BMC Infectious Diseases

RESEARCH Open Access

Rotavirus prevalence and genotypes in the Central African Republic, 2011–2021

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Abstract

Background Rotavirus gastroenteritis is one of major causes of death in infants, particularly in sub-Saharan Africa. In the Central African Republic (CAR), sentinel surveillance of rotavirus gastroenteritis was established in 2011. In this study, we assessed the burden of rotavirus gastroenteritis and identified rotavirus strains circulating in CAR during 2011–2021.

Methods Stool samples were collected from < 5-year-old children with diarrhoea according to WHO criteria, at the sentinel site in Bangui, CAR. Samples were screened for group A rotavirus antigen by EIA. RNA was extracted from all EIA-positive samples which were subjected to genotyping using a semi nested RT-PCR assay.

Results From 2011 to 2021, 1855 stool samples were collected and 854 (46.0%) were positive for rotavirus by EIA. Genotypes were obtained from 77.3% (660/854) EIA positive samples. Of these 660 samples, genotypes funds were: G1 (35.4%) and G2 (26.6%) for VP7, and P[6] (42.7%) and P[8] (35.6%) for the VP4 gene. The most frequent genotype combinations were G1P[8], 19.3% and G1P[6], 15.0%.

Conclusion This study reports the prevalence of rotavirus genotypes that circulated for ten years, providing a pre-vaccine baseline data genotype estimate for rotavirus gastroenteritis sentinel surveillance in the Central African Republic.

Clinical trial number Not applicable.

Keywords Rotavirus, Genotypes, Epidemiology, Pre-vaccine, CAR

Background

Rotaviruses, the most common aetiology of pediatric gastroenteritis (GE), remain the leading cause of infant death from diarrhoea worldwide, with approximately 200,000 deaths in 2016, the vast majority occurred in sub-Saharan Africa and Asia [1]. Rotaviruses cause watery diarrhoea that induces severe dehydration, resulting in acute hydro-electrolytic disorders and undernutrition, especially in developing countries [2]. To help reverse the trend in deaths from rotavirus GE, the WHO recommended in 2009 the introduction of routine rotavirus vaccination into the expanded immunization programs

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in all countries [3]. Currently, four effective oral vaccines, containing live attenuated rotavirus, are used: the monovalent Rotarix vaccine (GSK Biologicals, Belgium), and pentavalent RotaTeq vaccine (Merck-Co., USA) are both used routinely worldwide. In addition, two rotavirus vaccines produced in India, Rotavac™, RV1-116E (Bharat Biotech) and Rotasil™, RV5 (Serum Institute of India) have been prequalified by WHO [4–6]. Prior to the introduction of the first two vaccines, the number of deaths from rotavirus GE globally was more than 600,000 per year worldwide [7]. Today, more than 125 countries have introduced the vaccine into national vaccination programs [8].

Rotaviruses are double stranded, segmented RNA viruses belonging to *Sedoreoviridae* family [9]. Their genome contains 11 segments, giving them great genetic variability [10]. Rotaviruses are classified into nine groups from A to I, group I being the most recent [11, 12]. Among these nine groups, four are pathogenic for humans namely: A, B, C, and H [11, 13, and 14]. Group A RV is responsible for at least 90% of RV infections in humans [13, 15]. RVA genotypes are defined by the glycoprotein VP7 antigens (genotype G) and protease-sensitive VP4 (genotype P) [13]. There are currently 42 RVA genotype G and 58 RVA genotype P that have been isolated from humans and animals [16, 17].

The Central African Republic (CAR) established routine surveillance of rotavirus GE in 2011 for all children under 5 years of age with GE at the sentinel site, the Pediatric University Hospital Center of Bangui (PUHCB), the largest paediatric referral hospital in the country [18]. This surveillance was supported by the *Renforcement de la Surveillance en Afrique Centrale* (SURVAC) project, in collaboration with the Centers for Disease Control and Prevention (CDC) and WHO. The National Laboratory for rotavirus GE is hosted at the Instiut Pasteur de Bangui (IPB) within Enteric Viruses and Measles Laboratory (EVML). CAR is a developing country and prone to many political crises that have led the population to find refuge in Internal Displaced Population (IDP) camps. This creates and exacerbates the precarious level of hygiene, and *de facto* weakens the health status of children, especially those under 5 years of age who are at higher risk of suffering from serious forms of water-borne diseases including rotavirus GE.

Previous studies on rotavirus GE surveillance in CAR showed that the prevalence of rotavirus infection was 40% during 2008, of which G1 and P[8] genotypes were dominant [19], 47% during October 2011-September 2013 with G2 and P[6] as the predominant genotypes [18] and 45% during 2014–2016 when G1 and P[8] genotypes predominated [20].

To date, rotavirus vaccine has not been routinely introduced in CAR. The objective of this study is to assess the burden of rotavirus GE and identify rotavirus strains circulating in CAR during 2011–2021, ten years after establishment of the sentinel surveillance of rotavirus GE and to support decision to introduce rotavirus vaccine in the national immunization program.

Materials and methods

Sample collection

Stool samples were collected between October 2011 and December 2021 from < 5-year-old children admitted with GE (acute or chronic) according to the WHO case definition for rotavirus GE [21] at the sentinel site, the PUHCB.

Study population

Male or female children aged less than 5 years, who were hospitalized for acute GE (≥ 3 looser than normal stools per day with or without ≥ 2 episodes of vomiting within 24 h), were included as suspected cases. Subjects were excluded if the admitting diagnosis at the site did not include GE, or if the subject developed GE longer than 12 h following hospitalization (possible nosocomial infection). Enrolment was sequential and children hospitalized more than once were enrolled as new subjects on each occasion.

Rotavirus detection

Stool samples were collected, and fecal suspensions were tested by EIA at the sentinel site laboratory for group A rotavirus antigen with the commercial rotavirus Prospect® Rotavirus Kit, (Oxoid Ltd, Basingstoke, United Kingdom) according to the manufacturer's instructions. The ProSpecT™ Rotavirus EIA kit exhibited 75% sensitivity and 100% specificity in a NIH study performed at 2013 [22], as compared with 100% sensitivity and 99.2% specificity as reported by Oxoid, Ltd [23]. The kits were provided by CDC (2011–2015) and WHO/AFRO (2015-present). The samples were then shipped to the national laboratory at IPB for EIA quality control (QC), performed on 10% of specimens, and for molecular testing.

Rotavirus EIA-positive samples were subjected to RT-PCR assay for genotyping according to the WHO laboratory manual [24]. Double-stranded RNA (dsRNA) was extracted from fecal suspensions of rotavirus EIA-positive samples using a QIAamp viral RNA mini kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. The extracted dsRNA was subject to G- and P-typing by multiplex reverse transcription-polymerase chain reaction (RT-PCR) using the QIAGEN One-Step RT-PCR kit with type-specific primers as described previously [25].

Consensus primers VP7Rdeg and 9CON1-L were used in the first-round RT-PCR (1 cycle: 42 °C x 30 min, 1 cycle: 95° x 15 min, 35 cycles: 94 °C x 30 s; 42 °C x 30 s;

72 °C x 45 s; 72 °C x 7 min) to amplify the full-length VP7 gene (1,062 bp); dsDNA was used in the second-round PCR for G-typing (30 cycles: 95 °C x 1 min; 42 °C x 1 min; 72 °C x 1 min) with primer set 9T-1 (G1), 9T-2 (G2), 9T-3 (G3), 9T-4 (G4), 9T-9B (G9), G12S [26].

For P-typing, consensus primers Con2 and Con3 were used in a first-round RT-PCR (1 cycle: 42 °C x 30 min, 1 cycle: 95° x15min, 30 cycles: 95 °C x 1 min; 42 °C x 1 min; 72 °C x 1 min and 72 °C x 7 min) to amplify the 876 bp of the VP4 gene, and the second-round PCR (30 cycles) used primer set 1T-1 (P[8]), 2T-1 (P [4]), 3T-1 (P[6]), 4T-1 (P [9]), 5T-1 (P [10]) [26, 27].

All PCR products were analyzed by electrophoresis in 1.5% agarose gels, in Tris-borate- EDTA (TBE) buffer along with a 100-bp and 50 bp DNA ladders and visualized by UV transillumination after staining with gel red.

Data analysis

All statistical analysis was performed with the EPI-Info version 3.5.4 software (CDC Atlanta, USA) [28]. All categorical variables (Sociodemographic and clinical characteristics data, EIA results data and genotypes data) were summarized as proportions, and significance of their difference in distribution with the outcome was assessed using Pearson's chi-square and Fisher test at 5% significance level.

Results

From 2011 to 2021, 1855 stool samples were collected from GE children aged 0–59 months, and 854 (46.0%) were positive for rotavirus by EIA. The average case age was 8.75 months (standard deviation 7.04, median age 7 months, age range 0–59 months). The sex ratio was 1.4 (1074/781). These results are not statistically significant ($P = 0.07$) because the mode of transmission of the disease is fecal-oral and can affect all children regardless of sex.

The most affected age group was < 6 months with 358 EIA positives for686 included corresponding to 52.2% rotavirus positive rate, followed by age group 6–11 months with 423 EIA positive of 945 included children (44.7%) (Fig. 1). These data are statistically significant ($P = 0.001$) because the younger the children, the less developed their immune system is and the more at risk they are of developing the disease.

Approximately 10% of the children included had a critical clinical picture combining severe dehydration ($n = 182/1855$, 9.81%), severe vomiting ($n = 191/1855$, 10.30%) and a state of unconscious lethargy ($n = 192/1855$, 10.30%). It should also be noted that 2.5% of the children presented severe diarrhea with a stool frequency greater than 5/24 h. Lethargy ($P = 0.18$) dehydration ($P = 0.25$) are not statistically significant because they

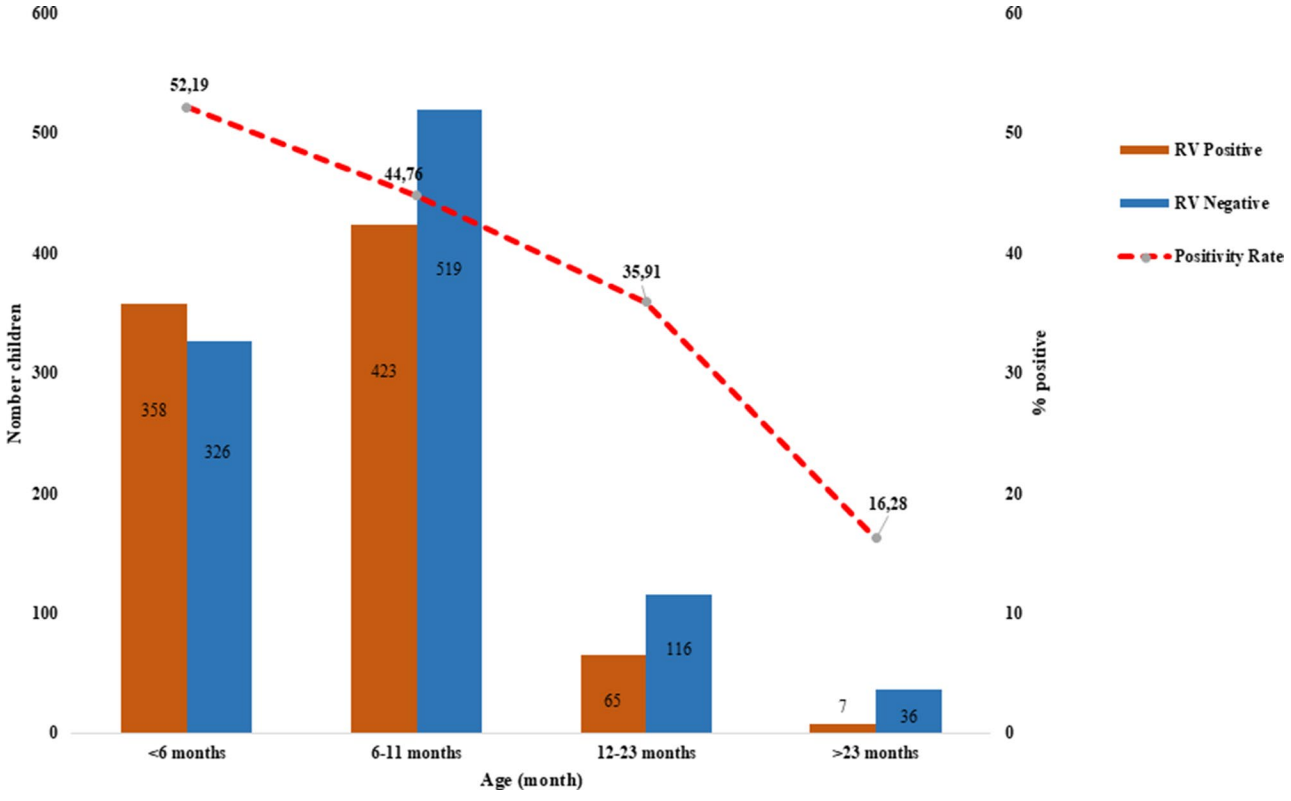

Fig. 1 EIA Results by age range, from 2011 to 2021

are a consequence of the late treatment of children and not related to the disease itself (Table 1).

Rotavirus infection was prevalent throughout the year, but was more common from November to March, with a high peak in February (Fig. 2). Most GE cases (83%) originated from Health Region 7(HR7), the capital city Bangui, where PUHB is located.

Genotyping results show that the most frequent genotype combinations were: G1P[8] 19.3% (165/854), G1P[6] 15.0% (128/854), G2P[6] 13.0% (110/854), G12P[6] 12.2% (104/854), and G2P [4] 6.6% (56/854) (Table 2).

The temporal distribution of rotavirus genotype varied over the surveillance period. Genotype G1 was present throughout 2012–2021 and circulated alone in 2019. G9 circulated from 2012 to 2017 and G8 circulated only in 2018. G2 was found every year except in 2019. Genotype G3 emerged in 2016 and was found almost every year except in 2019 (Fig. 3). For P genotypes, P [4], P[6] and P[8] co-circulated during all the described period except that P[8] was not found in 2011 and, P [4] was not detected in 2013 and 2019 (Fig. 3).

Samples were sent for quality assurance as follows: (i) CDC, Atlanta, USA from 2011 to 2016. A total of 208 ARN extracts of all positive and non-typable samples were sent for the period; (ii) NICD, Johannesburg, South Africa, from 2017 to 2019. A total of 58 stool samples could be sent.

Table 1 Sociodemographic and clinical characteristics

Carcteristics	Frequence		P-value
	Number	%	
Sex			0,07
F	781	42	
M	1074	**58**	
Age Range			**0,001**
< 6 months	686	36,98	
6–11 months	**945**	**50,94**	
12–23 months	181	9,76	
> 23 months	43	2,32	
Province			0,09
SR1	313	16,87	
SR7	1542	**83,13**	
Cities			**0,001**
Bangui	**1542**	**83,13**	
Begoua	98	5,28	
Bimbo	197	10,62	
Others cities	18	0,97	
Frequency of diarrhea in 24 h			**0,002**
Mild (< 3)	1105	59,57	
Moderate (3–5)	703	37,9	
Severe (> 5)	47	2,53	
Frequency of vomiting in 24 h			**0,03**
Mild (< 3)	873	47,06	
Moderate (3–5)	791	42,64	
Severe (> 5)	191	**10,3**	
Letargy unconscious			0,18
Yes	192	**10,3**	
No	1581	85,23	
Unknown	82	4,47	
Dehydration status			0,25
Severe	182	**9,81**	
Moderate	1485	80,05	
Shock	7	0,4	
Absence	173	9,33	
Unknown	8	0,41	

Discussion

From October 2011 to December 2021, a total of 1855 stools were collected at the sentinel site of rotavirus surveillance. Of those, 854 (46.0%) were positive by EIA test for rotaviruses. Similar proportions have been reported from Gabon and Nigeria [29, 30]. This rate was higher than in Nigeria (30.6%) and Côte d'Ivoire (27.1%) [30, 31]. Our rate was like the one described in Sub-Saharan Africa before introduction of rotavirus vaccine, where more than 40% of cases of acute diarrhea were attributed to rotaviruses with a high prevalence in children under two years of age [29–33]. Our result showed that rotavirus are likely to be most common cause of acute GE among children under five years of age hospitalized for diarrhoeal disease, representing almost half of the cases. This can be explained by low levels of hygiene and the consumption of contaminated water due to the inaccessibility to drinking water for a large part of the population [34].

The most common age range affected was 0–11 months (87.9%). In Niger, over 80% of children affected by rotaviruses were 0–11 months of age. Previous studies in Sub-Saharan Africa showed that rotavirus diarrhea most affected children under 2 years age [28].

Rotavirus GE was more common in dry season, from November to March, with a peak in February and a second one, less prominent, in August (rainy season). In Cote d'Ivoire, a peak was observed in rainy season between July and August [25], and a peak was observed in dry and cool season in the Niger [35]. Our study was similar to several studies from sub-Saharan African countries where higher prevalence of rotavirus infection was in the dry season, in tropical areas from East to West Africa [30, 35].

Most GE cases (83%) originated from Health Region 7(HR7), the capital city Bangui, where the sentinel site is located at PUHB, because it is the national reference center for pediatric diseases in the country. It should be noted that military and political crises have driven one-third of the population to seek refuge in Bangui and its surrounding areas. As a result, the two-thirds of the population living in rural areas could not be covered by our study, even though the exodus of these populations to the

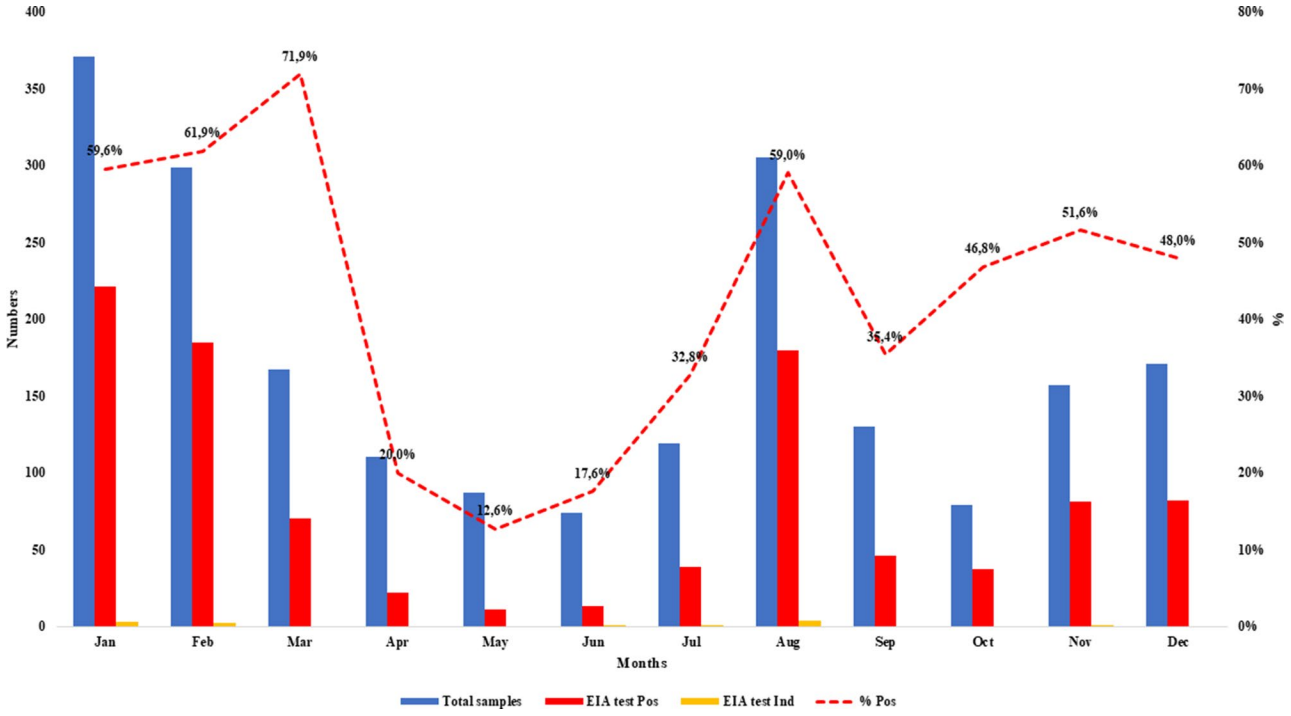

Fig. 2 Monthly distribution Rotavirus EIA results, from 2011 to 2021. **Test ELISA Indetermined (Ind)**: Value between the equivocal value (threshold value minus 0.010) and the threshold value (0.200 plus the optical density value of the negative control)

Table 2 Distribution of G and P combination of rotavirus genotypes

G Genotype	*P* Genotype					
	P[4] (%)	*P*[6] (%)	*P*[8] (%)	MIXED *P* genotypes	PNT (%)	Total (%)
G1	1 (0.1)	**128(15.0)**	**165(19.3)**	4(0.5)	20(2.3)	**318(37. 2)**
G2	**56 (6.6)**	**110(13.0)**	19(2.2)	0	5(0.6)	**190(22.4)**
G3	5(0.6)	13(1.5)	19(2.2)	4(0.5)	10(1.2)	51(6.0)
G8	3(0.3)	2(0.2)	0	0	0	5(0.5)
G9	1(0.1)	20(2.3)	28(3.3)	0	2(0.2)	51(5.9)
G12	1(0.1)	**104(12.2)**	10(1.2)	1(0.1)	4(0.5)	**120(14.1)**
GNT	1(0.1)	15(1.8)	0	1(0.1)	4(0.5)	21(2.5)
MIXED G genotypes	3(0.3)	35(4.1)	40(4.7)	0	20(2.3)	98(11.4)
Total (%)	71(8.2)	**427(50.1)**	**281(32.9)**	10(1.2)	65(7.6)	**854(100)**

GNT: G genotypes untyped. Positives samples by rotavirus EIA, from which PCR products did not show any G genotypes

PNT: P genotypes untyped. Positives samples by rotavirus EIA, from which PCR products did not show any P genotypes

Percentages are reported by the main total (854) as denominator

capital could provide a broad view of the circulation of RV genotypes in the country. Furthermore, overcrowding and poor hygiene conditions, as well as the lack of access to drinking water, could promote a high prevalence of RV GE in these remote areas, not to mention the difficulties of providing good quality food, which would have a significant impact on the growth and immunity of children living in rural areas, placing them at greater risk. It would be advisable to collaborate with medical NGOs working in pediatric settings in regional hospitals and remote districts of the country, in order to have a broader and more comprehensive view of the burden of RV GE and the actual distribution of genotypes circulating in the country.

The WHO recommends that at least 150 stool samples be collected annually by the sentinel site as part of rotavirus GE surveillance [21]. These indicators were negatively impacted during the years of military-political crises between 2014 and 2016, and by the Covid-19 pandemic in 2020 (129) and 2021 (135).

From 2011 to 2021, genotyping results showed genotypes obtained from 660 samples. The frequency of non-typeable strain (PNT, GNT) with global rate of 22,7%, was highly variable from year to year and ranged from 6% in 2013 to 0.6% in 2021 [18]. As requested by WHO,

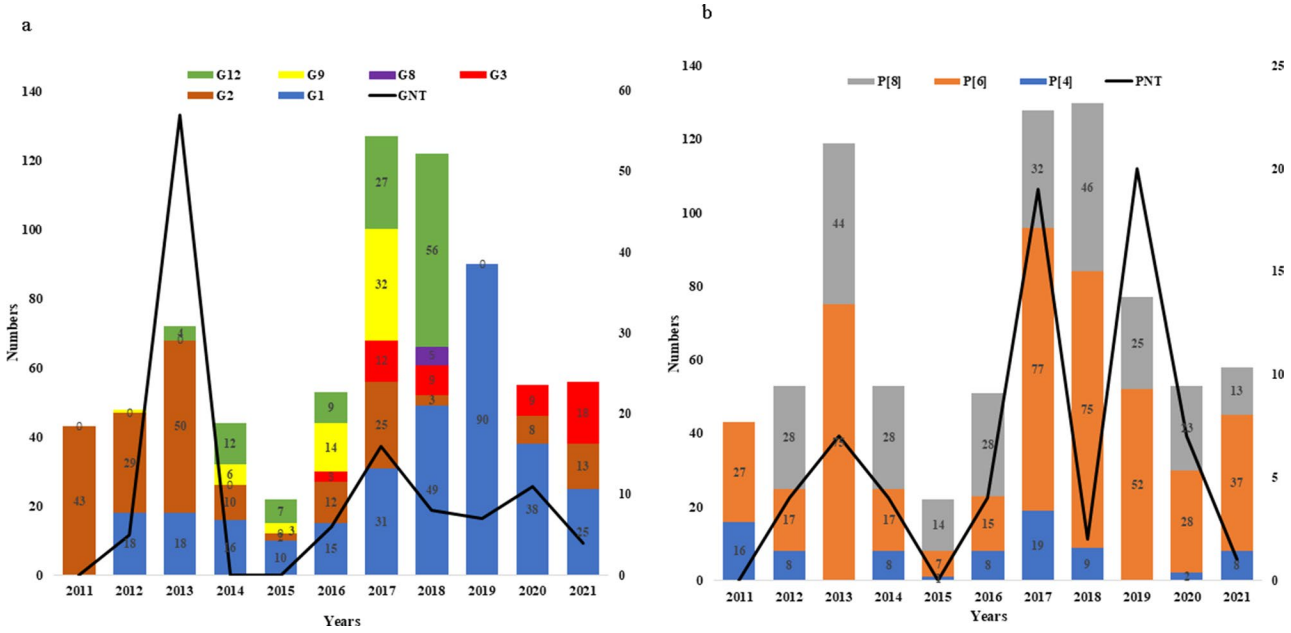

Fig. 3 **a** Rotavirus G genotypes strain distribution, from 2011 to 2021. **GNT**: G genotypes untyped. Positives samples by rotavirus EIA, from which PCR products did not show any G genotypes. **b**: Rotavirus P genotypes strain distribution, from 2011 to 2021. **PNT**: P genotypes untyped. Positives samples by rotavirus EIA, from which PCR products did not show any P genotypes

samples were sent for quality assurance purposes to different reference laboratories belonging to the global rotavirus network as follows: (i) CDC, Atlanta, USA from 2011 to 2016. ARN extracts of all positive and non-typable samples were sent. A total of 208 ARN extracts were sent for the period; (ii) NICD, Johannesburg, South Africa, from 2017 to 2019. A total of 58 stool samples could be sent. During the COVID period (2020–2021) we could not find any aircraft company accepting the transport of UN 3373 biological materials to RSA, therefore no sample could be sent for QA in 2020 and 2021. The high percentage of non-typeables in our study could be due to primer targeting limitations that do not cover all genotypes. It would be important to characterize these non-typeables by sequencing methods to determine genotypes missed by the usual genotyping method. This could have an impact on the detection of new genotypes or genotypic combinations that have circulated in the country, as was the case in India in a study conducted in 2009, where a rare G8 genotype was identified by molecular characterization of non-typeables [36].

Rotavirus genotype distribution showed that the most frequent G genotypes are G1 with 318 (37.2%) strains and G2 with 190 (22.2%) strains; and most common P genotypes were P[6] and P[8] with 427 (50.0%) and 281 (32.9%), respectively. Our study's results were similar to the globally common G genotype detected in several countries (Mozambique, Nigeria, Angola) during the same period [30, 33, 37]. Our results contrasted with those of a Kenyan study where G9 (50.9%) was most represented G genotypes, followed by G1 (26.8); G2 represented only 0.6% of all G genotypes reported [32]. The distribution of rotavirus genotypes worldwide and in African region differs according to time and space with emergence of novel genotypes along with disappearance of other genotypes. This distribution in CAR was similar to a report from DRC, where G1 genotype and P[6], P[8] genotypes were most common in circulation [38].

During our analysis, the most frequent genotype combinations were: G1P[8] and G1P[6] representing 19.3% and 15.0% respectively, followed by, G2P[6] (13.0%), G12P[6] (12.2%), and G2P [4] (6.6%). The G1P[8] genotype combination has been commonly associated with infections worldwide [39, 40]. These results were similar to those found in CAR in 2008 and 2011–2013 [18, 19]. The reappearance of the G12 genotype in 2013 [41] coincided with its emergence in some other African countries (Ghana, Tunisia, Kenya) [40, 42, 43]. Regarding Rotavirus vaccines, RotaTeq™ include human VP7 (G1-G4) and VP4 (P[8]) genotypes, and RotaSIIL® is a live attenuated human-bovine reassortant pentavalent RV vaccine containing VP7 genotypes (G1, G2,G3, G4, and G9) and VP4 genotype (P [5]) of bovine origin [44]. Rotarix®, which is G1P[8], would provide homologous protection against G1 strains and heterologous protection against G2 strains. Rotavac™ which is G9P [45], would provide heterologous immune protection [6, 38, 46, 47]. Although available vaccines do not cover the P[6] genotype that circulates predominantly in CAR (43% of P genotypes), and the G12 genotype that emerged from 2013 to 2018,

it is worth noting that the Rotarix vaccine showed evidence of cross-protection against this genotype, in a study conducted in Tanzania from 2013 to 2018 where the G3P[6] decreased from 11.2% in 2014 to 4.1% in 2018 [48]. Rotarix also showed evidence of cross-protection against G12P[6] genotypes in Brazil in a study conducted in 2010 [49]. This demonstrates that the introduction of this vaccine would protect children in CAR during a re-emergence of the G12 genotype.

Genotypes G1 and G2, representing more than half of the G genotypes circulating in CAR, this suggests that in any case, children in CAR could be protected from rotavirus infections if they are immunised with any one of these vaccines.

Conclusion

Our study shed light on the evidence regarding the distribution of RV genotypes in CAR over 10 years, from 2011 to 2021, compared to previous studies conducted in the country. We noted between the emergence of the G12 genotype from 2013 to 2018, the disappearance of the G9 genotype since 2017 and the circulation of the genotype G3 from 2016 until the end of our study. In addition, we also observed a constant circulation of Genotypes G1, G2, P [4], P[6] and P[8] in the country, with variable predominance over the years, allowing us to establish evidence on the distribution of RV genotypes in CAR before the introduction of routine immunization.

These data will be useful in supporting evidence-based decisions towards the introduction of the rotavirus vaccine to the National Vaccination Program in the CAR, expected in 2025, and will allow the rotavirus surveillance system to assess the impact of vaccination on the circulation of different genotypes of rotavirus after vaccine introduction in the country.

Acknowledgements
We thank the epidemiology department of the Institut Pasteur de Bangui, in particular Dr Brice YAMBIYO, for helping us in the data analysis and the production of figures and tables.

Author contributions
JD designed and drafted the article, VBM performed the RV genotyping analysis and contributed to the writing of manuscript, JF performed the RV EIA test and RV genotyping strains test, JCG, NPJK, JM, MDE and MDB contributed to manuscript drafting and revision, IGV and DWK are the initiators and scientific supervisors of the study and largely contributed to the writing and revision of the manuscript. All authors reviewed and approved the manuscript.

Funding
Financial support for this study was received from the World Health Organisation AFRO Region. Genotyping was supported by the Center of Disease Control, Atlanta, USA and Institut Pasteur de Bangui.

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Samples were collected and tested as part of the national rotavirus surveillance programme as described in the Technical Guide for Integrated Disease Surveillance and Response in the Central African Republic, revised in 2022. The guide is validated by the Ministry of Public Health and Population and its partners and does not require consent to participate for disease surveillance programmes. Rotavirus surveillance includes genotyping of Rotavirus strains. The "Comité Éthique et Scientifique" of the "Faculté des Sciences de la Santé de l'Université de Bangui" and "Institut Pasteur de Bangui" waived the informed consent for all public health surveillance programs as recommended by World Health Organization, in compliance with the Central African regulations and the Declaration of Helsinki. This article is published with the agreement of the "Comité Éthique et Scientifique" of the "Faculté des Sciences de la Santé de l'Université de Bangui" and "Institut Pasteur de Bangui" (N°41/UB/FACSS/IPB/CES/022, 21/09/2022).

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Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 6 December 2024 / Accepted: 29 April 2025
Published online: 08 May 2025

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