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Original Research

Title: Hospital-based surveillance of rotavirus gastroenteritis among children under five years of age in the Republic of Côte d'Ivoire

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Abbreviations:

AGE: acute gastroenteritis; CI: confidence interval; ER: emergency room; GE: gastroenteritis; GSK: GlaxoSmithKline; IV: intravenous; RT-PCR: reverse transcriptase polymerase chain reaction; RV: rotavirus.

ABSTRACT

Objectives: To estimate the proportion of rotavirus gastroenteritis (RVGE) among children aged less than five years who were diagnosed with acute gastroenteritis (AGE) and admitted to hospitals and emergency rooms (ERs). The seasonal distribution of RVGE and most prevalent RV strains were also assessed.

Design: An observational, prospective hospital-based surveillance study.

Setting: Five reference pediatric hospitals across Abidjan.

Participants: Children aged less than five years, hospitalized/ visiting ERs for AGE as defined by the WHO were enrolled. Written informed consent was obtained from parents/ guardians prior to enrollment. Children who acquired nosocomial infection were excluded from the study.

Primary and secondary outcome measures: The proportion of RVGE among AGE hospitalizations and ER visits were expressed with their 95% exact confidence interval (CI). Stool samples were collected from all enrolled children to test for the presence of RV using an enzyme immunoassay. RV positive samples were serotyped using reverse transcriptase polymerase chain reaction.

Results: Of 357 children (mean age 13.6 ± 11.14 months) enrolled, 332 were included in the final analyses; 56.3% (187/332) were hospitalized and 43.7% (145/332) were admitted to ER. The proportion of RVGE hospitalizations and ER visits among all AGE was 30.1% (95% CI: 23.6-37.3) and 26.9% (95% CI: 19.9-34.9), respectively. Ninety-five (28.6%) children were RV positive and the highest

number of RVGE cases was observed in children aged 6-11 months. The number of GE cases peaked in July and August 2008; the highest percentage of RV positive cases was observed in January 2008. G1P[8]wild-type and G8P[6] were the most commonly detected strains.

Conclusion: RVGE causes substantial morbidity among children under five years of age and remains a health concern in the Republic of Côte d'Ivoire, where implementation of prevention strategies such as vaccination might help to reduce the disease burden.

Trial registration: Not applicable

ARTICLE SUMMARY

Article focus

- Rotavirus gastroenteritis (RVGE) disease burden in the Republic of Côte d'Ivoire is substantial and recent data on the epidemiology of RVGE are limited.
- The main focus of this study was to estimate the proportion of RV among young children hospitalized for acute gastroenteritis (AGE) or treated at emergency rooms (ER) for AGE.
- Additionally, we sought to determine the seasonal distribution of RVGE and to identify the prevalent RV types in the study population.

Key messages

- RVGE accounts for about 28.6% of AGE hospitalizations and 30.1% ER visits in the Republic of Côte d'Ivoire and particularly affects children aged less than 24 months.
- The number of RVGE cases peaked during July and August 2008. The most prevalent RV strains were G1P[8] wild-type and G8P[6].
- Implementation of preventative measure such as RV vaccination could help to reduce the disease burden of RVGE in the Republic of Côte d'Ivoire.

Strengths and limitations of this study:

- The study was conducted in large pediatric hospitals across the city and hence our findings are likely to be representative of the whole population.
- The systematic approach followed to enroll children enabled easy identification of AGE cases.
- Only a reduced proportion of all the reported AGE cases could be enrolled in this study and included only severe cases.

INTRODUCTION

Wild-type, rotavirus (RV) causes approximately 111 million episodes of gastroenteritis (GE), 25 million clinic visits, two million hospitalizations and over 453,000 deaths per year among children younger than five years of age.[1, 2] It has been reported that RV mortality is the highest among the low income countries in Asia, Africa and Latin America.[3] A systematic review and meta-analysis (2009) of published studies reported that, in sub-Saharan Africa, the overall mortality rate associated with RV infection in children under five years of age was 243.3 (95% CI 187.6–301.7) deaths per 100,000 children.[4] Globally, RV infection rates are highest among children aged less than five years, with approximately 95% children having experienced at least one episode of RVGE by the time they are five years of age.[5]

RVGE is characterized by fever, diarrhea and vomiting that lead to severe dehydration and increased hospitalization. Over 90% of children with RVGE suffer from dehydration-associated mortality due to diarrhea and associated vomiting.[6-8] It has been suggested that RV infections are more common during the cooler months of the year and that RVGE disease burden is similar in both high and low income nations.[1] However, due to malnutrition and lack of access to appropriate treatment facilities, it is children in the low-income countries who die more frequently.[1]

As improvements in hygiene and sanitation have not been associated with reduction in the incidence of RV-associated diseases,[9] vaccination against RV is

therefore considered as a public health priority for low income nations.[10] The introduction of RV vaccination could have potential and visible benefits to children aged less than three years, and might assist the reduction of diarrhea-associated childhood morbidity and mortality in low income countries and of RV-associated hospitalizations in high income countries.[11, 12]

The most common RV serotypes associated with RVGE circulating worldwide are G1, G2, G3 and G4.[13] In addition to these, G9 has emerged as a globally important serotype in the last decade.[14] Together, these serotypes are responsible for 95% worldwide pediatric RVGE cases.[15]

In the Republic of Côte d'Ivoire, the epidemiology of RV infection has been followed in several small studies conducted in Abidjan,[16–21] but recent data on RVGE disease burden for this region are limited. Data on RVGE disease, the number of hospitalizations and the number of emergency room (ER) visits following acute GE (AGE) are critical to formulate effective policies to control RV-related AGE. These data are also important to fully determine the need for RV vaccines and understand the possible impact of their introduction.

This study aimed to estimate the proportion of RVGE among children younger than five years of age who were diagnosed with AGE and admitted to hospitals and ERs. Seasonal distribution of RVGE and identification of prevalent RV types in the Republic of Côte d'Ivoire was also studied.

METHODS

Study design

This observational, cross-sectional hospital-based surveillance study was conducted across five centers in Abidjan, the Republic of Côte d'Ivoire between December 2007 and February 2009. The study was conducted in accordance with the Good Clinical Practice, the Declaration of Helsinki (version 1996) and the applicable local regulations of the country and written informed consent was obtained from parents/ guardians before children were enrolled.

Children presenting AGE were enrolled in this study by checking the hospital and ER logbooks. Males or females aged less than five years, who were hospitalized or visited ER for AGE (≥3 looser than normal stools per day with or without ≥2 episodes of vomiting within 24 hours) were included in the study. Children were excluded if they acquired AGE by possible nosocomial infection (within 12 hours after hospital admission).

Unique study numbers were sequentially assigned to all enrolled children in order to maintain their confidentiality. Parents/ guardians were interviewed and medical records were reviewed by the site staff to complete the questionnaire and/ or case report form. Information such as demographic parameters (date of birth, gender, height and weight, nutritional status, and area of residence); admission date and diagnosis at admission, date of discharge, diagnosis at discharge and administration of oral and/ or intravenous rehydration/ antibiotics were recorded and encoded in the study database. Details such as body temperature, duration of

diarrhea or vomiting, treatment including hospitalization and behavioral symptoms were also recorded. The severity of RVGE was defined according to the Vesikari Scale (mild: score <7; moderate: score 7–10 and severe: score ≥11).[22]

Stool samples collected within 4–10 days of the onset of GE were refrigerated (4°C–8°C), frozen (-20°C to -70°C) and then transported to Pasteur Institute, Abidjan, within 72 hours of sample collection. RV testing was performed using IDEIA rotavirus kit (DAKO Ltd., Cambridgeshire, UK) provided by the regional laboratory (West Africa Regional Rotavirus Reference laboratory). RV positive stool samples were subsequently tested using reverse transcriptase-polymerase chain reaction (RT-PCR) of the VP7 and VP4 genes followed by reverse hybridization at DDL Diagnostic Laboratory (Rijswijk, the Netherlands) to identify G and P genotypes and to differentiate the presence of wild-type G1 RV from the vaccine strain virus.[23] As a complementary tool, sequence analysis was performed to identify the most prevalent genotypes for samples that yielded an aberrant or unclear pattern. The resulting sequence was analyzed by BLAST search against the GenBank database to determine the RV genotype.[23]

Analyses

All children meeting the pre-defined eligibility criteria were included in the final analyses.

Age at onset, the seasonal distribution of RVGE and the occurrence of RV types were recorded. The occurrence of severe dehydrating RVGE (based on Vesikari

scale,[22]) administered treatment (including intravenous [IV] re-hydration), duration of hospitalization and outcome were all reported.

All statistical analyses were performed using Statistical Analysis System (SAS®) version 9.2 and the graphs were generated using Microsoft Excel®. Categorical data such as gender, seasonal distribution and disease severity were presented as proportions with one decimal. Burden of GE/ RVGE among hospitalizations/ ER visits were expressed as proportions with their 95% exact confidence interval (CI). Exploratory analyses of estimation of the crude odds ratio were performed using univariate logistic regression considering RV status as the outcome variable with clinical characteristics and discharge outcome as confounding factors. Multinomial univariate logistic regression was also explored to estimate the association between outcome at discharge as the dependent variable and RV status and nutritional status as the independent factors. The 95% Walds CI was also estimated.

RESULTS

Demographic characteristics

A total of 1330 children (917 hospitalized and 413 visiting ERs) with AGE were identified from hospital logs, of whom 357 children were enrolled into the study. Informed consent was not collected from the patents/ guardians of 973 children, due to parent refusal, samples not collected, and failure of the surveillance to capture the children. The mean age (standard deviation) of enrolled children was 13.6 months (± 11.14 months) (Table 1).

Table 1: Demographic characteristics of enrolled children (N = 357)

Characteristics	Parameters	Total (N[a] = 357)		Emergency Room (N = 161)		Hospitalized (N = 196)	
		n[b]	%[c]	n	%	n	%
Age (Months)	N	357	-	161	-	196	-
	Mean	13.6	-	13.7	-	13.5	-
	SD[d]	11.14	-	11.39	-	10.96	-
Gender	Female	152	42.6	69	42.9	83	42.3
	Male	205	57.4	92	57.1	113	57.7
Live in the Abidjan		347	97.2	158	98.1	189	96.4

[a]Number of children
[b]Number of children in a given category
[c]n / N x 100
[d]standard deviation

A total of 332 children were included in the final analysis; there were 25 exclusions: two did not meet the inclusion/ exclusion criteria (protocol violation), stool samples were not collected or analyzed for RV (due to insufficient stool sample) for the remaining 23 children.

Among those included in the final analyses, 56.3% (187/332) children were hospitalized and the remaining 43.7% (145/332) visited the ER.

Proportion of GE and RVGE hospitalizations

The proportion of all AGE hospitalizations and ER visits diagnosed with RVGE was 30.1% (n = 56; 95% CI: 23.6–37.3) and 26.9% (n = 39; 95% CI: 19.9–34.9), respectively.

The number of children hospitalized and those who visited the ER for GE stratified by age groups is shown in Table 2. Ninety-five children (28.6%) were RV positive, of which over 80% occurred in children aged less than 24 months (Table 2). The highest number of RVGE cases was reported in children aged 6–11 months (40.0% [38/95]).

Table 2: Distribution of GE cases by ER visits, hospitalizations and RV status by age groups (N = 332)

Age (months)	Emergency Room N[a] = 145		Hospitalized N = 187		RV positive N[a] = 95		RV negative N = 236		RV missing N = 1	
	n[b]	%[c]	n	%	n	%	n	%	n	%
0–5	29	20	46	24.6	16	16.8	58	24.6	1	100.0

Age (months)	Emergency Room N[a] = 145		Hospitalized N = 187		RV positive N[a] = 95		RV negative N = 236		RV missing N = 1	
	n[b]	%[c]	n	%	n	%	n	%	n	%
6–11	47	32.4	57	30.5	38	40.0	66	28.0	0	0.0
12–23	47	32.4	55	29.4	33	34.7	69	29.2	0	0.0
24–35	14	9.7	13	7.0	7	7.4	20	8.5	0	0.0
36–47	4	2.8	12	6.4	0	0.0	16	6.8	0	0.0
48–59	4	2.8	4	2.1	1	1.1	7	3.0	0	0.0

[a]Number of children
[b]Number of children in a given category
[c]n / N x 100

The seasonal distribution of GE hospitalizations attributed to RV infection is shown in Figure 1. The number of GE cases was highest in July and August 2008 and the percentage of RV positive cases was highest in January 2008.

Clinical characteristics of GE and RVGE hospitalizations

Among both RV positive and RV negative children, severe GE (score ≥11 on the Vesikari scale) was reported in 64.2% (61/95) and 55.5% (131/236) children before hospitalization, respectively (Table 3).

The percentage of children recording the symptoms associated with GE (diarrhea, vomiting and fever) was similar across RV positive and negative groups. However, a significant (P-value = 0.0037) association between vomiting and RV positive status was observed prior to hospitalization (Table 3).

Nutritional status based on weight indicated that children who were adequately and moderately malnourished were similar across both RV positive and negative groups. However, a higher number of severely malnourished children were observed in the RV negative group (Table 3).

Oral rehydration was the most common treatment used for GE in both RV positive and negative groups. At discharge, the majority of children among both RV positive and RV negative groups (71.6% [68/95] and 78.0% [184/236], respectively) had ongoing GE, while 3.4% (8/236) of children in the RV negative group died (Table 3). Among the children who died, all children except one (87.5% [7/8]) were severely malnourished. The unadjusted odds ratio estimation indicated that the severely malnourished children had 22.2 (95% CI: 2.5–198.8) times higher risk of dying when compared to children with adequate nutritional status (P-value = 0.0056).

Table 3: Clinical characteristics of children by RV status (N=331)

Characteristic	RV positive (N[a] = 95) n[b] (%[c])	RV negative (N = 236) n (%)	P-value
Severity[d] before hospitalization			
Mild (<7)	6 (6.3)	27 (11.4)	
Moderate (7–10)	28 (29.5)	78 (33.1)	0.2300*
Severe (≥11)	61 (64.2)	131 (55.5)	
Severity during hospitalization			

Mild (<7)	28 (29.5)	55 (23.3)	
Moderate (7–10)	36 (37.9)	115 (48.7)	0.1946*
Severe (≥11)	31 (32.6)	66 (28.0)	
Symptoms before hospitalization			
Diarrhea	95 (100.0)	235 (99.6)	1.0000**
Vomiting	81 (85.3)	170 (72.0)	0.0037**
Fever	44 (46.3)	116 (49.2)	0.8557*
Symptoms during hospitalization			
Diarrhea	90 (94.7)	229 (97.0)	0.3359**
Vomiting	42 (44.2)	95 (40.3)	0.8065**
Fever	47 (49.5)	118 (50.0)	0.9639**
Treatment received before hospitalization			
Oral rehydration	39 (41.1)	96 (40.7)	0.7580*
IV rehydration	1 (1.1)	1 (0.4)	0.5810**
Antibiotics	25 (26.3)	47 (19.9)	0.3701*
Treatment received during hospitalization			
Oral rehydration	67 (70.5)	179 (75.8)	0.2049**
IV rehydration	52 (54.7)	125 (53.0)	0.9507**
Antibiotics	30 (31.6)	81 (34.3)	0.4843**
Classification of nutrition			
Overweight	5 (5.3)	8 (3.4)	
Adequate (Normal)	66 (69.5)	152 (64.4)	0.1981*
Moderately malnourished	15 (15.8)	32 (13.6)	
Severely malnourished	9 (9.5)	44 (18.6)	
Outcome at discharge			

Recovered	27 (28.4)	40 (16.9)	
Ongoing GE	68 (71.6)	184 (78.0)	0.0145**
Transferred	0 (0.0)	4 (1.7)	
Died	0 (0.0)	8 (3.4)	

Note: One child was excluded from analysis as RV status was not determined.
[a]Number of children
[b]Number of children in a given category
[c]n / N x 100
[d]Severity using the 20-point Vesikari scale
*chi square P-value
**Fisher Exact test P-value

RV type distribution

Fifty three of the 95 RV positive stool samples were assessed in this study. Among these, the most prevalent RV types were G1P[8] wild-type (34.0% [18/53]) and G8P[6] (18.9% [10/53]). Mixed RV types were detected in 30.2% (16/53). The RV vaccine strain (G1P[8] vaccine strain) was not detected in any of the samples. The other common RV types detected are depicted by decreasing order of prevalence in Figure 2.

DISCUSSION

This study describing RVGE disease burden found that RV infection is the primary cause of hospitalization due to GE in children aged less than five years in the Republic of Côte d'Ivoire.

We detected RV in 30.1% and 26.9% children hospitalized and visiting the ER, respectively, which is consistent with an earlier epidemiological study in Abidjan that demonstrated the general prevalence of RVGE in children less than five years of age to be 27.9% between 1997 and 2000.[21] In addition, a review of published studies (1975 to 1992) of RVGE in Africa detected RV in 24–29% of children hospitalized for diarrhea.[9]

In the present study, RV disease burden was predominantly observed among young children (aged 6–24 months), which is in line with previous studies conducted across the African continent.[9] A study conducted in Nigeria showed that over 90.0% of RVGE positive cases were observed in children aged less than two years[24] and two independent studies conducted in Egypt (1995–1996) [25] and Libya (October 2007–September 2008) [26] indicated that the incidence of RVGE was highest among children aged 6–11 months; all comparable to the results of the present study.

As observed in previous studies conducted in sub-Saharan African regions between 1975 and 1992,[9] most GE cases in this study were observed between July and August of 2008.

Almost all children who died following AGE cases in this study were severely malnourished, indicating the importance of nutritional status in potentially determining the outcome of AGE. Previous reports substantiate these findings where malnourishment has been associated with a considerable risk of diarrhea-associated mortality.[27, 28]

Circulation of mixed RV types in the African countries have been reported previously,[29, 30] and in this study, although wild-type G1P[8] was the most commonly detected (34.0% [18/53]) RV type, several (30.2% [16/53]) mixed RV types were detected in this study.

There is no available anti-viral therapy for RV infection[31] and the management of RVGE includes replacement of fluids and electrolytes and improvements in sanitation and water supply.[32] Antibiotic treatment is not justified during RVGE and its use is limited to cases with documented bacterial co-infection. However, it has been suggested that improvements in hygiene and provision of safe water supply may not be as effective in the prevention of RVGE as they are to other causes of GE.[32]

Previous studies have established that RV vaccination confers protection against severe RVGE disease and has helped relieve the global burden of this disease [33–36] and more specifically in similar settings in Asia, Africa and Latin America.[29, 37, 38] The efficacy of RV vaccines against severe RVGE has been found to be 59% in South Africa and Malawi [39] and 64% in Kenya, Ghana and Mali.[40] RV vaccination may therefore represent the most effective primary public

health intervention against RVGE. Indeed in 2009, the world health organization (WHO) recommended the inclusion of RV vaccines in the routine childhood vaccine programs of all countries.[41] In the Republic of Côte d'Ivoire, RV vaccines are available in the private sector; however, no RV vaccine is currently included in the universal mass vaccination program.

This study provided baseline epidemiological data that will allow policy makers to assess the magnitude of the RV problem and determine the need for the implementation of prevention strategies in the Republic of Côte d'Ivoire. The inclusion of a RV vaccine might aid to reduce the burden of AGE and AGE-associated hospitalizations.

The results of this study need to be interpreted in the light of several strengths and limitations. Among the strengths, the systematic approach followed in this study to enroll children by checking the hospital and ER logbooks enabled easy identification of AGE cases using standard case definitions. Secondly, the study was conducted in reference hospitals that reported over 1,300 AGE cases annually, which complies with the recommendations of WHO's generic protocol for hospital-based surveillance to estimate the burden of RVGE in children [42]. By including multiple centers, these data more closely represent the population in Abidjan, Republic of Côte d'Ivoire. In addition, the quality check processes performed on the laboratory testing of RV positive samples provides credibility to the results.

However, the study results need to be interpreted with caution due to some of the limitations. The possibility of selection bias might be considered since a large number of children presenting with GE were not enrolled and subsequently not tested for RV. Hence, the reported prevalence of RVGE might have been affected by the selection of only severe GE cases with more severe disease characteristics, including longer hospital stays. Nonetheless, this study provides a realistic picture of the role of RV among more severe cases of RVGE, which incur direct and indirect medical costs and impact public health in this setting. In addition, most subjects who were not enrolled either were not captured during surveillance or were not consented to participate in the study. Secondly, only 53 out of 95 RV positive stool samples were available for strain identification which limits the possibility of describing the circulating strains. Nevertheless, by using a reference laboratory with validated techniques and experience for PCR confirmation, it was possible to provide accurate estimates for the identified strains. Lastly, the seasonality of RV and the variation in circulating RV strains could not been considered as the surveillance activities were conducted for just one year.

CONCLUSION

RVGE in children aged less than five years continues to be a major public health challenge in the Republic of Côte d'Ivoire. The disease which peaks in July and August, mainly affects infants aged 6–11 months. Wild-type G1P[8] and G8P[6] were the most frequently reported RV types. The inclusion of a RV vaccine into preventative programs disease in the Republic of Côte d'Ivoire might help to reduce the disease burden of RVGE.

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Contributors

AKC was the principal investigator and contributed to the conception, design, analysis and interpretation of the study. AKV and YAJ coordinated the study together with AKC and contributed to the interpretation of the results. All authors participated in the development of this manuscript.

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Competing interests

All the authors have no competing interest to declare.

Trademark

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EPI-RV-Ivory Coast
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31-May-13

Figure 1: Seasonality of acute GE and RVGE hospitalizations (N=331)

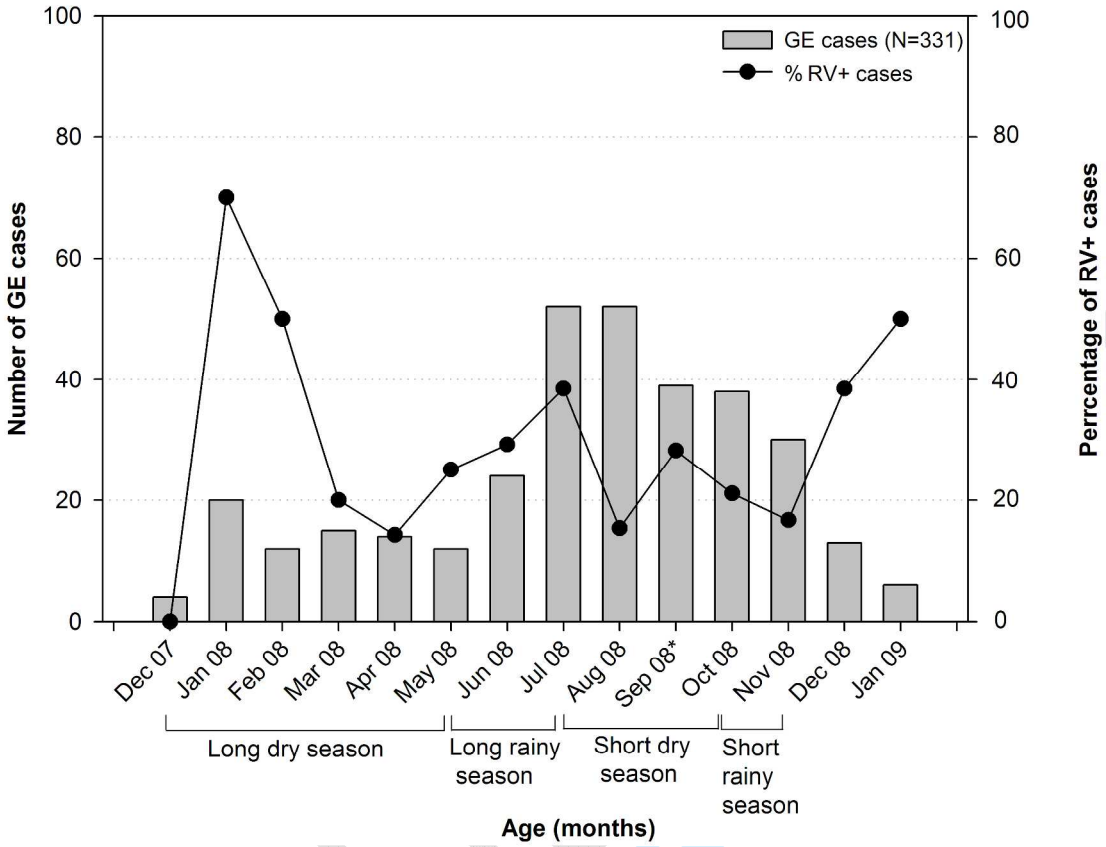

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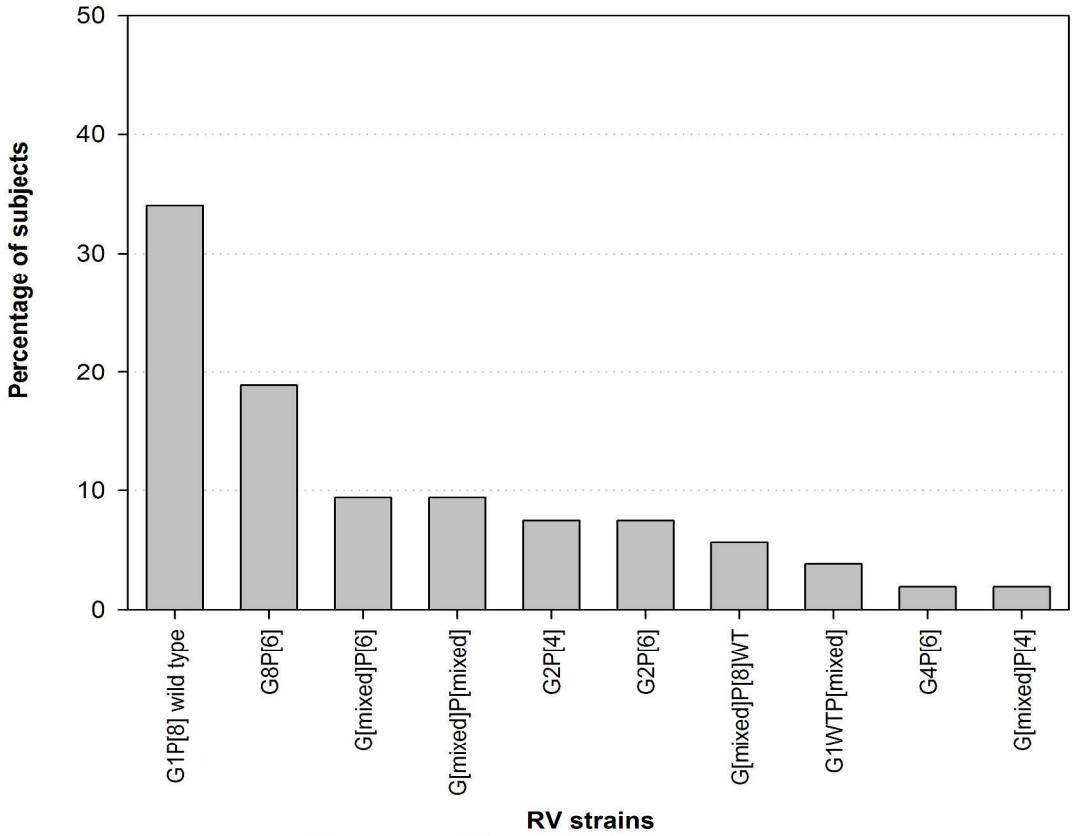
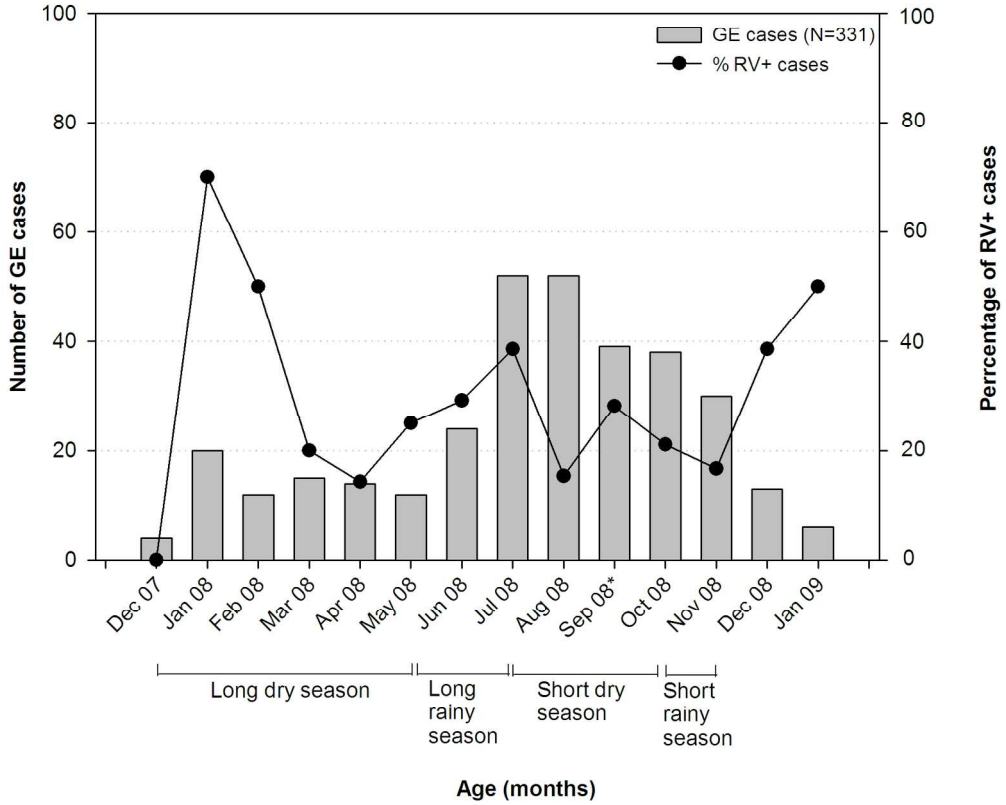
Figure 2: Distribution of RV G and P types (N=331)





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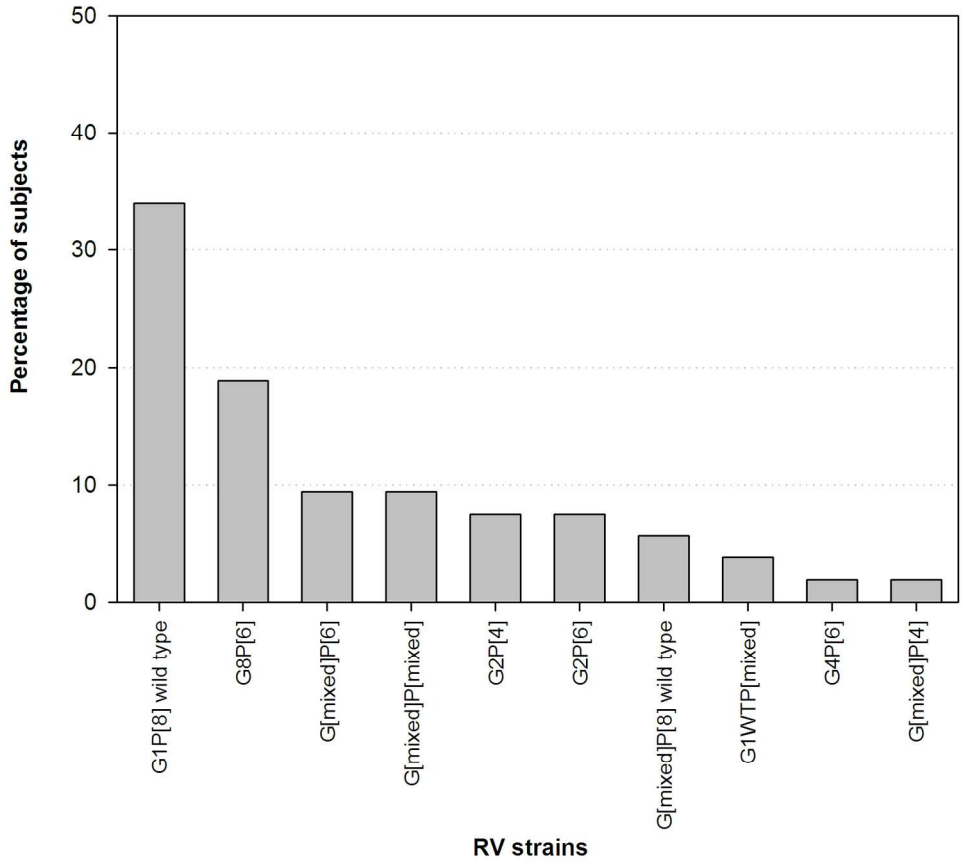

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STROBE Statement

http://www.strobe-statement.org/index.php?id=available-checklists

Checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3,4
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	7,8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9,10
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	9
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-11
Data sources/	8*	For each variable of interest, give sources of data and	10,11

measurement		details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10,11
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12,13
		(b) Give reasons for non-participation at each stage	12,13
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12,13
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure	NA

		category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	12,13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-17
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-17
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/).

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Hospital-based surveillance of rotavirus gastroenteritis among children under five years of age in the Republic of Ivory Coast: A cross-sectional study

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Original Research

Title: Hospital-based surveillance of rotavirus gastroenteritis among children under five years of age in the Republic of Ivory Coast: A cross-sectional study

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Abbreviations:

AGE: acute gastroenteritis; CI: confidence interval; ER: emergency room; GE: gastroenteritis; GSK: GlaxoSmithKline; IV: intravenous; RT-PCR: reverse transcriptase polymerase chain reaction; RV: rotavirus; WAZ: weight-for-age Z-scores.

ABSTRACT

Objectives: To estimate the proportion of rotavirus gastroenteritis (RVGE) among children aged less than five years who had been diagnosed with acute gastroenteritis (AGE) and admitted to hospitals and emergency rooms (ERs). The seasonal distribution of RVGE and most prevalent RV strains were also assessed.

Design: A cross-sectional hospital-based surveillance study.

Setting: Five reference pediatric hospitals across Abidjan.

Participants: Children aged less than five years, who were hospitalized/ visiting ERs for WHO-defined AGE were enrolled. Written informed consent was obtained from parents/ guardians before enrollment. Children who acquired nosocomial infection were excluded from the study.

Primary and secondary outcome measures: The proportion of RVGE among AGE hospitalizations and ER visits were expressed with 95% exact confidence interval (CI). Stool samples were collected from all enrolled children and were tested for the presence of RV using an enzyme immunoassay. RV positive samples were serotyped using reverse transcriptase polymerase chain reaction.

Results: Of 357 enrolled children (mean age 13.6 ± 11.14 months), 332 were included in the final analyses; 56.3% (187/332) were hospitalized and 43.7% (145/332) were admitted to ERs. The proportion of RVGE hospitalizations and ER visits among all AGE cases was 30.1% (95% CI: 23.6-37.3) and 26.9% (95% CI: 19.9-34.9), respectively. Ninety-five children (28.6%) were RV positive; the highest

number of RVGE cases was observed in children aged 6-11 months. The number of GE cases peaked in July and August 2008; the highest percentage of RV positive cases was observed in January 2008. G1P[8]wild-type and G8P[6] were the most commonly detected strains.

Conclusion: RVGE causes substantial morbidity among children under five years of age and remains a health concern in the Republic of Ivory Coast, where implementation of prevention strategies such as vaccination might help to reduce disease burden.

ARTICLE SUMMARY

Article focus

- The burden of rotavirus gastroenteritis (RVGE) in the Republic of Ivory Coast is substantial and recent epidemiological data are limited.
- The main focus of this study was to estimate the proportion of RV among young children hospitalized or treated at emergency rooms (ER) for acute gastroenteritis (AGE).
- We also investigated the seasonal distribution of RVGE and the prevalent RV types in the study population.

Key messages

- RVGE accounts for about 28.6% of AGE hospitalizations and 30.1% ER visits in the Republic of Ivory Coast and particularly affects children younger than 24 months of age.
- The number of RVGE cases peaked during July and August 2008. The most prevalent RV strains were G1P[8] wild-type and G8P[6].
- Implementation of preventative measure such as RV vaccination could help to reduce the burden of RVGE in the Republic of Ivory Coast.

Strengths and limitations of this study:

- Our study was conducted in large city-based pediatric hospitals and our findings are therefore likely to be representative of the whole population.
- Our systematic approach for enrolment allowed the easy identification of AGE cases.
- Our study enrolled only a proportion of all reported AGE cases and only severe cases were included.

INTRODUCTION

Wild-type, rotavirus (RV) causes approximately 111 million gastroenteritis (GE) episodes, 25 million clinic visits, two million hospitalizations and over 453,000 deaths each year among children younger than five years of age.[1, 2] It has been reported that RV mortality is highest among the low income countries of Asia, Africa and Latin America.[3] A systematic review and meta-analysis of published studies in 2009 found that the overall mortality rate associated with RV infection in children under five years of age in sub-Saharan Africa was 243.3 deaths per 100,000 children (95% CI 187.6–301.7).[4] Globally, RV infection rates are also highest among younger children, with approximately 95% children experiencing at least one episode of RVGE by the time they reach five years of age.[5]

RVGE is characterized by fever, diarrhea and vomiting, leading to severe dehydration and increased hospitalization. Over 90% of children with RVGE suffer from dehydration-associated mortality due to diarrhea and associated vomiting.[6-8] It has been suggested that RV infections are more common during the cooler months of the year and that RVGE disease burden is similar in both high and low income nations.[1] However, due to malnutrition and lack of access to appropriate treatment facilities, it is the children from the low-income countries who die more frequently.[1]

As improvements in hygiene and sanitation have not been accompanied by reductions in the incidence of RV-associated diseases,[9] vaccination against RV is therefore considered as a public health priority for low income nations.[10] The

introduction of RV vaccination could have significant benefits for children aged less than three years, and might help to reduce diarrhea-associated childhood morbidity and mortality in low income countries and RV-related hospitalization in high income countries.[11, 12]

The most common globally circulating RV serotypes associated with RVGE are G1, G2, G3 and G4.[13] In addition, G9 has emerged over the past decade as a globally important serotype.[14] Together, these serotypes are responsible for 95% of worldwide pediatric RVGE cases.[15]

The epidemiology of RV infection has been followed in several small studies conducted in Abidjan in the Republic of Ivory Coast,[16–21] but recent data for this region are limited. Nevertheless, data on RVGE disease, the number of hospitalizations and the number of emergency room (ER) visits following acute GE (AGE) are critical to formulate effective policies to control RV-related AGE and are important to fully determine the need for RV vaccines and the possible impact of their introduction.

This study was designed to estimate the proportion of RVGE among children younger than five years of age who were diagnosed with AGE and admitted to hospitals and ERs in the Republic of Ivory Coast. The seasonal distribution of RVGE and the prevalent RV types were also studied.

METHODS

Study design

This cross-sectional hospital-based surveillance study was conducted across five reference pediatric hospitals in Abidjan, the Republic of Ivory Coast between December 2007 and February 2009. The study was approved by the national Independent Ethics Committee (Ministère de la Santé et de l'Hygiène Publique, Abidjan) and conducted in accordance with Good Clinical Practice, Declaration of Helsinki (version 1996) and applicable local regulations. Written informed consent was obtained from parents/ guardians before children were enrolled.

Children presenting AGE were identified by checking hospital and ER logbooks. Male or female children aged less than five years, who were hospitalized or visited ER for AGE (≥3 looser than normal stools per day with or without ≥2 episodes of vomiting within 24 hours) were included in the study. Children were excluded if they acquired AGE by possible nosocomial infection (within 12 hours after hospital admission).

Unique study numbers were assigned sequentially to all enrolled children in order to maintain their confidentiality. Parents/ guardians were interviewed and medical records were reviewed by the site staff to complete the study questionnaire and/ or case report form. Information including demography (date of birth, gender, height and weight, nutritional status, and area of residence); admission date and diagnosis at admission, date of discharge and administration of oral and/ or intravenous rehydration/ antibiotics were recorded and encoded in the study

database. Details such as body temperature, duration of diarrhea or vomiting, treatment and behavioral symptoms were also recorded. The severity of RVGE was defined according to the Vesikari Scale (mild: score <7; moderate: score 7–10 and severe: score ≥11).[22]

Stool samples collected within 4–10 days of the onset of GE from all enrolled children as part of the study procedures were labeled, stored at a temperature of -20°C to -70°C and then transported to the Pasteur Institute, Abidjan, within 72 hours of collection for testing. RV testing was performed using the IDEIA rotavirus kit (DAKO Ltd., Cambridgeshire, UK) provided by the regional laboratory (Ivory Coast National laboratory for rotavirus, affiliated to the World Health Organization [WHO] regional reference laboratory located in Accra-Ghana [West Africa], at the Noguchi Memorial Institute for Medical Research). A random subset of RV positive stool samples were subsequently tested using reverse transcriptase-polymerase chain reaction (RT-PCR) of the VP7 and VP4 genes followed by reverse hybridization on a strip at the DDL Diagnostic Laboratory (Rijswijk, The Netherlands) to identify G and P genotypes and to differentiate the presence of wild-type G1 RV from the vaccine strain virus.[23] A visible pattern is observed on the strip after hybridization which is specific to each genotype. As a complementary tool, sequence analysis was performed to identify the genotypes for samples that yielded an unclear pattern that could not be recognized. The resulting sequence was analyzed by BLAST search against the GenBank database to determine the RV genotype.[23]

Analyses

All children meeting the pre-defined eligibility criteria were included in the final analyses.

The occurrence of severe dehydrating RVGE (based on the Vesikari scale [22]) administered treatment (including intravenous [IV] re-hydration), duration of hospitalization and outcome were all reported, together with the seasonal distribution of RVGE and the occurrence of RV types.

All statistical analyses were performed using Statistical Analysis System (SAS®) version 9.2 and the graphs were generated using Microsoft Excel®. Categorical data such as gender, seasonal distribution and disease severity were presented as proportions with one decimal. Burden of GE/ RVGE among hospitalizations/ ER visits were expressed as proportions with their 95% exact confidence interval (CI). Exploratory analyses of estimation of the crude odds ratio were performed using univariate logistic regression considering RV status as the outcome variable with clinical characteristics and discharge outcome as confounding factors. Multinomial univariate logistic regression was also explored to estimate the association between outcome at discharge as the dependent variable and RV status as the independent factors. Nutritional status was derived using the weight-for-age Z-scores (WAZ) based on the WHO child growth standards. Association between these derived nutritional status and the RV positivity were analyzed using the chi-square test with 95% exact CI. The 95% Walds CI was also estimated.

RESULTS

Demographic characteristics

A total of 1330 children (917 hospitalized and 413 visiting ER) presenting AGE were identified from hospital logs. Of these, 357 children were enrolled into the study. Informed consent was not collected for 973 children, due to: parent refusal; non-collection of samples; and failure of the surveillance to capture the cases. The mean age (standard deviation) of the enrolled children was 13.6 months (± 11.14 months) (Table 1).

Table 1: Demographic characteristics of enrolled children (N = 357)

Characteristics	Parameters	Total (N[a] = 357)		Emergency Room (N = 161)		Hospitalized (N = 196)	
		n[b]	%[c]	n	%	n	%
Age (Months)	N	357	-	161	-	196	-
	Mean	13.6	-	13.7	-	13.5	-
	SD[d]	11.14	-	11.39	-	10.96	-
Gender	Female	152	42.6	69	42.9	83	42.3
	Male	205	57.4	92	57.1	113	57.7

[a]Number of children
[b]Number of children in a given category
[c]n / N x 100
[d]standard deviation

A total of 332 children were included in the final analysis; ; 25 were excluded due to not meeting the inclusion/ exclusion criteria (protocol violation) in two cases and

failure to either collect or analyze the stool samples for RV in the remaining 23 children.

Among those included in the final analysis, 56.3% (187/332) children had been hospitalized and the remaining 43.7% (145/332) had visited an ER.

Proportion of GE and RVGE hospitalizations

The proportion of all AGE-related hospitalizations and ER visits that were diagnosed with RVGE was 30.1% (n = 56; 95% CI: 23.6–37.3) and 26.9% (n = 39; 95% CI: 19.9–34.9), respectively.

Most of the children hospitalized and visiting the ER due to AGE corresponded to children under two years of age (84.8% and 84.5%, respectively). The number of RV positive and negative children stratified by age is shown in Figure 1. Ninety-five children (28.6%) were RV positive, of whom over 80% were aged less than 24 months. The highest number of RVGE cases was seen in children aged 6–11 months (40.0% [38/95]) (Figure 1).

The seasonal distribution of RV-attributable GE hospitalization is shown in Figure 2. The number of GE cases was highest in July and August 2008 and the percentage of RV positive cases was highest in January 2008.

Clinical characteristics of GE and RVGE hospitalizations

Among RV positive and negative children, severe GE (score ≥11 on the Vesikari scale) was recorded in 64.2% (61/95) and 55.5% (131/236) children before hospitalization, respectively (Table 2).

The percentage of children recording GE-associated symptoms (diarrhea, vomiting and fever) was similar across RV positive and negative groups before hospitalization. However, a significant (P-value = 0.0037) association between vomiting and RV positive status was observed before hospital admission (Table 2).

Nutritional status based on weight indicated that adequately and moderately malnourished children were distributed similarly across both RV positive and negative groups. However, a higher number of severely malnourished children was observed in the RV negative group (Table 2).

Oral rehydration was the most commonly used treatment for GE in both RV positive and negative groups (70.5% and 75.8%, respectively), followed by intravenous rehydration therapy (54.7% and 53.0%, respectively).

At discharge, the majority of children among both RV positive and negative groups (71.6% [68/95] and 78.0% [184/236], respectively) had ongoing GE. Eight RV negative children (3.4%) died, of whom all but one (87.5% [7/8]) were severely malnourished. The unadjusted odds ratio estimate indicated that severely malnourished children had 22.2 (95% CI: 2.5–198.8) times higher risk of dying as compared to children with adequate nutritional status (P-value = 0.0056) (Table 2).

Table 2: Clinical characteristics of children by RV status (N=331)

Characteristic	RV positive (N[a] = 95) n[b] (%[c])	RV negative (N = 236) n (%)	P-value
Severity[d] before hospitalization			
Mild (<7)	6 (6.3)	27 (11.4)	
Moderate (7–10)	28 (29.5)	78 (33.1)	0.2300*
Severe (≥11)	61 (64.2)	131 (55.5)	
Symptoms before hospitalization			
Diarrhea	95 (100.0)	235 (99.6)	1.0000**
Vomiting	81 (85.3)	170 (72.0)	0.0037**
Fever	44 (46.3)	116 (49.2)	0.8557*
Classification of nutrition			
Overweight	5 (5.3)	8 (3.4)	
Adequate (Normal)	66 (69.5)	152 (64.4)	0.1981*
Moderately malnourished	15 (15.8)	32 (13.6)	
Severely malnourished	9 (9.5)	44 (18.6)	
Outcome at discharge			
Recovered	27 (28.4)	40 (16.9)	
Ongoing GE	68 (71.6)	184 (78.0)	0.0145**
Transferred	0 (0.0)	4 (1.7)	
Died	0 (0.0)	8 (3.4)	

Note1: One child was excluded from analysis as RV status was not determined.
Note 2: Nutritional status were derived using the weight-for-age Z-scores (WAZ)
[a]Number of children
[b]Number of children in a given category
[c]n / N x 100
[d]Severity using the 20-point Vesikari scale
*chi square P-value
**Fisher Exact test P-value

RV type distribution

Fifty three of 95 RV positive stool samples were assessed for RV type in this study. The most prevalent RV types were G1P[8] wild-type (34.0% [18/53]) and G8P[6] (18.9% [10/53]). Mixed RV types were detected in 30.2% (16/53). The RV vaccine strain (G1P[8] vaccine strain) was not detected in any sample. The other detected RV types are shown in Figure 3.

DISCUSSION

This study into RVGE disease burden found that RV infection is the primary cause of hospitalization due to GE in children aged less than five years in the Republic of Ivory Coast.

We identified RV in 30.1% and 26.9% children either hospitalized or visiting an ER for AGE, respectively. This is consistent with an earlier epidemiological study in Abidjan that demonstrated the general prevalence of RVGE in children younger than five years to be 27.9% between 1997 and 2000.[21] In addition, a review of published studies (1975 to 1992) of RVGE in Africa detected RV in 24–29% of children hospitalized for diarrhea.[9]

In the present study, RV disease burden was predominantly observed among young children (over 90.0% [87/95] were aged up to 23 months), which is consistent with previous studies conducted across the African continent.[9] A study conducted in Nigeria showed that over 90.0% of RVGE positive cases were observed in children aged less than two years [24] and two independent studies conducted in Egypt (1995–1996) [25] and Libya (October 2007–September 2008) [26] indicated that the incidence of RVGE was highest among children aged 6–11 months; all comparable to the results of the present study.

As observed in previous studies conducted in sub-Saharan Africa between 1975 and 1992,[9] most GE cases in this study were observed between July and August 2008.

Almost all children who died following AGE in this study were severely malnourished, indicating the importance of nutritional status in potentially determining the outcome of AGE. Previous reports substantiate these findings where malnourishment has been associated with a considerable risk of diarrhea-associated mortality.[27, 28]

The circulation of mixed RV types in the African countries has been previously reported.[29, 30] In this study, although wild-type G1P[8] was the most commonly detected (34.0% [18/53]) RV type, several (30.2% [16/53]) mixed RV types were detected. The proportion of mixed RV types observed in this study is comparable to that reported by the WHO's RV surveillance in the African Region.[31] In this report, nearly 42% of the circulating RV types during 2006–2009 comprised of mixed RV types.[31]

There is no available anti-viral therapy for RV infection [32] and RVGE management predominantly includes fluid and electrolyte replacement and improvements in sanitation and water supply.[33] Antibiotic treatment is not justified during RVGE and its use is limited to cases with documented bacterial co-infection. However, it has been suggested that improvements in hygiene and provision of safe water may not be as effective in the prevention of RVGE as they are to GE due to other causes.[33]

Previous studies have established that RV vaccination confers protection against severe RVGE and has helped relieve the global burden of this disease.[34–37] These effects have been observed in similar settings in Asia, Africa and Latin

America.[29, 38, 39] The efficacy of RV vaccines against severe RVGE has been found to be 59% in South Africa and Malawi [40] and 64% in Kenya, Ghana and Mali.[41] RV vaccination may therefore represent the most effective primary public health intervention against RVGE. Indeed in 2009, the WHO recommended the inclusion of RV vaccines in the routine childhood vaccine programs of all countries.[42] RV vaccines are available in the private sector in the Republic of Ivory Coast, but no RV vaccine is currently included in the universal mass vaccination program.

Data presented in this study highlight the magnitude of RV-associated disease burden and might allow policy makers to determine the need to implement of prevention strategies in the Republic of Ivory Coast. Indeed, the inclusion of a RV vaccine, as a prevention strategy, might help to reduce the burden of AGE and AGE-associated hospitalizations.

The results of this study need to be interpreted in the light of several strengths and limitations. Among the strengths, the systematic approach followed in this study to identify children by checking hospital and ER logbooks enabled easy identification of AGE cases using standard case definitions. Secondly, the study was conducted in reference hospitals seeing over 1,300 AGE cases annually, which complies with the recommendations of WHO's generic protocol for hospital-based of RVGE in children [43]. By including multiple centers, these data more closely represent the local population. In addition, the quality check processes performed on the laboratory tests of RV positive samples provides credibility to the results.

However, the study does have limitations. As a large number of children who presented with GE were not enrolled and tested for RV, the possibility of selection bias might be considered. Our reported prevalence of RVGE might have been affected by selecting only severe GE cases with more severe disease characteristics, including longer hospital stays. Nonetheless, this study provides a realistic picture of the role of RV among more severe cases of RVGE, which incur substantial direct and indirect medical costs and impact public health in this setting. It should be noted that most of the subjects who were not enrolled were either not captured during surveillance or did not consent to participate in the study. Secondly, only 53 out of 95 RV positive stool samples were available for strain identification which limits the possibility of describing the circulating strains. Nevertheless, by using a reference laboratory with validated techniques and experience for PCR confirmation, it was possible to provide accurate estimates for the identified strains. Lastly, firm conclusions regarding the seasonality of RV and the variation in circulating RV strains could not been drawn as the surveillance activities were conducted for just one year following recommendations from WHO.[43] Nevertheless, routine surveillance is warranted as rotavirus circulation might vary from one calendar year to another.

CONCLUSION

RVGE in children aged less than five years continues to be a major public health challenge in the Republic of Ivory Coast. In our study, the disease, which peaked in July and August, mainly affected infants aged 6–11 months. Wild-type G1P[8] and G8P[6] were the most frequently reported RV types. The inclusion of a RV vaccine into local preventative programs might therefore help to reduce the disease burden of RVGE.

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Contributors

AKC was the principal investigator and contributed to the conception, design, analysis and interpretation of the study. AKV and YAJ coordinated the study together with AKC and contributed to the interpretation of the results. All authors participated in the development of this manuscript.

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Competing interests

All the authors have no competing interest to declare.

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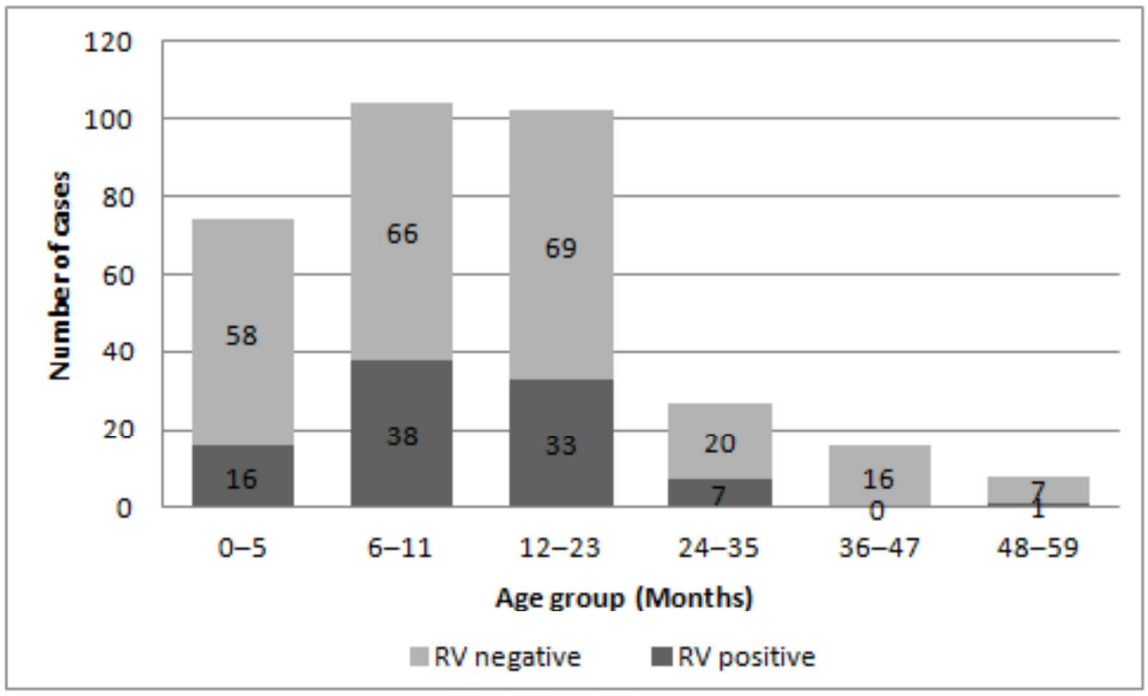
Figure 1: Distribution of GE cases by RV status by age groups (N = 332)



Note: RV status of one subject in the age group 0–5 Months was unknown

Figure 2: Seasonality of acute GE and RVGE hospitalizations (N=331)

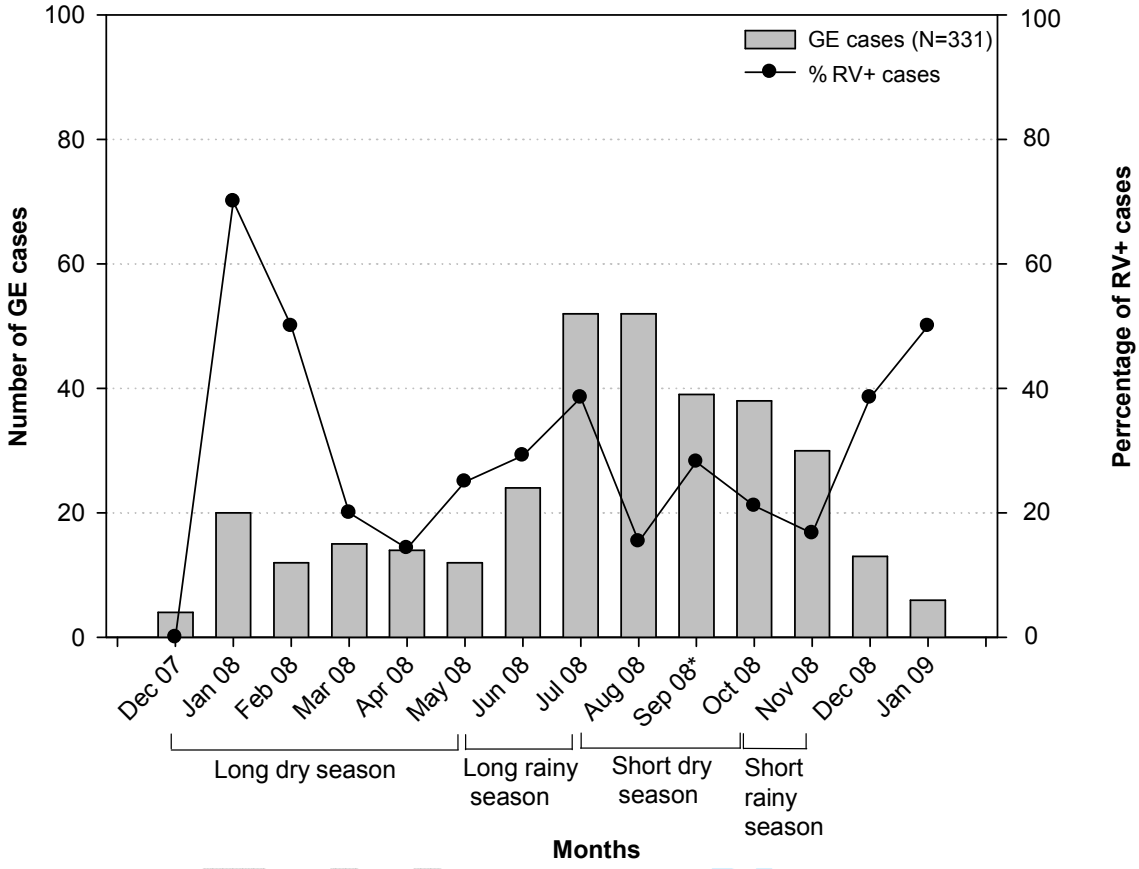
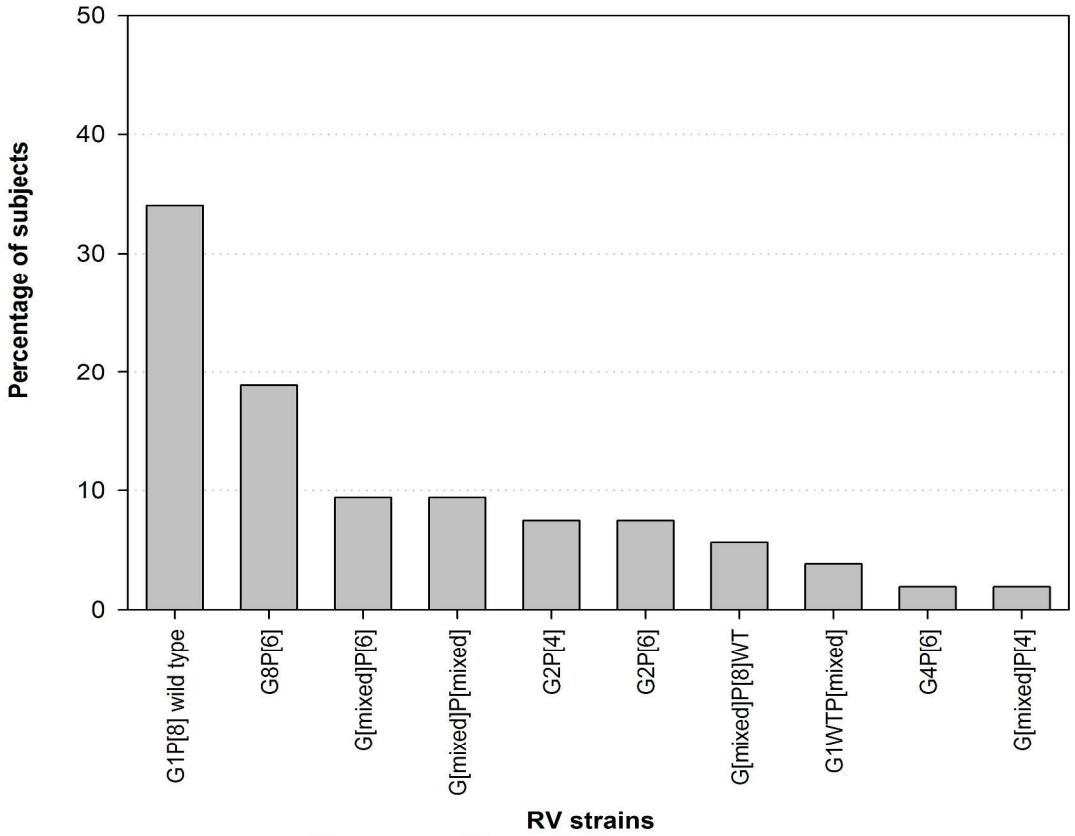
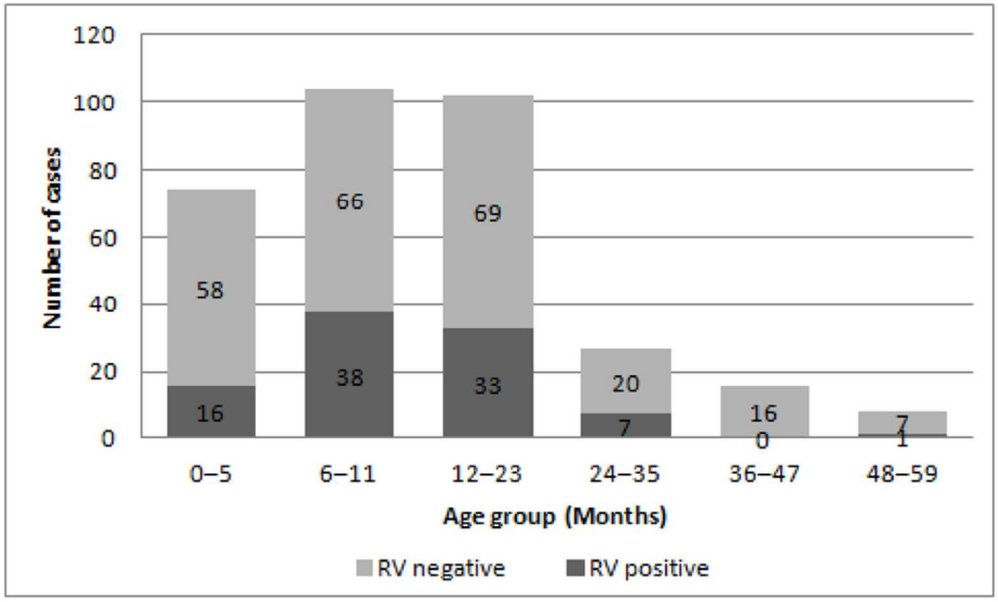


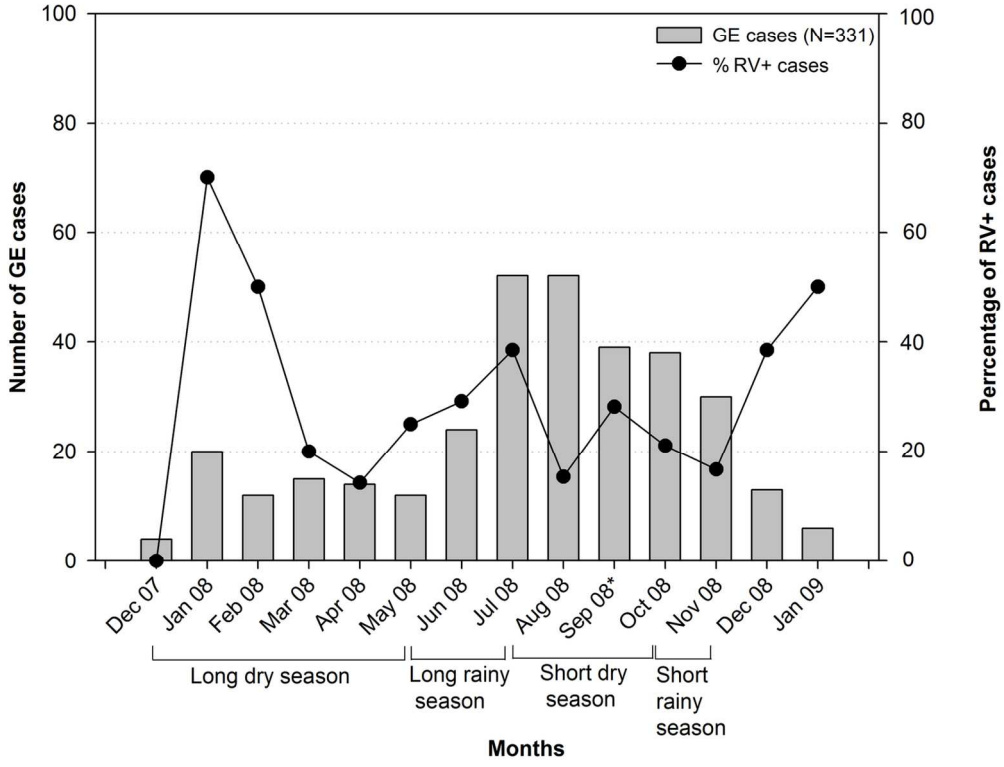
Figure 3: Distribution of RV G and P types (N=331)



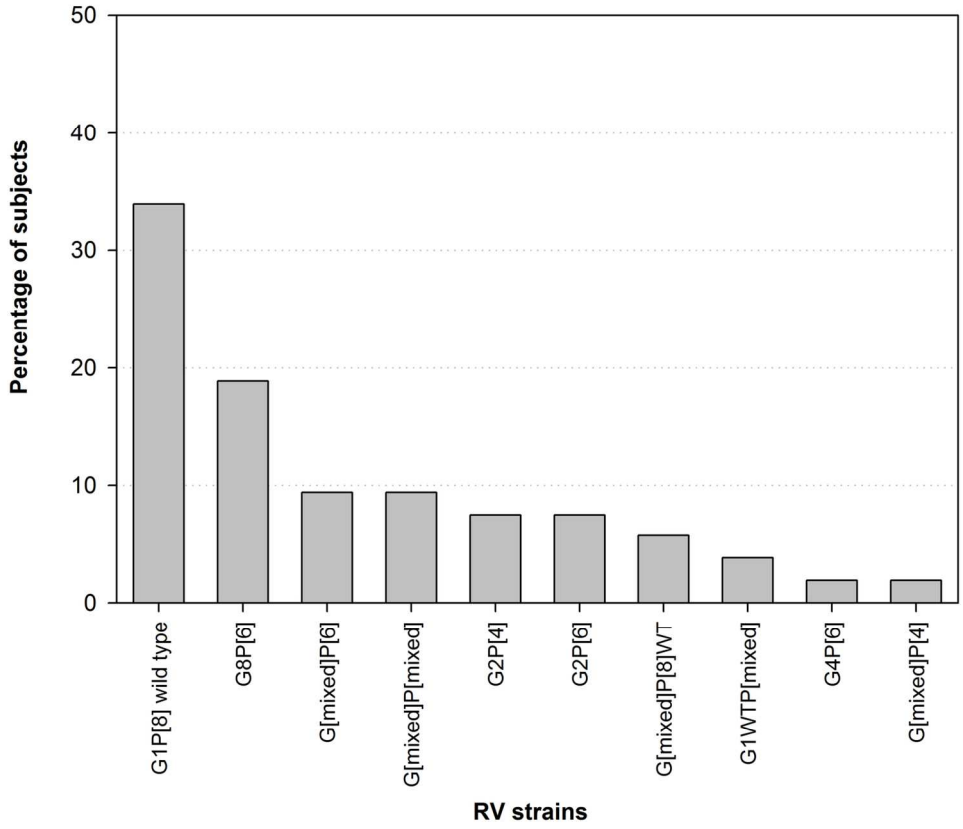


Distribution of GE cases by RV status by age groups (N = 332)

Note: RV status of one subject in the age group 0–5 Months was unknown
77x47mm (300 x 300 DPI)



Seasonality of acute GE and RVGE hospitalizations (N=331)
134x112mm (300 x 300 DPI)



Distribution of RV G and P types (N=331)
136x122mm (300 x 300 DPI)

STROBE Statement

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Checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3,4
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	7,8
Objectives	3	State specific objectives, including any prespecified hypotheses	9
Methods			
Study design	4	Present key elements of study design early in the paper	10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10,11
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	10
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-12
Data sources/	8*	For each variable of interest, give sources of data and	12-13

measurement		details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12-13
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	14-15
		(b) Give reasons for non-participation at each stage	14-15
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14-15
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure	NA

		category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	15-16
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15-19
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	16-19
Discussion			
Key results	18	Summarise key results with reference to study objectives	20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	23
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	25
Generalisability	21	Discuss the generalisability (external validity) of the study results	23-24
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	27

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/).

Information on the STROBE Initiative is available at www.strobe-statement.org.

Original Research

Title: Hospital-based surveillance of rotavirus gastroenteritis among children under five years of age in the Republic of ~~Côte d'Ivoire~~Ivory Coast: A cross-sectional study

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Keywords: ~~Côte d'Ivoire~~Ivory Coast, disease burden, rotavirus, gastroenteritis

Word count: Abstract: ~~272~~289/300; **Manuscript**: ~~3065~~3159/4000

Abbreviations:

AGE: acute gastroenteritis; CI: confidence interval; ER: emergency room; GE: gastroenteritis; GSK: GlaxoSmithKline; IV: intravenous; RT-PCR: reverse transcriptase polymerase chain reaction; RV: rotavirus; WAZ: weight-for-age Z-scores.

ABSTRACT

Objectives: To estimate the proportion of rotavirus gastroenteritis (RVGE) among children aged less than five years who ~~were~~ had been diagnosed with acute gastroenteritis (AGE) and admitted to hospitals and emergency rooms (ERs). The seasonal distribution of RVGE and most prevalent RV strains were also assessed.

Design: A~~n observational, prospective~~ cross-sectional hospital-based surveillance study.

Setting: Five ~~refer~~reference~~ence~~ pediatric hospitals across Abidjan.

Participants: Children aged less than five years, who were hospitalized/ visiting ERs for WHO-defined AGE ~~as defined by the WHO~~ were enrolled. Written informed consent was obtained from parents/ guardians ~~prior to~~before enrollment. Children who acquired nosocomial infection were excluded from the study.

Primary and secondary outcome measures: The proportion of RVGE among AGE hospitalizations and ER visits were expressed with ~~their~~ 95% exact confidence interval (CI). Stool samples were collected from all enrolled children ~~to~~ and were tested for the presence of RV using an enzyme immunoassay. RV positive samples were serotyped using reverse transcriptase polymerase chain reaction.

Results: Of 357 enrolled children (mean age 13.6 ± 11.14 months) ~~enrolled~~, 332 were included in the final analyses; 56.3% (187/332) were hospitalized and 43.7% (145/332) were admitted to ERs. The proportion of RVGE hospitalizations and ER

visits among all AGE cases was 30.1% (95% CI: 23.6-37.3) and 26.9% (95% CI: 19.9-34.9), respectively. Ninety-five ~~(28.6%)~~ children (28.6%) were RV positive; ~~and~~ the highest number of RVGE cases was observed in children aged 6-11 months. The number of GE cases peaked in July and August 2008; the highest percentage of RV positive cases was observed in January 2008. G1P[8]wild-type and G8P[6] were the most commonly detected strains.

Conclusion: RVGE causes substantial morbidity among children under five years of age and remains a health concern in the Republic of ~~Côte d'Ivoire~~Ivory Coast, where implementation of prevention strategies such as vaccination might help to reduce ~~the~~ disease burden.

~~**Trial registration:** Not applicable~~

ARTICLE SUMMARY

Article focus

- The burden of ~~R~~rotavirus gastroenteritis (RVGE) ~~disease burden~~ in the Republic of ~~Côte d'Ivoire~~Ivory Coast is substantial and recent epidemiological data ~~on the epidemiology of RVGE~~ are limited.
- The main focus of this study was to estimate the proportion of RV among young children hospitalized ~~f~~or treated at emergency rooms (ER) for acute gastroenteritis (AGE) ~~or treated at emergency rooms (ER) for AGE~~.
- We also investigated ~~Additionally, we sought to determine~~ the seasonal distribution of RVGE and ~~to identify~~ the prevalent RV types in the study population.

Key messages

- RVGE accounts for about 28.6% of AGE hospitalizations and 30.1% ER visits in the Republic of ~~Côte d'Ivoire~~Ivory Coast and particularly affects children ~~aged less~~ younger than 24 months of age.
- The number of RVGE cases peaked during July and August 2008. The most prevalent RV strains were G1P[8] wild-type and G8P[6].
- Implementation of preventative measure such as RV vaccination could help to reduce the ~~disease~~ burden of RVGE in the Republic of ~~Côte d'Ivoire~~Ivory Coast.

Strengths and limitations of this study:

- ~~The~~ Our study was conducted in large city-based pediatric hospitals ~~across the city~~ and ~~hence~~ our findings are therefore likely to be representative of the whole population.
- ~~The~~ Our systematic approach for ~~followed to~~ enrol~~l~~ment ~~children enabled~~ allowed the easy identification of AGE cases.
- ~~Only~~ Our study enrolled only a ~~reduced~~ proportion of all ~~the~~ reported AGE cases ~~could be enrolled in this study~~ and ~~included~~ only severe cases were included.

INTRODUCTION

Wild-type, rotavirus (RV) causes approximately 111 million episodes of gastroenteritis (GE) episodes, 25 million clinic visits, two million hospitalizations and over 453,000 deaths per each year among children younger than five years of age.[1, 2] It has been reported that RV mortality is the highest among the low income countries in of Asia, Africa and Latin America.[3] A systematic review and meta-analysis (2009) of published studies in 2009 reported found that, in sub-Saharan Africa, the overall mortality rate associated with RV infection in children under five years of age in sub-Saharan Africa was 243.3 (95% CI 187.6–301.7) deaths per 100,000 children (95% CI 187.6–301.7).[4] Globally, RV infection rates are also highest among younger children aged less than five years, with approximately 95% children having experiencinged at least one episode of RVGE by the time they are reach five years of age.[5]

RVGE is characterized by fever, diarrhea and vomiting, that leading to severe dehydration and increased hospitalization. Over 90% of children with RVGE suffer from dehydration-associated mortality due to diarrhea and associated vomiting.[6-8] It has been suggested that RV infections are more common during the cooler months of the year and that RVGE disease burden is similar in both high and low income nations.[1] However, due to malnutrition and lack of access to appropriate treatment facilities, it is the children in from the low-income countries who die more frequently.[1]

As improvements in hygiene and sanitation have not been ~~associated with~~accompanied by reductions in the incidence of RV-associated diseases,[9] vaccination against RV is therefore considered as a public health priority for low income nations.[10] The introduction of RV vaccination could have significant ~~potential and visible~~ benefits ~~to~~ for children aged less than three years, and might help to ~~assist the~~ reduc~~e~~tion ~~of~~ diarrhea-associated childhood morbidity and mortality in low income countries and ~~of~~ RV-~~associated~~ related hospitalization~~s~~ in high income countries.[11, 12]

The most common globally circulating RV serotypes associated with RVGE ~~circulating worldwide~~ are G1, G2, G3 and G4.[13] In addition ~~to these~~, G9 has emerged over the past decade as a globally important serotype ~~in the last decade~~.[14] Together, these serotypes are responsible for 95% of worldwide pediatric RVGE cases.[15]

~~In the Republic of Côte d'Ivoire, t~~The epidemiology of RV infection has been followed in several small studies conducted in Abidjan in the Republic of Ivory Coast,[16–21] but recent data ~~on RVGE disease burden~~ for this region are limited. Nevertheless, ~~D~~data on RVGE disease, the number of hospitalizations and the number of emergency room (ER) visits following acute GE (AGE) are critical to formulate effective policies to control RV-related AGE and~~. These data~~ are ~~also~~ important to fully determine the need for RV vaccines and ~~understand~~ the possible impact of their introduction.

This study ~~aimed~~ was designed to estimate the proportion of RVGE among children younger than five years of age who were diagnosed with AGE and admitted to hospitals and ERs in the Republic of Ivory Coast. ~~Seasonal~~ The seasonal distribution of RVGE and ~~identification of~~ the prevalent RV types ~~in the Republic of Côte d'Ivoire was~~ were also studied.

METHODS

Study design

This ~~observational,~~ cross-sectional hospital-based surveillance study was conducted across five ~~centers~~ reference pediatric hospitals in Abidjan, the Republic of ~~Côte d'Ivoire~~Ivory Coast between December 2007 and February 2009. The study was approved by the national Independent Ethics Committee (Ministère de la Santé et de l'Hygiène Publique, Abidjan) and conducted in accordance with ~~the~~ Good Clinical Practice, ~~the~~ Declaration of Helsinki (version 1996) and ~~the~~ applicable local regulations ~~of the country.~~ ~~and w~~Written informed consent was obtained from parents/ guardians before children were enrolled.

Children presenting AGE were ~~enrolled in this study~~identified by checking ~~the~~ hospital and ER logbooks. Male~~s~~ or female children~~s~~ aged less than five years, who were hospitalized or visited ER for AGE (≥3 looser than normal stools per day with or without ≥2 episodes of vomiting within 24 hours) were included in the study. Children were excluded if they acquired AGE by possible nosocomial infection (within 12 hours after hospital admission).

Unique study numbers were ~~sequentially~~ assigned sequentially to all enrolled children in order to maintain their confidentiality. Parents/ guardians were interviewed and medical records were reviewed by the site staff to complete the study questionnaire and/ or case report form. Information ~~such as~~including demography ~~ic parameters~~ (date of birth, gender, height and weight, nutritional status, and area of residence); admission date and diagnosis at admission, date of

discharge , diagnosis at discharge and administration of oral and/ or intravenous rehydration/ antibiotics were recorded and encoded in the study database. Details such as body temperature, duration of diarrhea or vomiting, treatment including hospitalization and behavioral symptoms were also recorded. The severity of RVGE was defined according to the Vesikari Scale (mild: score <7; moderate: score 7–10 and severe: score ≥11).[22]

Stool samples collected within 4–10 days of the onset of GE from all enrolled children as part of the study procedures were labeled, refrigerated (4°C–8°C), frozen stored at a temperature of (-20°C to -70°C) and then transported to the Pasteur Institute, Abidjan, within 72 hours of sample collection for testing. RV testing was performed using the IDEIA rotavirus kit (DAKO Ltd., Cambridgeshire, UK) provided by the regional laboratory (Ivory Coast National laboratory for rotavirus, affiliated to the World Health Organization [WHO] regional reference laboratory located in Accra-Ghana [West Africa], at the Noguchi Memorial Institute for Medical ResearchWest Africa Regional Rotavirus Reference laboratory). A random subset of RV positive stool samples were subsequently tested using reverse transcriptase-polymerase chain reaction (RT-PCR) of the VP7 and VP4 genes followed by reverse hybridization on a strip at the DDL Diagnostic Laboratory (Rijswijk, The Netherlands) to identify G and P genotypes and to differentiate the presence of wild-type G1 RV from the vaccine strain virus.[23] A visible pattern is observed on the strip after hybridization which is specific to each genotype. As a complementary tool, sequence analysis was performed to identify

the ~~most prevalent~~ genotypes for samples that yielded an ~~aberrant or~~ unclear pattern that could not be recognized. The resulting sequence was analyzed by BLAST search against the GenBank database to determine the RV genotype.[23]

Analyses

All children meeting the pre-defined eligibility criteria were included in the final analyses.

~~Age at onset, the seasonal distribution of RVGE and the occurrence of RV types were recorded.~~ The occurrence of severe dehydrating RVGE (based on the Vesikari scale [22]) administered treatment (including intravenous [IV] re-hydration), duration of hospitalization and outcome were all reported, together with~~.~~ the seasonal distribution of RVGE and the occurrence of RV types.

All statistical analyses were performed using Statistical Analysis System (SAS®) version 9.2 and the graphs were generated using Microsoft Excel®. Categorical data such as gender, seasonal distribution and disease severity were presented as proportions with one decimal. Burden of GE/ RVGE among hospitalizations/ ER visits were expressed as proportions with their 95% exact confidence interval (CI). Exploratory analyses of estimation of the crude odds ratio were performed using univariate logistic regression considering RV status as the outcome variable with clinical characteristics and discharge outcome as confounding factors. Multinomial univariate logistic regression was also explored to estimate the association between outcome at discharge as the dependent variable and RV status ~~and nutritional status~~ as the independent factors. ~~The 95% Walds CI was also~~

~~estimated.~~ Nutritional status was derived using the weight-for-age Z-scores (WAZ) based on the WHO child growth standards. Association between these derived nutritional status and the RV positivity were analyzed using the chi-square test with 95% exact CI. The 95% Walds CI was also estimated.

RESULTS

Demographic characteristics

A total of 1330 children (917 hospitalized and 413 visiting ERs) with presenting AGE were identified from hospital logs, . Of whom these, 357 children were enrolled into the study. Informed consent was not collected from for the patents/ guardians of 973 children, due to: parent refusal, ; samples nont collection of samplesed, ; and failure of the surveillance to capture the childrencases. The mean age (standard deviation) of the enrolled children was 13.6 months (± 11.14 months) (Table 1).

Table 1: Demographic characteristics of enrolled children (N = 357)

Characteristics	Parameters	Total (N[a] = 357)		Emergency Room (N = 161)		Hospitalized (N = 196)	
		n[b]	%[c]	n	%	n	%
Age (Months)	N	357	-	161	-	196	-
	Mean	13.6	-	13.7	-	13.5	-
	SD[d]	11.14	-	11.39	-	10.96	-
Gender	Female	152	42.6	69	42.9	83	42.3
	Male	205	57.4	92	57.1	113	57.7
~~Live in the Abidjan~~		~~347~~	~~97.2~~	~~158~~	~~98.1~~	~~189~~	~~96.4~~

[a]Number of children
[b]Number of children in a given category
[c]n / N x 100

[d]standard deviation

A total of 332 children were included in the final analysis; ; 25 were excluded due to not meetingthere were 25 exclusions: two did not meet the inclusion/ exclusion criteria (protocol violation) in two cases, and failure to either collect or analyze the stool samples were not collected or analyzed for RV (due to insufficient stool sample) for in the remaining 23 children.

Among those included in the final analysesanalysis, 56.3% (187/332) children were had been hospitalized and the remaining 43.7% (145/332) had visited the an ER.

Proportion of GE and RVGE hospitalizations

The proportion of all AGE-related hospitalizations and ER visits that were diagnosed with RVGE was 30.1% (n = 56; 95% CI: 23.6–37.3) and 26.9% (n = 39; 95% CI: 19.9–34.9), respectively.

Most of the children hospitalized and visiting the ER due to AGE corresponded to children under two years of age (84.8% and 84.5%, respectively). The number of RV positive and negative children hospitalized and those who visited the ER for GE stratified by age groups is shown in Figure 1Table 2. Ninety-five children (28.6%) were RV positive, of which whom over 80% occurred were in children aged less than 24 months (Table 2). The highest number of RVGE cases was reported seen in children aged 6–11 months (40.0% [38/95]) (Figure 1).

Table 2: Distribution of GE cases by ER visits, hospitalizations and RV status by age groups (N = 332)

[a]Number of children

[b]Number of children in a given category
[c]n / N x 100

The seasonal distribution of RV-attributable GE hospitalizations attributed to RV infection is shown in Figure 21. The number of GE cases was highest in July and August 2008 and the percentage of RV positive cases was highest in January 2008.

Clinical characteristics of GE and RVGE hospitalizations

Among both RV positive and RV negative children, severe GE (score ≥11 on the Vesikari scale) was reported recorded in 64.2% (61/95) and 55.5% (131/236) children before hospitalization, respectively (Table 23).

The percentage of children recording the GE-associated symptoms associated with GE (diarrhea, vomiting and fever) was similar across RV positive and negative groups before hospitalization. However, a significant (P-value = 0.0037) association between vomiting and RV positive status was observed prior tobefore hospital admissionization (Table 23).

Nutritional status based on weight indicated that children who were adequately and moderately malnourished children were distributed similarly across both RV positive and negative groups. However, a higher number of severely malnourished children were was observed in the RV negative group (Table 23).

Oral rehydration was the most commonly used treatment ~~used~~ for GE in both RV positive and negative groups (70.5% and 75.8%, respectively), followed by intravenous rehydration therapy (54.7% and 53.0%, respectively).

At discharge, the majority of children among both RV positive and ~~RV~~ negative groups (71.6% [68/95] and 78.0% [184/236], respectively) had ongoing GE~~,~~. Eight RV negative children ~~while~~ (3.4% ~~(8/236)~~ ~~of children in the RV negative group~~ died~~,~~ of whom ~~(Table 3). Among the children who died,~~ all but one ~~children except one~~ (87.5% [7/8]) were severely malnourished. The unadjusted odds ratio ~~estimation~~ estimate indicated that ~~the~~ severely malnourished children had 22.2 (95% CI: 2.5–198.8) times higher risk of dying ~~when~~ as compared to children with adequate nutritional status (P-value = 0.0056) (Table 2).

Table ~~3~~2: Clinical characteristics of children by RV status (N=331)

Characteristic	RV positive (N[a] = 95) n[b] (%[c])	RV negative (N = 236) n (%)	P-value
Severity[d] before hospitalization			
Mild (<7)	6 (6.3)	27 (11.4)	
Moderate (7–10)	28 (29.5)	78 (33.1)	0.2300*
Severe (≥11)	61 (64.2)	131 (55.5)	
~~**Severity during hospitalization**~~			
~~Mild (<7)~~	~~28 (29.5)~~	~~55 (23.3)~~	
~~Moderate (7–10)~~	~~36 (37.9)~~	~~115 (48.7)~~	~~0.1946*~~
~~Severe (≥11)~~	~~31 (32.6)~~	~~66 (28.0)~~	

Symptoms before hospitalization			
Diarrhea	95 (100.0)	235 (99.6)	1.0000**
Vomiting	81 (85.3)	170 (72.0)	0.0037**
Fever	44 (46.3)	116 (49.2)	0.8557*
~~**Symptoms during hospitalization**~~			
~~Diarrhea~~	~~90 (94.7)~~	~~229 (97.0)~~	~~0.3359**~~
~~Vomiting~~	~~42 (44.2)~~	~~95 (40.3)~~	~~0.8065**~~
~~Fever~~	~~47 (49.5)~~	~~118 (50.0)~~	~~0.9639**~~
~~**Treatment received before hospitalization**~~			
~~Oral rehydration~~	~~39 (41.1)~~	~~96 (40.7)~~	~~0.7580*~~
~~IV rehydration~~	~~1 (1.1)~~	~~1 (0.4)~~	~~0.5810**~~
~~Antibiotics~~	~~25 (26.3)~~	~~47 (19.9)~~	~~0.3701*~~
~~**Treatment received during hospitalization**~~			
~~Oral rehydration~~	~~67 (70.5)~~	~~179 (75.8)~~	~~0.2049**~~
~~IV rehydration~~	~~52 (54.7)~~	~~125 (53.0)~~	~~0.9507**~~
~~Antibiotics~~	~~30 (31.6)~~	~~81 (34.3)~~	~~0.4843**~~
Classification of nutrition			
Overweight	5 (5.3)	8 (3.4)	0.1981*
Adequate (Normal)	66 (69.5)	152 (64.4)	
Moderately malnourished	15 (15.8)	32 (13.6)	
Severely malnourished	9 (9.5)	44 (18.6)	
Outcome at discharge			
Recovered	27 (28.4)	40 (16.9)	0.0145**
Ongoing GE	68 (71.6)	184 (78.0)	
Transferred	0 (0.0)	4 (1.7)	
Died	0 (0.0)	8 (3.4)	

Note1: One child was excluded from analysis as RV status was not determined.
Note 2: Nutritional status were derived using the weight-for-age Z-scores (WAZ)
[a]Number of children
[b]Number of children in a given category
[c]n / N x 100
[d]Severity using the 20-point Vesikari scale
*chi square P-value
**Fisher Exact test P-value

RV type distribution

Fifty three of ~~the~~ 95 RV positive stool samples were assessed for RV type in this study. ~~Among these, t~~The most prevalent RV types were G1P[8] wild-type (34.0% [18/53]) and G8P[6] (18.9% [10/53]). Mixed RV types were detected in 30.2% (16/53). The RV vaccine strain (G1P[8] vaccine strain) was not detected in any ~~of the~~ sample~~s~~. The other ~~common RV types~~ detected RV types are ~~depicted by decreasing order of prevalence~~ shown in Figure 3~~2~~.

DISCUSSION

This study ~~describing~~ into RVGE disease burden found that RV infection is the primary cause of hospitalization due to GE in children aged less than five years in the Republic of ~~Côte d'Ivoire~~Ivory Coast.

We ~~detected~~ identified RV in 30.1% and 26.9% children either hospitalized ~~and~~ or visiting ~~the~~ an ER for AGE, respectively~~,~~. ~~which~~ This is consistent with an earlier epidemiological study in Abidjan that demonstrated the general prevalence of RVGE in children ~~less~~ younger than five years ~~of age~~ to be 27.9% between 1997 and 2000.[21] In addition, a review of published studies (1975 to 1992) of RVGE in Africa detected RV in 24–29% of children hospitalized for diarrhea.[9]

In the present study, RV disease burden was predominantly observed among young children (over 90.0% [87/95]~~(~~ were aged ~~6–~~up to ~~24~~ 23 months), which is ~~in line~~consistent with previous studies conducted across the African continent.[9] A study conducted in Nigeria showed that over 90.0% of RVGE positive cases were observed in children aged less than two years [24] and two independent studies conducted in Egypt (1995–1996) [25] and Libya (October 2007–September 2008) [26] indicated that the incidence of RVGE was highest among children aged 6–11 months; all comparable to the results of the present study.

~~-~~As observed in previous studies conducted in sub-Saharan Africa ~~n regions~~ between 1975 and 1992,[9] most GE cases in this study were observed between July and August ~~of~~ 2008.

Almost all children who died following AGE ~~cases~~ in this study were severely malnourished, indicating the importance of nutritional status in potentially determining the outcome of AGE. Previous reports substantiate these findings where malnourishment has been associated with a considerable risk of diarrhea-associated mortality.[27, 28]

~~Circulation~~ The circulation of mixed RV types in the African countries ~~have~~ has been previously reported ~~previously,~~.[29, 30] ~~and i~~In this study~~, a~~, although wild-type G1P[8] was the most commonly detected (34.0% [18/53]) RV type, several (30.2% [16/53]) mixed RV types were detected ~~in this study~~. The proportion of mixed RV types observed in this study is comparable to that reported by the WHO's RV surveillance in the African Region.[31] In this report, nearly 42% of the circulating RV types during 2006–2009 comprised of mixed RV types.[31]

There is no available anti-viral therapy for RV infection [~~31~~32] and ~~the~~ RVGE management ~~of RVGE~~ predominantly includes ~~replacement of~~ fluid~~s~~ and electrolyte replacement~~s~~ and improvements in sanitation and water supply.[~~32~~33] Antibiotic treatment is not justified during RVGE and its use is limited to cases with documented bacterial co-infection. However, it has been suggested that improvements in hygiene and provision of safe water ~~supply~~ may not be as effective in the prevention of RVGE as they are to ~~other causes of~~ GE due to other causes.[~~32~~33]

Previous studies have established that RV vaccination confers protection against severe RVGE ~~disease~~ and has helped relieve the global burden of this

disease.[3334–3637] and These effects have been observed more specifically in similar settings in Asia, Africa and Latin America.[29, 3738, 3839] The efficacy of RV vaccines against severe RVGE has been found to be 59% in South Africa and Malawi [3940] and 64% in Kenya, Ghana and Mali.[4041] RV vaccination may therefore represent the most effective primary public health intervention against RVGE. Indeed in 2009, the World Health Organization (WHO) recommended the inclusion of RV vaccines in the routine childhood vaccine programs of all countries.[4142] In the Republic of Côte d'Ivoire, RV vaccines are available in the private sector in the Republic of Ivory Coast, but ; however, no RV vaccine is currently included in the universal mass vaccination program.

This study provided baseline epidemiological dData presented in this study that will highlight allow policy makers to assess the magnitude of the RV-associated disease burdenRV problem and and might allow policy makers to determine the need for the to implementation of prevention strategies in the Republic of Côte d'IvoireIvory Coast. The Indeed, the inclusion of a RV vaccine, as a prevention strategy, might aid help to reduce the burden of AGE and AGE-associated hospitalizations.

The results of this study need to be interpreted in the light of several strengths and limitations. Among the strengths, the systematic approach followed in this study to enroll identify children by checking the hospital and ER logbooks enabled easy identification of AGE cases using standard case definitions. Secondly, the study was conducted in reference reference hospitals that reported seeing over 1,300

AGE cases annually, which complies with the recommendations of WHO's generic protocol for hospital-based ~~surveillance to estimate the burden~~ of RVGE in children [~~42~~43]. By including multiple centers, these data more closely represent the local population ~~in Abidjan, Republic of Côte d'Ivoire~~. In addition, the quality check processes performed on the laboratory ~~testing~~ tests of RV positive samples provides credibility to the results.

However, the study ~~results need to be interpreted with caution due to some of the~~ does have limitations. As a large number of children who presented with GE were not enrolled and tested for RV, t~~T~~he possibility of selection bias might be considered ~~since a large number of children presenting with GE were not enrolled and subsequently not tested for RV~~. ~~Hence, the~~ Our reported prevalence of RVGE might have been affected by ~~the selection of~~ selecting only severe GE cases with more severe disease characteristics, including longer hospital stays. Nonetheless, this study provides a realistic picture of the role of RV among more severe cases of RVGE, which incur substantial direct and indirect medical costs and impact public health in this setting. ~~In addition~~It should be noted that~~,~~ most of the subjects who were not enrolled ~~either~~ were either not captured during surveillance or ~~were~~ did not consent~~ed~~ to participate in the study. Secondly, only 53 out of 95 RV positive stool samples were available for strain identification which limits the possibility of describing the circulating strains. Nevertheless, by using a reference laboratory with validated techniques and experience for PCR confirmation, it was possible to provide accurate estimates for the identified strains. Lastly, firm conclusions

regarding the seasonality of RV and the variation in circulating RV strains could not been ~~considered~~ drawn as the surveillance activities were conducted for just one year following recommendations from WHO.[43] Nevertheless, routine surveillance is warranted as rotavirus circulation might vary from one calendar year to another.

CONCLUSION

RVGE in children aged less than five years continues to be a major public health challenge in the Republic of ~~Côte d'Ivoire~~Ivory Coast. In our study, ~~T~~the disease, which peaked~~s~~ in July and August, mainly affected~~s~~ infants aged 6–11 months. Wild-type G1P[8] and G8P[6] were the most frequently reported RV types. The inclusion of a RV vaccine into local preventative programs ~~disease in the Republic of Côte d'Ivoire~~ might therefore help to reduce the disease burden of RVGE.

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AKC was the principal investigator and contributed to the conception, design, analysis and interpretation of the study. AKV and YAJ coordinated the study together with AKC and contributed to the interpretation of the results. All authors participated in the development of this manuscript.

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Competing interests

All the authors have no competing interest to declare.

Trademark

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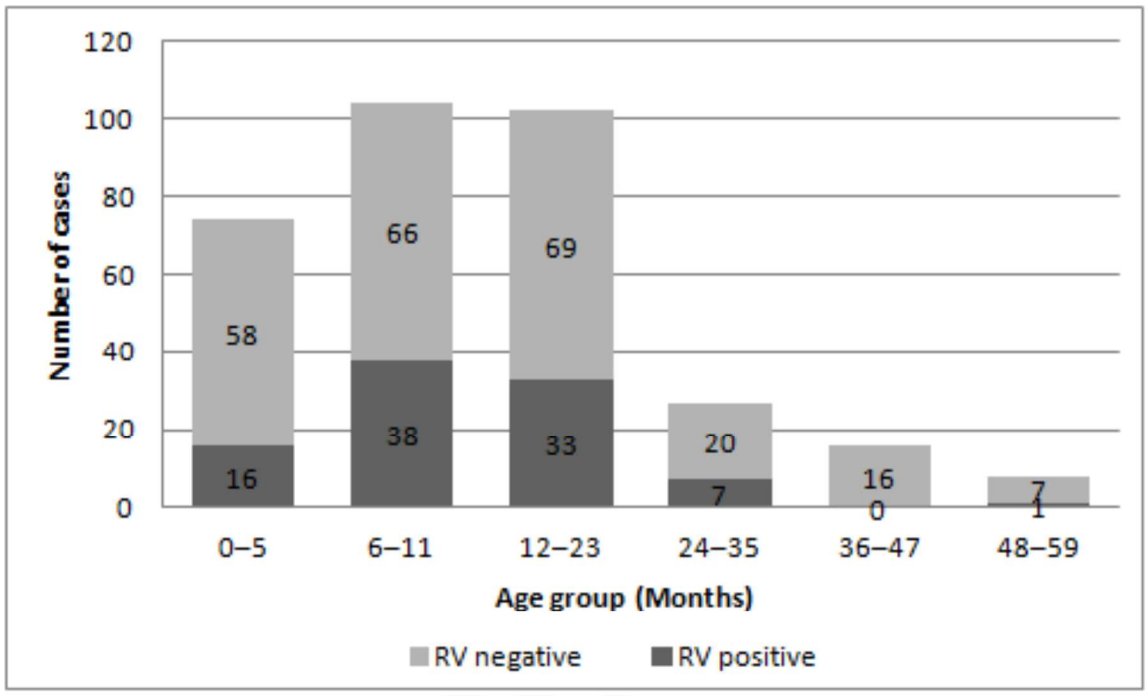
Figure 1: Distribution of GE cases by RV status by age groups (N = 332)



Note: RV status of one subject in the age group 0–5 Months was unknown

Figure 2: Seasonality of acute GE and RVGE hospitalizations (N=331)

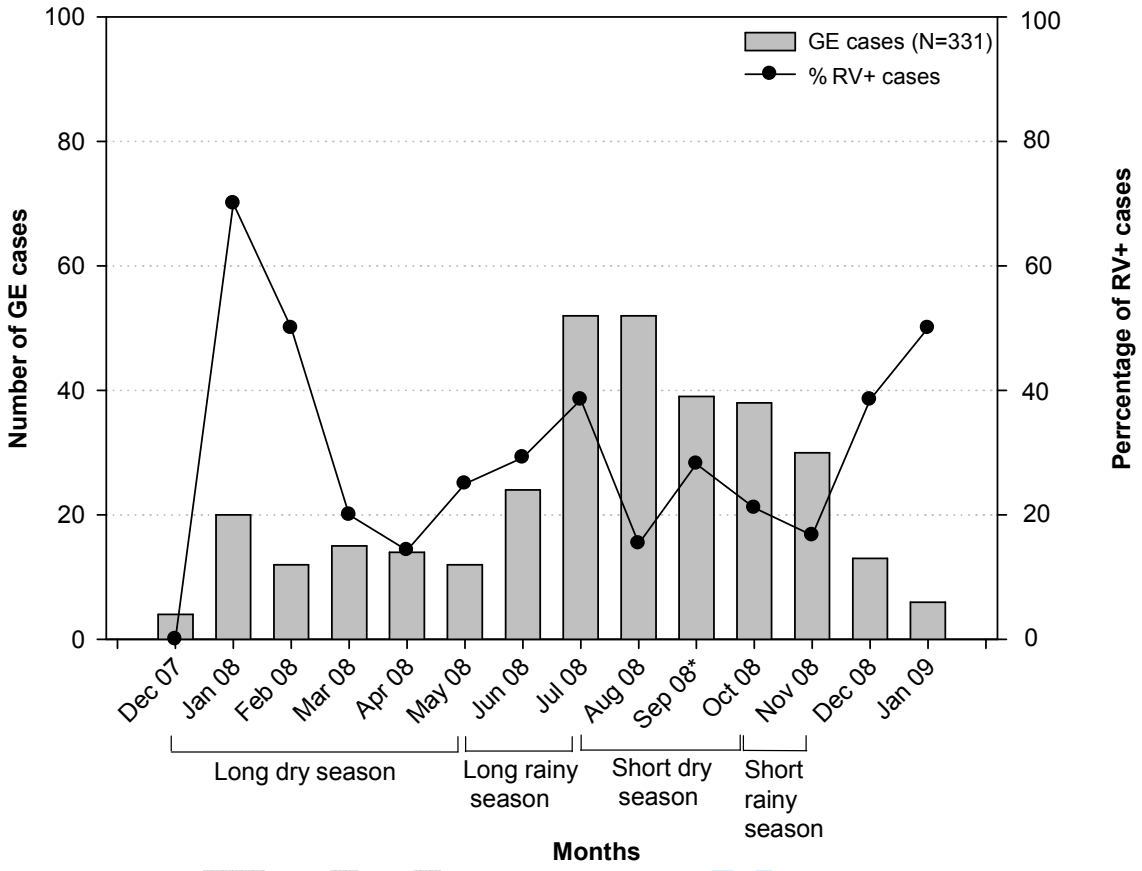


Figure ~~2~~3: Distribution of RV G and P types (N=331)