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Morbidity, Mortality and the Impact of Climate on the Evolution of Acute Rotavirus Diarrhea in Children under 5 Years Old in Bangui

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Abstract

Background: Rotavirus is the most common pathogen of severe acute diarrhea in children under five years of age worldwide. **Objective:** The objective of this study was to determine the morbidity and mortality of rotavirus diarrhea while describing the seasonal kinetics of the infection according to climatic parameters in Bangui. **Methodology:** This was a descriptive and analytical cross-sectional study conducted from January 1, 2011 to December 31, 2020 in the Central African Republic (CHUPB). The health data were recorded and processed with the Access 2019 software, then analyzed with the STATA version 14 software. The climatic trends in the study area and its seasonal variations were highlighted by the monthly rainfall coefficient of Alfred Angot: Cm = 12 Pm/P. **Results:** Morbidity was 45.99% of cases. The 1 to 12 months old represented 93.81% of cases. The mean age of the children was 6.8 months, the sex ratio was 1.20. The symptomatic triad was diarrhea (100%), vomiting (90.20%) and fever (87.5%). Moderate dehydration was reported in 81.05% of cases. The main genotype combinations found were P[8]G1 in 34.02% (n = 115/338), P[6]G1 in 21.59% (n = 73/338) and P[6]G2 in 16.86% (n = 57/338). Case fatality was 11.45%. The risk of death was influenced by rural origin, severe dehydration, hypovolemic cloc and duration of hospitalization > 5 days. Low rainfall correlated with the highest rates of rotavirus diarrhea. Likewise, high temperature correlated with the highest number of cases of rotavirus diarrhea. **Conclusion:** Acute rotavirus diarrhea is an important morbidity and mortality issue in children under 5 years old in Bangui.

Keywords

Diarrhea, Rotavirus, Children, Climate, Bangui

1. Introduction

Rotavirus infection is the leading cause of severe acute diarrhea in children < 5 years of age worldwide. Before rotavirus vaccines became available in 2006, rotavirus infected almost all children aged 3 to 5 years [1] [2]. It was responsible for approximately 527,000 deaths of children in this age group in 2004; more than 85% of which occurred in South Asia and sub-Saharan Africa [3] [4]. The 10 countries with rotavirus mortality rates > 100 per 100,000 children aged < 5 years were in sub-Saharan Africa [4]. The magnitude of the problem on a global scale has justified the need for effective interventions from an early age to reduce the global burden of severe rotavirus gastroenteritis. With this in mind, in 2009, the world health organization (WHO) recommended the inclusion of the rotavirus vaccine in all national immunization programs [5] [6]. In 2013 the evaluation of the impact of the vaccine on the number of deaths revealed that deaths due to rotavirus had decreased to 33 deaths per 100,000 children aged < 5 years [4], and from 2013 to 2017 it was between 122,000 and 215,000, depending on the estimates, a decrease of 59% to 77% Parra port to 2004 [4] [6] [7] [8]. Sub-Saharan Africa continues to pay the highest price with 104,000 deaths and 600,000 hospitalizations per year in children aged 5 years, despite the rotavirus vaccine [4] [9]. Around rotavirus vaccination WHO coordinates a global rotavirus surveillance network in which sentinel hospitals use standardized case definitions and laboratory methods to record cases of rotavirus diarrhea [10]. As a prelude to the introduction of the rotavirus vaccine in the Central African Republic, which was initially planned for 2013 and then 2017, the Ministry of Health, with the support of the Surveillance Epidemiology in Central Africa (SURVAC) project, initiated sentinel surveillance of rotavirus diarrhea in 2011. The purpose of this surveillance was to assess the burden of rotavirus diarrhea and to identify the rotavirus strains circulating in the Central African Republic (CAR) in order to prepare for vaccine introduction in the country. After the SURVAC project ended in 2014, the surveillance continued with the support of WHO and the Centers for Diseases Control and Prevention (CDC), in collaboration with the Institut Pasteur in Bangui and the CHUPB. The objective of this study was to determine morbidity, seasonality, sociodemographic, clinical, and evolutionary characteristics, while identifying the rotavirus strains circulating in children under 5 years of age in CAR, as well as the impact of climatic factors on the kinetics of the infection.

2. Patients and Methods

2.1. Location of the Study Area

This work was carried out in the only sentinel site for the surveillance of rotavi-

rus infections in the Central African Republic (CHUPB). The CHUPB is located in the heart of the Central African capital. The capital of the Central African Republic is located in the southwest of the country and is bathed by the Oubangui River. It lies between 4˚20'50" and 4˚25'21" north latitude and 18˚31'41" to 18˚38'00" longitude. This locality covers an area of 94 km2 in 2010, with an estimated population of 1,145280 inhabitants in 2015. The CHUPB is the only pediatric facility in the country where all cases of severe diarrhea from Bangui and its surroundings are referred for better care.

2.2. Data Collection Methods

Health data were collected in a descriptive and analytical cross-sectional manner over a 9-year period from January 1, 2011, to December 31, 2020. We included in the study children aged 1 - 59 months hospitalized at the CHUPB during the study period who met the definition of rotavirus diarrhea cases of the "Sentinel Surveillance of Rotavirus Gastroenteritis in Bangui" program [10] [11]. A suspected case was any child aged 1 - 5 months hospitalized at the CHUPB during the study period with at least three watery, liquid, or soft stools per day for less than seven days. Confirmed cases were those suspected of having rotavirus antigen by enzyme immunoassay (EIA). Suspected cases with negative EIA tests were considered unconfirmed cases [11]. For all positive cases, genotyping tests were performed using a multiplex reverse transcriptase PCR technique (RT-PCR) [11]. The climatic data used were related to rainfall and temperature provided by the Bangui M'poko station (ASECNA) and the National Delegation of Meteorology in Bangui.

2.3. Conduct of the Study

Once informed consent was obtained from the parents or legal guardians of the suspected cases, the team proceeded to record on a questionnaire predefined by the national surveillance program of rotavirus diarrhea in children under 5 years of age, data related to age, sex, period of the episode of rotavirus diarrhea (month and year), place of residence, functional signs associated with the diarrhea, and hydration status. Then stool samples were collected for initial examination in the sentinel site laboratory for group A rotavirus antigen by enzyme immunoassay (EIA) using the ProSpecT™ Rotavirus Microplate Assay (Oxoid, Ltd., Basingstoke, Hampshire, UK). Then aliquots of all samples were then stored at −20˚C before being sent to the Institut Pasteur in Bangui (the only WHO National Reference Center for rotavirus) where results were confirmed by EIA using the same kit and genotyping tests were performed using a multiplex reverse transcriptase PCR technique (RT-PCR). This technique involved subjecting RNA extracts to a semi-nested multiplex reverse transcription-polymerase chain reaction (RT-PCR) analysis. Two genes, VP7 (896 bp) and VP4 (876 bp) were reverse transcribed and amplified using primer pairs 9Con1-L/VP7-R and Con3, respectively [12] [13]. Reverse transcription of double-stranded RNA (dsRNA)

was performed with the OneStep RT-PCR kit (Qiagen, Inc). Kit (Qiagen, Inc, Valencia, CA, USA). After a 5-minute denaturation at 97˚C, RNA was mixed with kit reagents and incubated at 42˚C for 30 minutes and incubated at 42˚C for 30 minutes to obtain complementary DNA (cDNA). (30 cycles: 94˚C for 30 s; 42˚C for 30 s; 72˚C for 45 s; one cycle at 72˚C for 45 s). 45 s; one cycle at 72˚C for 7 min). These first-round RTPCR products were then used in a semi-nested PCR (30 cycles, 94˚C for 45 s, 72˚C for 45 s). cycles, 94˚C for 45 s, 42˚C for 30 s 72˚C for 1 min; and 1 cycle at 72˚C for 7 min) to identify G-types (G1, G2, G3, G4, G9, and G12) and P-types (P[4], P[6], P[8]) [12] [13]. All PCR products were analyzed by electrophoresis in 2-containing agarose gels of Gel Red (Biotium) and visualized under UV illumination. Samples of RNA extracts were sent to CDC for genotyping quality control and sequencing confirmation.

2.4. Sample Selection and Ethical Considerations

Considering the criteria for confirmed cases, 776 children were selected for the study.

Rotavirus testing in stools was free of charge as part of the surveillance of diarrhea cases. Our study protocol was approved by the local ethical and scientific council. Informed consent from the parents or legal guardians of the children was required before inclusion in the study according to the recommendations of the CAR rotavirus surveillance activity.

2.5. Method of Statistical Processing of the Data

Several statistical methods were used to process and analyze the data: The health data had been recorded and processed by Access 2019 software, then analyzed with STATA version 14 software. The Chi-square test and ANOVA test were used to compare proportions at the $p < 0.05$ threshold. The climatic trends in the study area and its seasonal variations were highlighted by the monthly rainfall coefficient of Alfred Angot: Cm = 12 Pm/P, with, Gaussen aridity index P = 2 t. The relationship between rotavirus diarrhea, temperature and rainfall was established by Pearson's linear correlation coefficient (r), showing the strength and direction of the relationship: $R = \frac{\frac{1}{N}\sum(xi-\bar{x})(yi-\bar{y})}{\sigma(x)\cdot\sigma(y)}$.

3. Descriptive Results

3.1. Incidence of Rotavirus Diarrhea

During the study period, we recorded 1687 cases of acute watery diarrhoea in children aged 1 - 59 months in the department. Of these, 776 were due to rotavirus, *i.e.* an incidence of 45.99% (see Digram 1).

3.2. Cumulative Annual Distribution of Rotavirus Infections

From 2011 to 2020 CHUPB recorded two peaks of acute rotavirus diarrhea, one

in 2013 (19.07%; n = 148) and the other in 2017 (19.32%; n = 150). The other years had recorded 3.6% (n = 28) in 2011; 7.21% (n = 56) in 2012; 5.54% (n = 43) in 2014; 7.98% (n = 62) in 2015; 2.57% (n = 20) in 2016; 15.59% (n = 121) in 2018; 13.01% (n = 101) in 2019 and 6.05% (n = 47) in 2020 respectively. The annual average cumulative case count was 86.2. The distribution of cumulative case numbers by year is recorded in Figure 1.

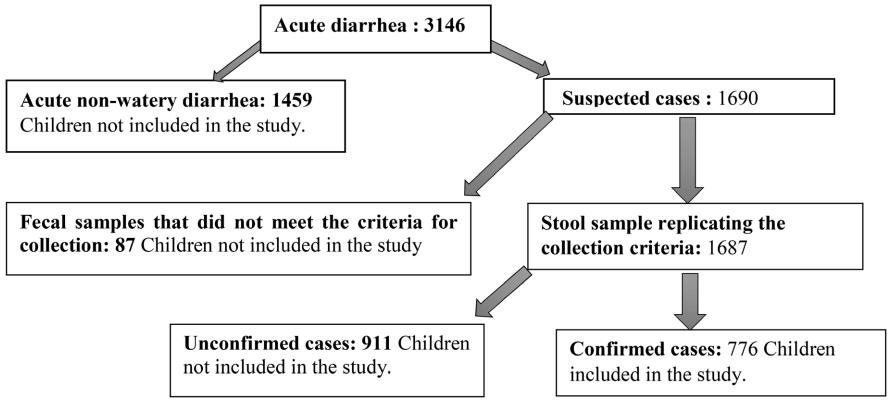
3.3. Cumulative Monthly Distribution of Rotavirus Infections

The virus circulated throughout the year with a recrudescence in the dry season 57.73% (n = 448) which covered the period from December to January versus 42.26% (328) of cases for the rainy season which covered the month of March to April.

The monthly peak in cumulative incidence of rotavirus diarrhea was observed at the beginning of the year with a rate of 26.54% (n = 206) of cases in January. Then the incidence gradually decreased to its lowest rate in May 1.04% (n = 8) of cases. Finally, the incidence gradually increases to reach 9.54% (n = 74) in December. The average monthly cumulative number of cases was 64.66. The distribution of rotavirus incidence by month is shown in Figure 2.

3.4. General Characteristics of the Study Population

The mean age of the children was 6.8 months with extremes of 1 to 53 months. Most of our children 93.81% (n = 728) infected with rotavirus were younger than 12 months versus 6.18% (n = 48) with an age greater than or equal to 12 months. We also noted that children older than 24 months were the least infected with



Digram 1. Case flow.

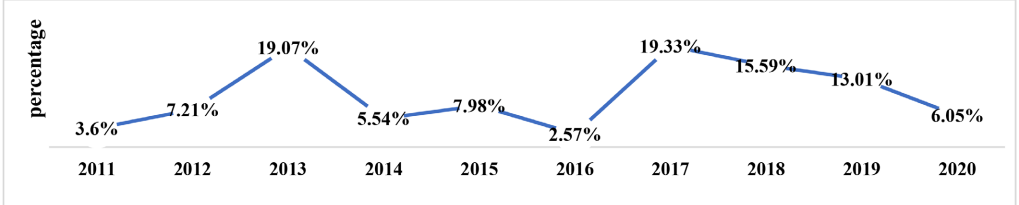


Figure 1. Distribution of cases by year.

rotavirus 0.91% (n = 7). A male predominance was noted 54.64% (n = 424) versus 45.36% (n = 352) for the female sex with a sex ratio of 1.20. The children lived in the urban area of Bangui in 85.05% (n = 660) of cases and in rural areas in 14.95% (n = 116). The distribution of cases according to socio-demographic characteristics is shown in Table 1.

3.5. Functional Signs Associated with Diarrhea and Degree of Dehydration

The two main symptoms that accompanied diarrhea were vomiting 90.20% (n = 700) and fever 87.5% (n = 679) of cases. The rest of the symptoms coupled with physical examination allowed to evaluate the degree of dehydration of children according to WHO criteria in moderate dehydration 81.05% (n = 629) versus 16.62% (n = 129) of severe dehydration. The data of the hydration status assessment are recorded in Table 2.

Hypovolemic pre-shock was noted in 1.41% (n = 11) and hypovolemic shock in 0.91% (n = 7) (see Figure 3).

3.6. Characteristics of Rotavirus Strains

Among the 776 samples, genotyping was performed for 76.55% (n = 594) and

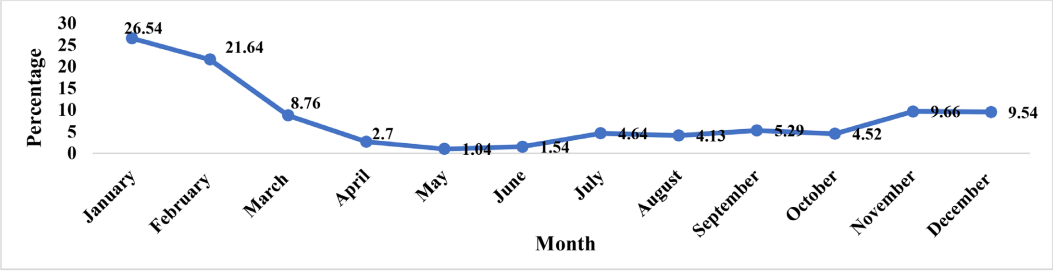


Figure 2. Cumulative distribution of rotavirus cases by month.

Table 1. Distribution of children by sociodemographic characteristics.

Characteristics (n = 776)	Numbers	Percentage
Age (in months)		
[1 - 6[	422	54.38
[6 - 12[	306	39.44
[12 - 24[	41	5.28
[24 - 59[	7	0.91
Sex		
Male	424	54.64
Female	352	45.36
Origin		
Urban	660	85.05
Rural	116	14.95

Table 2. Degree of dehydration of cases.

WHO parameters	Moderate dehydration (n = 629)* Elements of quotation	Numbers	Percentage
Neuropsychic	Restless	489	77.75
	Irritable	140	22.25
Radial pulse	Palpable	629	100.0
Eyes	Hollow	457	72.65
	Normal	172	27.34
Skin folds	Fades slowly (2 < seconds)	629	100.0
Thirst	Thirsty	512	81.39
	Drinks greedily	117	18.61
	Severe dehydration (n = 129)**		
Neuropsychic	Lethargic	107	82.95
	Coma	22	17.05
Radial pulse	Weak	102	79.16
	Unimaginable	26	20.84
Eyes	Hollow	81	62.50
	Normal	48	
Skin folds	Fades very slowly (>2 seconds)	129	100.0
Thirst	Difficulty drinking	105	81.95
	Inability to drink	23	18.05

*Moderate dehydration if at least 2 of the above signs. **Severe dehydration if at least 2 of the above signs.

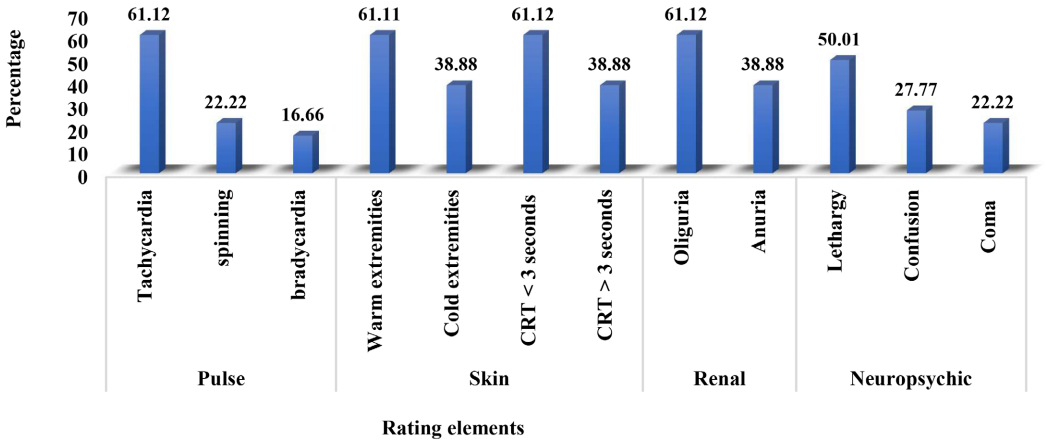


Figure 3. Distribution of cases according to the elements of the shock.

the viral genome was detected in 81.14% (n = 482/594) of samples by the Institut Pasteur in Bangui. Quality control was performed by the CDC laboratory on the 482 samples sent in and the genome was identified in 70.13% (n = 338/482) of

cases versus 29.87% (n = 144/482) of cases whose genomes were not clearly identifiable. The correlation of genotyping results between the two laboratories was 70.13%. The main genotypic combination found was P[8]G1 in 34.02%(n = 115/338) of samples, followed by P[6]G1 in 21.59%(n = 73/338) of samples, P[6]G2 in 16.86%(n = 57/338), P[6]G12 in 9.76%(n = 33/338) and P[8]G9 in 6.51%(n = 22/338). The remaining genotypic combinations consisted of P[4]G2 in 2.66%(n = 9/338) of retorts, P[8]G2 in 2.66%(n = 9/338) of retorts, P[6]G9 in 2.07%(n = 7/338) of retorts, P[8]G3 in 1.47%(n = 5/338) of retorts, P[8]G12 in 1.18%(n = 4/338) of retorts, P[8]G8 in 0.59%(n = 2/338) of retorts, P[6]G3 in 0.29%(n = 1/338) of retorts (see Figure 4).

3.7. Average Monthly Umbrothermal Diagram of Bangui from 2011 to 2020

In Bangui, the average annual cumulative rainfall from 2011 to 2020 was 1535 mm of water. The average cumulative rainfall was lowest in January (20 mm of water) and August recorded the highest average cumulative rainfall (230 mm). Similarly in Bangui, the average temperature in the coldest month (July) was 25.8˚C and the average temperature in the hottest month (March) was 28.5˚C (see Figure 5).

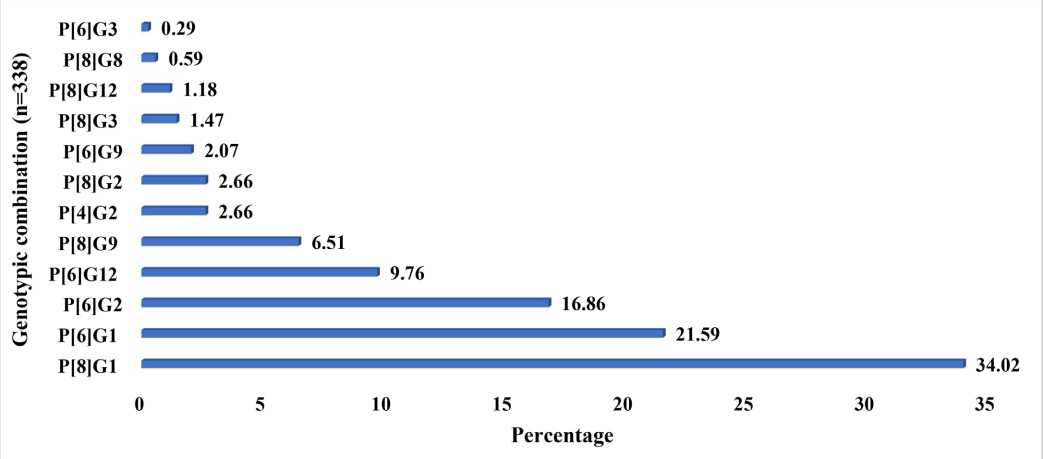


Figure 4. Distribution of cases by genotype combinations.

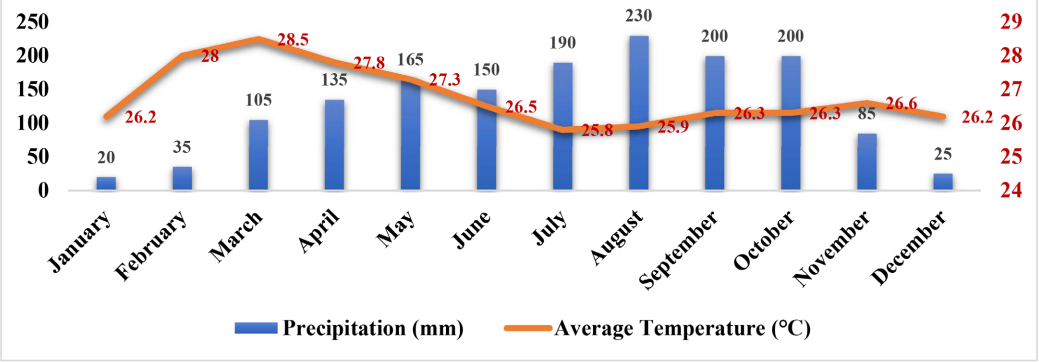


Figure 5. Average monthly umbrothermal diagram of Bangui from 2011 to 2020.

3.8. Distribution of Cases according to Rehydration Protocol

During hospitalization, all cases had received infusion fluids. For children with moderate dehydration (81.05%), lactated Ringer's solution was administered at 75 mL/kg over 4 hours. For those with severe dehydration (16.62%), a rehydration plan involving 0.09% isotonic saline or lactated Ringer's was applied at 100 mL/kg over 6 hours (children under 1 year of age) or 3 hours (children 1 year of age or older).

Children with hypovolemic shock received three 20-mL boluses of 0.09% isotonic saline in 0.64% (n = 5) of cases, two boluses in 0.51% (n = 4) of cases and one bolus in 1.16% (n = 9) of cases. After the signs of shock were resolved, the hydration status of the cases was reassessed and the hydration plan readjusted. Oral rehydration with ORS (50 mL after each bowel movement) was prescribed for all patients. Zinc tablets were administered in 87.62% (n = 680) of cases and an antipyretic in 87.5% (n = 679) of cases.

3.9. Distribution of Cases by Outcome

The outcome was known for 98.96% (n = 768) of cases, some of them being discharged against medical advice 1.04% (n = 8). For the 768 cases whose outcome was known; 88.55% (n = 680) were discharged alive and 11.45% (n = 88) were dead. The average length of hospitalization was 2.6 days. This duration was less than 5 days in 87.5% (n = 679) of cases and more than 5 days in 12.5% (n = 97) of cases.

3.9.1. Analytical Results

For cases with known outcome 98.96% (n = 768), the risk of death was influenced by rural origin ($p < 0.001$; OR = 248 [101 - 611]), severe dehydration ($p < 0.001$; OR = 784 [106 - 5750]), hypovolemic cloc ($p < 0.001$; OR = 1330 [153 - 11,504]) and duration of hospitalization greater than 5 days ($p < 0.00$; OR = 34.4 [19.7 - 59.69]). Analytical data on case outcome are reported in **Table 3**.

3.9.2. Correlation between Rainfall and Rotavirus Diarrhea

The month of January which had the lowest average cumulative rainfall (20 mm) had the highest rate of rotavirus diarrhea 206 (26.54%) cases, then the number of cases gradually decreased with the increase in average annual rainfall to reach 32 cases per 230 mm of rainfall in August. The correlation coefficient between rainfall and rotavirus diarrhea is positive and strong, the r2 being 0.151 or 15.1% which indicates the existence of a statistically significant link between low rainfall and high number of rotavirus diarrhea in Bangui (**Figure 6**).

3.9.3. Correlation between Temperature and Rotavirus Acute Diarrhea

From 2011 to 2020, analysis of the correlation between temperature and acute rotavirus diarrhea showed that rotavirus infection had higher rates during the warmer months of Bangui and lower rates during the colder months (see **Figure 7**). The correlation coefficient (R^2) between temperature and the number of cases of rotavirus diarrhea was 0.2524, indicating a statistically significant relationship

Table 3. Analytical data.

Characteristics (N = 768)	Evolution		P	OR
	Living (n = 681)	Dying (n = 88)		
Sex				
Male (n = 420)	373	47	0.39	1.05 [0.67 - 1. 65]
Female (n = 348)	307	41		
Age in months				
<12 (n = 720)	637	83	0.42	0.88 [0.34 - 2.31]
≥12 (n = 48)	43	5		
Provenance				
Urban (653)	647	6	<0.001	248 [101 - 611]
Rural (116)	35	81		
Season				
Dry (n = 448)	392	56	0.13	0.77 [0.48 - 1.22]
Rainy (n = 321)	289	32		
Hydration status				
Moderate dehydration (n = 622)	621	1	<0.001	784 [106 - 5750]
Severe dehydration (n = 129)	57	72		
Hypovolemic shock (n = 18)	7	15	<0.001	1330 [153 - 11,504]
Genotyping				
viral genome detected (n = 338)	293	45	0.06	0.07 [0.45 - 1.1]
viral genome not detected (n = 438)	395	43		
Length of hospitalization in days				
<(n = 671)	64	29	<0.001	34.4 [19.7 - 59.69]
>(n = 97)	38	59		

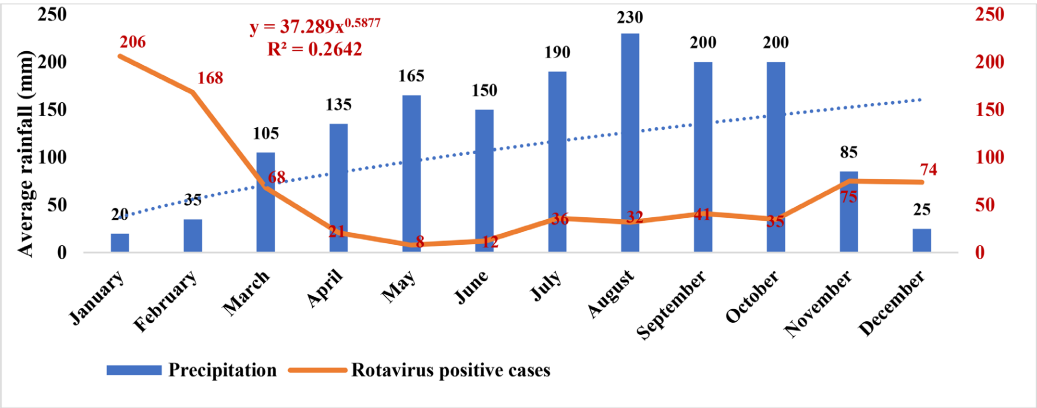


Figure 6. Correlation between rainfall and rotavirus diarrhea at CHUPB.

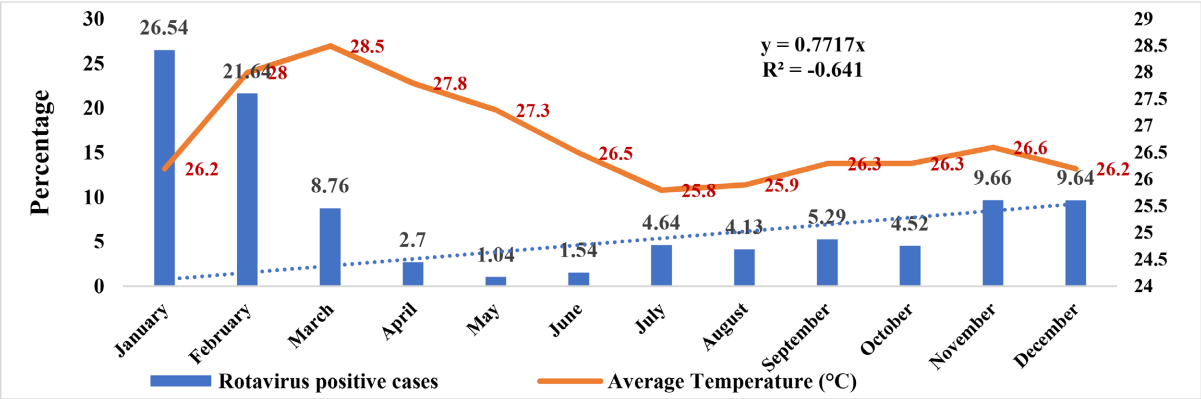


Figure 7. Correlation between temperature and rotavirus acute diarrhea.

between high temperature and high rotavirus diarrhea cases.

4. Discussion

4.1. Morbidity of Rotavirus Diarrhea

During the study period, the incidence of rotavirus diarrhea was associated with a child morbidity of 45.99%. This incidence was lower than the 55.9% found in Nigeria [14], the 53.8% in the Democratic Republic of Congo [15] and the 55% in the Malaysian study [16]. On the other hand, our results were close to the 42.8% observed in the Ndze study in Cameroon [17] and the 45% of Douti in Niger [18]. Several African authors have noted higher incidences than ours: 21.9% in Cameroon; 29% in Zimbabwe; 29% in Tanzania and 30% in Ethiopia [19] [20]. The same is true of the 22.73% noted in Burkina Faso in 2007 [21] and the 33.8% in 2010, again in the same country but in another region [22]. Several studies carried out in different regions of Nigeria have also shown incidences lower than ours: 15.5% by Solberg in 2009 [23]; 25.70% by Ojobor in 2020 [24]. Beyond Africa, a Korean study noted an incidence of 56.9 cases/1000 [25]. Globally, the incidence of rotavirus is almost similar in developed and developing countries and varies from one country to another and even from one region to another within the same country [26] [27]. Rotavirus is estimated to cause approximately 111 million episodes of outpatient gastroenteritis worldwide and about 2 million hospitalizations each year [2]. In 2009, results from 43 countries participating in the global rotavirus surveillance network concluded that 36% of hospitalizations in children under 5 years of age were due to rotavirus infection [3]. In Central and Eastern Europe, among the pediatric population, rotavirus infection accounts for between 22% and 55% of acute gastroenteritis cases [28] [29] [30].

The average annual cumulative number of hospitalizations of children under 5 years of age at CHUPB for rotavirus diarrhea in our series was 86.2. Annual incidences vary according to the continent. Thus, in Europe, approximately 100,000 to 200,000 children are hospitalized each year for rotavirus gastroenteritis [2]. In another study conducted in five European Union countries (France,

Germany, Italy, Spain, and the United Kingdom) in children under 5 years of age, rotavirus accounted for 56.2% of all causes of hospitalization for acute gastroenteritis, ranging from 33.2% in Italy to 64.4% in France [31]. In Western Europe, between 2004 and 2005, approximately 10.4% to 36.0% of children under five years of age were hospitalized for acute gastroenteritis due to rotavirus [32]. In France, rotavirus infection is estimated to be responsible for 300,000 annual episodes of acute diarrhea in children under 5 years of age, including 18,000 hospitalizations [33] [34]. In a Chinese study, 44% of hospitalizations for severe diarrhea in urban areas were attributable to rotavirus [35]. A multicenter Asian study revealed that 44% to 53% of hospitalized gastroenteritis in Indonesia, Myanmar, Vietnam, and Thailand were attributable to rotavirus [36]. In Great Britain it is estimated that 4.5 per 1000 hospitalizations of children under 5 years of age per year are attributable to rotavirus [37]. A multicenter study in Spain and New Zealand noted that the percentages of hospitalizations for acute gastroenteritis attributable to rotavirus in children under 5 years of age were 25.3% and 34% respectively [38]. A Finnish study conducted over 10 years estimated that rotavirus was responsible for 54% of hospitalizations for gastroenteritis [39] and the Dutch study estimated that this percentage was 58% [40]. These data, both on a global and continental scale, show the magnitude of rotavirus diarrhea, which is a public health problem not only in developing countries, but also in developed countries where hygiene conditions are good. In developing countries (Africa), the problem remains important despite the absence of data in the general population. The existing data refer exclusively to hospitalizations as shown in **Table 4**.

These different incidences, which confirm the etiological role of rotavirus infection in severe diarrhea in children under 5 years of age worldwide, emphasize the need for effective interventions, such as vaccination, to control this disease as part of a comprehensive diarrhea control strategy [10].

4.2. Age of Onset of Rotavirus Diarrhea

In our study, the average age of the children was 6.8 months similar to the 6.9 months found by Sangaji in the Democratic Republic of Congo [15]. On the other hand, higher average ages were found by Bonkoungou (8 months) [22], Kaboré (9.3 months) [44], Koueta (9.5 months) [45] and Nakawesi (10 months) [46].

Rotavirus diarrhea in Central African children was found to be a pathology of

Table 4. Annual incidence of rotavirus infections in children under 5 years of age.

Location	Hospitalization	Consultation	Episodes
USA [41]	1/80 (60,000 - 70,000)	1/7 (500,000)	1/0.9 (3.2 millions)
World [2]	1/65 (2 millions)	1/5 (25 millions)	1/1 (111 millions)
Venezuela [42]	1/72 (39,000)	----------	1/24 (118,567)
Salvador [43]	1/56 (7951)	1/7 (23,080)	3262
Africa	----------	----------	----------

infants under 12 months of age (93.81%). Our results corroborate those of Sangaji in the Democratic Republic of Congo (92%) [15] and those of two other African authors (66% by Kouéta and 53% by Nitièma) [45] [47]. In contrast to our results, a Tunisian study noted that 93.3% of rotavirus diarrhea cases were infants under 2 years of age [48]. This could be explained in our study by the instruction by the mothers of infants of traditional porridges from the age of 3 months with precarious hygiene conditions. This would increase the risk of contamination in this age group as demonstrated by the study of Ruuska, which states that the excess risk of rotavirus infection is estimated at 2.27 in non-breastfed children aged 6 - 11 months compared to those who are breastfed [49]. The paradox of our series is that the peak of rotavirus infection was found in infants younger than 6 months (54.38%) supposed to be exclusively breastfed. Contrary to the other works where the peak of incidence is beyond 6 months. This is the case in European countries where the peak incidence varies from 6 to 12 months [50] and 12 to 18 months [51]. The same is true of African countries, where peaks are recorded at 7 to 12 months in the Nigerian study [52] and 7 to 9 months in Cameroon [53]. The paradox found in our work in infants less than 6 months of age in supposedly protected by maternal anti-rotavirus antibodies [54], can be explained by dietary diversification which starts very early in our communities with the introduction of maize and semolina porridges from the age of 3 months. Poor hygiene during this dietary diversification would be an important source of contamination and rotavirus diarrhea. The peak incidence of rotavirus diarrhea in infants aged 6 to 12 months found in all other studies is related to the fact that this period coincides with the gradual development of the child's own immunity, while maternal antibodies decline, and it is at this time that the child's dietary diversification begins [55]. Since the rate of breastfeeding begins to decline after 6 months, Clemens points out that the protective effects of breastfeeding also seem to decline with age. The infant is then more vulnerable to infections [56]. The low proportion of children over 24 months of age in our series, as in most studies, can be explained by the fact that repeated infections in children over two years of age induce the development of natural anti-rotavirus protective immunity, which justifies the principle of vaccination. This is clearly elucidated in experiments carried out around the world, notably in a Mexican study which revealed that previous rotavirus infection conferred 87% protection against subsequent rotavirus infection and 2 previous infections ensured 100% protection [57]. Several other studies corroborate the fact that the protection against a digestive reinfection with rotavirus would increase according to the number of previous infections recorded during the first two years of life [58] [59].

4.3. Occurrence of Rotavirus Diarrhea by Sex

A male predominance was noted in our series with a sex ratio of 1.20. Several authors had also recorded a male predominance in their series [35] [44] [54] [60] [61] [62] [63]. On the other hand, a female predominance of rotavirus di-

arrhea was reported in several other studies [15] [17] [22] [64] [65]. The male predominance found in our series is consistent with the conclusions of several studies which state that there is a non-Mendelian genetic and immunological susceptibility of the male sex to infections [66] [67].

4.4. Evaluation of Clinical Signs

In our study, vomiting was the most common functional sign (90.20%), very often associated with fever, which was the second most common functional sign (87.5%). The combination of these two symptoms associated with diarrhea makes the digestive rotavirus infection of Central African children a febrile-acute gastroenteritis picture. This symptomatic triad (diarrhea-vomiting-fever) found in our series had also been reported by several authors [68]-[71]. This symptomatology reported by most studies could be explained by the pathophysiology of rotavirus diarrhea itself [72].

4.5. Hydration Status

Dehydration is the greatest threat associated with rotavirus diarrhea in children under 5 years of age. The symptomatic triad (diarrhea, vomiting, and fever) found in our disease, as in many others, often results in water loss and electrolyte (sodium, chloride, potassium, and bicarbonate) leakage. Dehydration occurs when these losses are not compensated as stated by Dupont in 2010 [73]. This risk of dehydration is primarily related to the very young age of the cases (less than 12 months in 93.81% of our series) and especially less than those less than six months (54.38% of cases in our series).

This could be explained by the coexistence of several risk factors in infants under 12 months of age, notably the physiological existence of a greater proportion of body water ranging from 80% of body weight at birth to about 60% around the age of 12 months [73] [74]. Secondly, this body water is distributed in an inequitable manner since the extracellular space represents 45% of the body weight of the newborn whereas it is less than or equal to 23% in adulthood [73] [74]. In addition, the rate of turnover of the fluid component of the infant's body is much faster and occurs from birth (25% per 24 hours at birth, compared to only 6% in adults). Another factor in the susceptibility of small infants to dehydration during diarrhoea would be their more limited renal concentration capacity (insufficient corticomedullary gradient due to the inefficiency of the chlorine pumps of the loop of Henle) [27] [73]. Finally, these infants are totally dependent on their environment for water intake, which is an aggravating factor [27]. These different factors contribute to the rapid onset of severe fluid deficit in infants under 12 months of age and explain why they can lose 10% - 20% of their intravascular volume in a few hours during acute gastroenteritis [27] [73] [74] [75]. The high rate of dehydration in our study (81.05% for moderate and 16.62% for severe) is in agreement with the data of the literature which stipulates that in developing countries, the proportion of dehydrated children is very im-

portant and can justify 60% to 90% of hospitalization of children for rotavirus gastroenteritis [22] [47] [48] [76] [77]. In contrast, the rate of dehydration is lower in developed countries [54] [78]. This low rate of dehydration observed in high resource countries as opposed to developing countries could be explained by the fact that in these countries parents seek early consultation at the first signs of illness. On the other hand, in developing countries, parents first resort to herbal medicine and it is only when signs of severity appear that they resort to a consultation.

4.6. Seasonal Kinetics of Rotavirus Diarrhea

Rotavirus had a per-annual circulation with a seasonal distribution. This distribution showed a recrudescence of contamination during the dry season (57.73% of cases) which covered the period from December to January and a low transmission during the rainy season (42.26% of cases) which covered the month of March to April. This finding is consistent with the conclusions of most studies conducted in low-income countries in Asia and Africa, where the epidemiology of rotavirus is characterized by one or more periods of relatively intense virus circulation, as opposed to year-round background transmission with seasonal peaks [15] [25] [47] [79] [80] [81] [82]. In contrast, in temperate regions, many studies have shown that rotavirus infections occur mainly during the winter. This is the case in Iran [83], China [84], France [54], Europe [31] [85] and the USA [1] [86]. A study in Mexico City found that the incidence of rotavirus infection peaked in autumn [87].

4.7. Relationship between Rotavirus Cases and Weather Characteristics

In our study, low rainfall (20 mm) correlated with the highest rates of rotavirus diarrhea 26.54% cases and the relationship was statistically significant. Similarly, there was a correlation between high temperature and high number of cases of rotavirus diarrhea. Generally, in Bangui low rainfall and high temperature coincides with the dry season where the highest rates of rotavirus infection were recorded (57.73%) without statistically significant relationship ($p < 0.13$). This could be explained by the fact that during the first episode of rotavirus gastroenteritis after infection, the viruses are excreted for several days in very high concentrations ($>10^{12}$ particles/gram) in the stools and vomit of infected subjects [88]. Drought is usually accompanied by the airborne transport of contaminated fecal material dried by the wind, which contaminates food, drinking water sources, and even all surfaces exposed to dust [79]. In the absence of good hygienic conditions and antirotavirus vaccination coverage, rotavirus transmission is important in the households where these children live [88]. In an Asian meta-analysis, the authors demonstrated that a decrease of 1˚C in the monthly ambient temperature and a decrease of 10 mm in precipitation are associated with an increase of 1.3% and 0.3% above the annual level of rotavirus infections, re-

spectively. According to the findings of this metanalysis, temperature and precipitation are significant predictors of rotavirus gastroenteritis incidence [80]. The Costa Rican study reinforces the findings made in our series. In fact, the authors noted that the increase in the number of hospitalizations of children under 5 years of age for rotavirus gastroenteritis coincided with dry and cold weather conditions [89].

4.8. Lethalities and Risk Factors

During our study, the case fatality rate was 11.45%. Our data corroborate the estimates made by the WHO before the introduction of the rotavirus vaccine in more than 60 countries worldwide in the late 2013s [4]. Before the introduction of rotavirus vaccines, the number of children under 5 years of age who died from rotavirus infection was 527,000 in 2004, with more than 85% of these deaths occurring in South Asia and sub-Saharan Africa [3]. However, very low rates were found in a 5-month Malian study (1.31%) [90] and in the Jenney study, which found a case fatality rate of 2% in 2009 [91]. In the United States, rotavirus infection is responsible for 20 deaths per year among the 50,000 hospitalizations of children under five years of age [92]. However, other authors have not recorded any deaths in their studies [93] [94]. The high rates of death from rotavirus infection before the introduction of the vaccines, even in settings with high standards of hygiene, reflect the severity of acute diarrhea in children under 12 months of age [95]. After the introduction of the vaccine the number of rotavirus deaths worldwide had decreased from 528,000 in 2000 to 215,000 in 2013 of which four countries (India, Nigeria, Pakistan, and the Democratic Republic of Congo) accounted for about half (49%) of all its deaths [4]. Ongoing global monitoring of rotavirus mortality rates to assess the effectiveness of the impact of vaccination to show that between 2013 and 2017, the annual number of rotavirus deaths in children ranged from 122,000 to 215,000, a decrease of 59% to 77% from 2000 [7] [8]. The high case-fatality rate in our series may be explained by a number of risk factors, including rural origin of cases, which multiplied the risk of death by 248 ($p < 0.001$; OR = 248 [101 - 611]), severity of dehydration which exposed children to a 784-fold risk of death ($p < 0.001$; OR = 784 [106 - 5750]), as well as hypovolemic cloc ($p < 0.001$) and long hospital stay of more than 5 days ($p < 0.001$).

4.9. Rotavirus Vaccination in CAR

During our study, none of our children were vaccinated against rotavirus. This was related to the absence of the vaccine in CAR, as the government was reluctant to consider the risk of intussusception induced by this vaccine in small infants. However, cohort follow-up experiments of approximately 9.5 million infants in 14 countries have shown that rotavirus vaccine prevents 144,746 hospitalizations and 4124 deaths due to rotavirus each year during the first 5 years of life [96]. These experiments report that rotavirus vaccine caused 172 hospitaliza-

tions and 10 deaths due to intestinal obstruction, resulting in benefit-risk ratios of 841 for hospitalization and 395 for death [96]. The health benefits of the vaccine for children far outweighed the short-term risks [96]. This analysis should motivate the Central African government to introduce rotavirus vaccination into the expanded program on immunization in CAR.

5. Limitations and Constraints

This study had recorded some pitfalls linked on the one hand to the fact that CAR had only one sentinel site, which prevented from reaching the objectives set by WHO which recommended a collection and screening of 250 cases per year. In our series, the annual average was about 86 cases per year. The presence of only one sentinel site is mainly due to the socio-military-political crisis that shook the country in 2013 with the destruction of a large number of health facilities. On the other hand, the CDC, which performed quality control and confirmed genotyping, reported that some tubes supposed to contain rotavirus samples were coming back empty. The reason given was that the samples had leaked during transport. This is justified by the 482 samples where a genome could be identified by the Bangui Pasteur Institute before being sent to the CDC laboratory, or where a genome was only identifiable in 338 samples, sometimes evoking a problem of priming by the Bangui team or virus leakage by the CDC team. This justified the CDC laboratory sending a new set of primers to the CAR laboratory to improve the results. These constraints do not call into question the results obtained in this study; on the contrary, it has the advantage of being carried out in the only sentinel site, also considered as the only pediatric referral facility in the country where all cases of severe diarrhea originating from Bangui and its surroundings are referred for better management. This constitutes sufficient coverage of the urban and rural child population. In addition, the methodological rigor and sample size increased the reliability of the statistical analysis.

6. Conclusion

Rotavirus infections are a major health problem in CAR. This study, conducted over a period of 9 years, confirms the importance of rotavirus in acute diarrhea in children under 5 years of age and especially in infants under 12 months of age in the Central African Republic. The high mortality rate highlights the need for targeted interventions in the Central African Republic, such as explicit guidelines that encourage the education of parents on the prevention of dehydration while urgently seeking medical attention at the first signs of dehydration in their children. The weather characteristics highlighted in this study should allow the Ministry of Health to better target darling to strengthen community prevention through public health actions.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix

SURVEY SHEET N°.....

Admission: Month...../Year.....

I. IDENTITY

- ✓ Age (in months): .....
- ✓ Sex: ...../ 1 = Male 2 = Female
- ✓ Origin: ...../ 1= Bangui 2= Province
- ✓ If 1: Specify district: .....
- ✓ If 2: Specify province name: .....
- ✓ Telephone number: .....

II. ANAMNESE

- ✓ Diarrhea: Yes /...../ No /...../
- ✓ Number of episodes/24hours: .....
- ✓ Duration: ..... (in days)
- ✓ Vomiting: Yes /...../ No /...../
- ✓ Number of episodes/24hours: .....
- ✓ Duration: ..... (in days)
- ✓ Fever: Yes /...../ No /...../

III. DIAGNOSTIC

- ✓ PHYSICAL **SIGNS**
  - Weight: .....
  - Lethargy/Unconsciousness: Yes /...../ No /..... /
  - Hollow eyes: Yes /...../ No /..... /
  - Difficulty drinking: Yes /...../ No /..... /
  - Skin fold: Yes /...../ No /...../
  - Dehydration status:
    - Severe: Yes /...../ No /..... /
    - Moderate: Yes /...../ No /..... /
    - Mild: Yes /...../ No /..... /
  - Hypovolemic shock: Yes /...../ No /..... /

IV. BIOLOGICAL SIGNS

- Stool samples taken: Yes /...../ No /..... /

❖ ELISA test results:

- ✓ Positive /..... /
- ✓ Negative /..... /

❖ Genotyping results:

- ✓ VP7 [G] genotype: G1 /..... /; G2 /..... /; G3 /..... /; G4 /..... /; G8 /..... /; G9 /..... /; G12 /..... /; Other, specified: .....
- ✓ VP4 [P] genotype: P4 /..... /; P6 /..... /; P8 /..... /; Other, specified: .....

V. TREATMENT: Rehydration

- ✓ Oral /..... /
- ✓ Infusion /..... /
- ✓ Oral and infusion /..... /

VI. Duration of hospitalization

- ✓ Less than 7 days /..... /
- ✓ Between 7 and 14 days /..... /
- ✓ More than 7 days /..... /

VII. PATIENT'S OUTCOME

- ✓ Alive /..... /
- ✓ Deceased /..... /
- ✓ Discharge without medical advice /..... /

Table 5. Primers.

Typing	Used Primer	Combination with primers
G	*9Con1-L*	9T1–1, 9T1-Dg, 9T-2, 9T-3P, 9T-4 and 9T-9B
P	*Con3*	1T-1, 1T1-VN, 2T-1, 3T-1, 4T-1, 5T-1, and 1T1-Wa