks 1 to 32, in week 33, cases began to be reported, with 2 cases in week 33, 7 cases in weeks 34 and 35, and 14 cases in week 36. Subsequently, some variability is observed in the number of cases reported in each week (A).

We also examined the dynamics of dengue cases in the pediatric cohort during 2019. During the first 25 weeks, sporadic cases were reported in weeks 1, 6, 22, and 23, with a single case in each week. However, week 26 had an increase to two cases, marking the beginning of an upward trend in the number of cases that varied but was maintained until the last weeks of 2019 (B).

Figure 4

Number of dengue cases by epidemiological week in the pediatric cohort of district II of Managua.



(A) Dengue cases per epidemiological week in 2009.

(B) Dengue cases per epidemiological week in 2019.

The 2019 epidemic

The pediatric dengue cohort for 2019 had 4086 participants of which 243 were outside the sector so they were excluded from the following analyses. An individual analysis of the socio-clinical variables obtained from the survey applied to the participants of the pediatric dengue cohort in 2019 was performed, to identify possible associations with the dengue cases involved in the most recent epidemic.

We were able to identify as variables of importance: Age group (X2 = 71.345, df = 2, N = 1225, p = <0.001), Neighborhood (X2 = 34.84, df = 16, N = 1225, p = <0.004) and Grade of schooling (X2 = 51.78, df = 3, N = 1225, p = <0.001). In the logistic regression analysis, the age group '>10' (coefficient = 1.5205, p < 0.001) was the most relevant. The p-values were less than 0.005, indicating a statistically significant relationship between these variables and dengue cases. Collinearity was observed between age group and education level as a function of dengue cases (M2 = 1234.5, df = 6, N = 1225, p = <0.001). The other variables showed no statistically significant association with dengue infection.

Table 1

Demographic characteristics of participants in the 2019 pediatric dengue cohort.

Variable	Participants	Cases (%)	Statistical test	Result	p
Age group			Chi-square	71.345	<0.001*
2–5	337	41 (12%)			
6–9	393	105 (27%)			
> 10	495	192 (39%)			
Gender			Chi square	0.1182	0.73
Mujer	626	176 (28%)			
Hombre	599	162 (27%)			
Grade of schooling			Chi-square	51.78	<0.001*

Variable	Participants	Cases (%)	Statistical test	Result	p
Not aplicable	168	18 (11%)			
Preeschool	192	31 (16%)			
Elementary	624	204 (33%)			
Highschool	241	85 (35%)			
Neighborhoods (N=18)	1225	338 (28%)	Chi-square	34.833	0.004*
Stores water			Chi square	0.31565	0.5742
Yes	458	122 (27%)			
No	749	212 (28%)			
Asthma			Chi-square	2.5426	0.1108
yes	97	34 (35%)			
No	1128	304 (27%)			
Other illnesses			Chi square	3.4882	0.06181
Yes	87	16 (18%)			
no	1138	322 (28%)			

2-5 337 41 (12%)

6-9 393 105 (27%)

> 10 495 192 (39%)

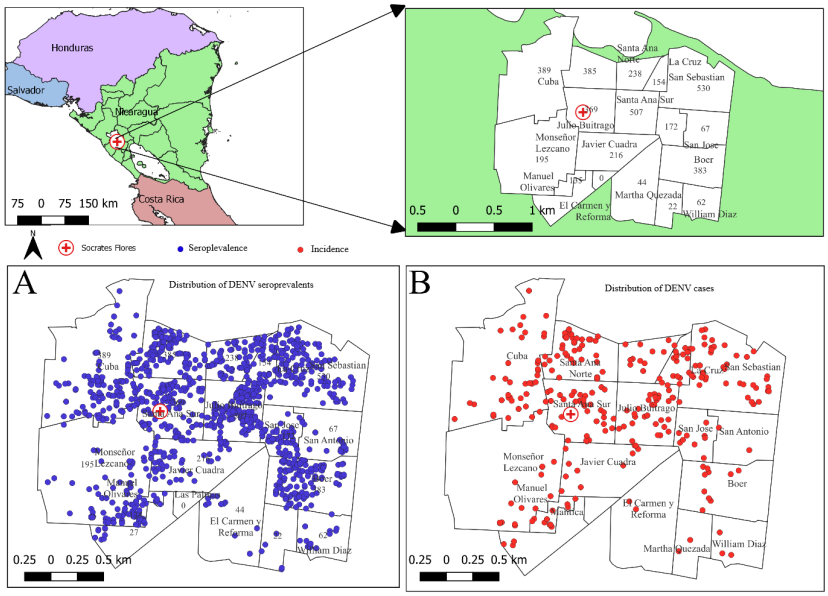
Note: Demographic variables were analyzed for 2019 and the percentage of dengue cases by group is in (%) for each group analyzed.

* p-value less than 0.005.

Participants with antibodies for dengue and those reported as dengue cases for the year 2019 were represented geospatially mind (Figure 5). It was found that the neighborhood with the highest number of children seroprevalent for dengue was Julio Buitrago with 249 cases, followed by Santa Ana Norte with 173 and San Sebastián with 164 (A). Regarding the distribution of dengue cases, we found that the neighborhoods with the highest number of dengue cases were Cuba with 78 cases, Santa Ana Norte with 75 cases, and San Sebastián with 71 cases (B).

Figure 5

Pediatric cohort study region of district II of Managua, Nicaragua, in 2019.



(A) Participants with antibodies for DENV (Seroprevalent).

(B) Participants with a confirmed diagnosis of DENV.

Map developed with freely available administrative bandanas.

DISCUSSION

Against the backdrop of a growing interest in understanding and addressing the burden of dengue disease, our study in the pediatric cohort of Managua, Nicaragua, has revealed an interesting finding, in 2019, children older than 10 years were the most affected with dengue. This result becomes more relevant when compared with previous research, such as a study in India that highlighted a high incidence (50%) among children aged 5 to 10 years (Sinha et al., 2022).

Regarding the evolution of the disease, in 2004, seroprevalence rates of 42% in the 2-5 years age group and 84% in the 6-9 years age group were recorded. However, by the year 2021, these rates decreased considerably, reaching 12% in the 2 to 5-year age group, 30% in the 6 to 9-year age group, and 60% in the group older than 10 years. This suggests that age-related protection against dengue virus is experiencing a decline over time.

Beyond our local results, dengue seroprevalence in Central America is an important issue. Our study reflects patterns observed in other countries in the region, such as in South America, where seroprevalence ranging from 24% to 91% has been documented (Gallón et al., 2020; Pereira et al., 2015), and in Singapore, where a seroprevalence of 22% was found in a

cohort of university students aged 19-26 years (Chow et al., 2005). The low seroprevalence in recent cohort years is a warning of possible dengue outbreaks in the coming years (Fiallo et al., 2022). This decrease could be related to epidemiological factors, such as changes in the circulation of DENV serotypes or control measures implemented in the region. The introduction of other arboviruses, such as Chikungunya and Zika, as well as the impact of the COVID-19 pandemic, influenced the low circulation of dengue in recent years (European Centre for Disease Prevention and Control, 2023). Finally, the possibility of cross-protection between different dengue serotypes may be influencing the seroprevalence of DENV in the Managua pediatric cohort.

In terms of age, a clear trend of decrease is observed from the beginning of the cohort until 2021, as previously described. However, it is important to note that there is a consistent trend that as the age of the children increases, the seroprevalence also increases. This pattern is consistent with what was found in a seroprevalence study in Malaysia, where a gradually increasing trend with increasing age was highlighted (Ng et al., 2022). The higher seroprevalence in the 6- to 9-year age group could be attributed to increased exposure to the virus due to factors such as mobility and participation in outdoor activities. These findings are consistent with the results obtained in Colombia (Gallón et al., 2020), where the seroprevalence of DENV in children aged 5 to 9 years was found to be significantly higher than in other age groups. In our case, it was found that the age group older than 10 years presented a greater association with dengue cases in 2019. In contrast to us, a study in Costa Rica found a decrease in dengue cases as the level of schooling increased (Alvarado-Prado & Nieto López, 2019). This suggests that age may play an important role in the transmission of the virus, with older children potentially being more susceptible to infection due to their greater exposure to the environment.

Furthermore, a significant association was observed between the variable of neighborhood of residence and dengue cases, supporting the idea that environmental factors play an important role in the spread of the disease, as mentioned in previous literature (Kourí, 2011). However, in the analysis of other variables, such as gender, water storage, presence of pre-existing medical conditions (asthma, heart disease, diabetes, high blood pressure), and other diseases, no statistically significant associations with dengue cases were found. We hope that our results, with their focus on age and geographic location, will be a crucial piece of complementary information for the management of knowledge about dengue disease in Nicaragua, as well as for the strengthening of effective prevention and control strategies, with a direct impact on public health and the quality of life of our communities.

One of the limitations of our study is the selection bias due to the lack of randomization in the sampling, which reduces the generalizability of the results since data collected over several years and multiple sources can distort the results. However, the temporality of data collection over 18 years provides us with a robust sample size that should allow us to reduce the risk of selection.

CONCLUSIONS

Analysis of dengue seroprevalence from 2004 to 2022 identifies a decrease in protection against DENV over time. The highest incidence of dengue in the dengue cohort was in 2019 with 100.25 cases x 1000 participants. Children older than 10 years presented a greater association with dengue cases for the 2019 epidemic. Epidemiological indicators identified the Cuba neighborhood as having the highest concentration of dengue cases and the Julio Buitrago neighborhood as having the highest number of participants with antibodies for DENV. These findings show that certain age groups are at risk of contracting dengue due to a decrease in the protection of antibodies; therefore, it is suggested to strengthen the dengue prevention and control strategies of the Ministry of Health (MINSA) to reduce the impact of this disease in the pediatric population.

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PEDIATRIC GLOSSARY

- Pediatric Cohort: A group of children who are followed over time to study a specific health condition or outcome.
- Dengue: A mosquito-borne viral disease that can cause flu-like symptoms and serious complications.
- Geospatial distribution: The spatial pattern or distribution of a particular health condition or outcome.
- Risk factors: variables or characteristics that increase the likelihood of developing a particular health condition or outcome.
- Incidence: The number of new cases of a specific health condition or outcome that occur in a population during a specified period.
- Geographic Information System (GIS): A system for collecting, analyzing, and visualizing geographic data and information.
- Seroprevalence: The proportion of individuals in a population who have antibodies to a specific virus or antigen.

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