Incidence and Clinical Characteristics of Group A Rotavirus Infections among Children Admitted to Hospital in Kilifi, Kenya

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Abbreviations: CI, confidence interval; DSS, demographic surveillance system; GARV, group A rotavirus; IQR, interquartile range; KDH, Kilifi District Hospital; MUAC, mid-upper arm circumference; OR, odds ratio; WHO, World Health Organization

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ABSTRACT

Background

Rotavirus, predominantly of group A, is a major cause of severe diarrhoea worldwide, with the greatest burden falling on young children living in less-developed countries. Vaccines directed against this virus have shown promise in recent trials, and are undergoing effectiveness evaluation in sub-Saharan Africa. In this region limited childhood data are available on the incidence and clinical characteristics of severe group A rotavirus disease. Advocacy for vaccine intervention and interpretation of effectiveness following implementation will benefit from accurate base-line estimates of the incidence and severity of rotavirus paediatric admissions in relevant populations. The study objective was to accurately define the incidence and severity of group A rotavirus disease in a resource-poor setting necessary to make informed decisions on the need for vaccine prevention.

Methods and Findings

Between 2002 and 2004 we conducted prospective surveillance for group A rotavirus infection at Kilifi District Hospital in coastal Kenya. Children $<$ 13 y of age were eligible as "cases" if admitted with diarrhoea, and "controls" if admitted without diarrhoea. We calculated the incidence of hospital admission with group A rotavirus using data from a demographic surveillance study of 220,000 people in Kilifi District. Of 15,347 childhood admissions 3,296 (22%) had diarrhoea, 2,039 were tested for group A rotavirus antigen and, of these, 588 (29%) were positive. 372 (63%) rotavirus-positive cases were infants. Of 620 controls 19 (3.1%, 95% confidence interval [CI] 1.9–4.7) were rotavirus positive. The annual incidence (per 100,000 children) of rotavirus-positive admissions was 1,431 (95% CI 1,275–1,600) in infants and 478 (437–521) in under-5-y-olds, and highest proximal to the hospital. Compared to children with rotavirus-negative diarrhoea, rotavirus-positive cases were less likely to have coexisting illnesses and more likely to have acidosis (46% versus 17%) and severe electrolyte imbalance except hyponatraemia. In-hospital case fatality was 2% among rotavirus-positive and 9% among rotavirus-negative children.

Conclusions

In Kilifi $>$ 2% of children are admitted to hospital with group A rotavirus diarrhoea in the first 5 y of life. This translates into over 28,000 vaccine-preventable hospitalisations per year across Kenya, and is likely to be a considerable underestimate. Group A rotavirus diarrhoea is associated with acute life-threatening metabolic derangement in otherwise healthy children. Although mortality is low in this clinical research setting this may not be generally true in African hospitals lacking rapid and appropriate management.

The Editors' Summary of this article follows the references.

Introduction

Rotavirus is a major cause of severe diarrhoea worldwide causing in excess of 2 million hospitalisations per annum in under-5-y-old children [1], and group A rotavirus (GARV) is responsible for the vast majority of this disease [2]. In terms of both morbidity and mortality, the greatest burden of GARV diarrhoea falls on young children living in less-developed countries [1,3], with Africa only second behind the Indian subcontinent in suffering the major disease impact [1]. Two vaccines directed against this virus have been shown to be safe and highly effective [4,5], and trials of effectiveness are now in progress in sub-Saharan Africa. Evidence-based decisions regarding the wide-scale use of rotavirus vaccine intervention will benefit from accurate baseline estimates of the incidence and clinical characteristics of GARV in representative target populations [6,7].

Considerable effort has been expended in defining the burden of GARV-associated diarrhoeal disease burden in Africa. A recent review of data from 14 countries within the region reported a median prevalence of GARV in children admitted to hospitals with diarrhoea of 24% (range 13%–55%), 81% in children < 12 mo of age [8]. In Kenya, GARV has been identified in 14%–39% of hospital diarrhoea cases [9–11]. More recently rotavirus surveillance has intensified through the support of the African Rotavirus Network [12] and Rotavirus Vaccine Program [13]. Nevertheless, there is a remarkable paucity of data on GARV incidence where the population from which the patients arise is demographically well defined. Furthermore, the clinical spectrum of GARV presentations is not well characterised. Accurate incidence estimation and clear case definitions are vital components for the evaluation of vaccine trial planning and programme evaluation. The objectives of this study were to define these components among paediatric inpatients in Kilifi.

Methods

Study Location and Population

The study was conducted at Kilifi District Hospital (KDH) in a rural area on the coast of Kenya. The population of Kilifi District are predominantly subsistence farmers of the Mgiriama tribe. Malaria transmission occurs in this area throughout the year, with peaks in November–January and May–August following seasonal rains. The paediatric wards at KDH include a 36-bed general ward and a six-bed high-dependency unit, which together admit over 5,000 children each year. A standardized clinical history, examination, and routine set of investigations (haematology, malaria parasite microscopy, and blood culture) are conducted on all admitted children [14–17] and the data entered directly into a computer database. Further investigations, including blood gas and biochemical analysis, are undertaken at the discretion of the admitting clinician and dependent on the needs of research studies in progress.

Since 2000 a demographic surveillance system (DSS) has followed a population of approximately 220,000 individuals residing in the area close to KDH [18]. The DSS area encompasses 891 km^2 and includes 15 administrative locations, which are further divided into 40 sublocations (Figure 1). This area included the residences of 80% of children admitted to KDH in the period 1998–2000. Every household was mapped and censused in 2000–2001 and was re-enumerated at subsequent visits; in total there have been ten enumeration rounds to-date, six occurring during the present 3 y study. A resident was defined as an individual who lives (sleeps more than 50% of nights) in the identified homestead or who intends to live there for a period of ≥ 3 mo and has already spent at least one night there. Births, deaths, and in- and out-migration events are recorded at re-enumeration visits; births and deaths among children are also recorded at the maternity department, vaccine clinic, and wards of KDH. All sources of demographic data are uploaded within 48 h to an integrated database system. From 16 April 2002 we have attempted to match each child admitted to KDH paediatric ward to the register of DSS residents to create accurate correspondence between numerator and denominator data for incidence estimates.

Rotavirus Surveillance

All children aged < 13 y admitted to the wards of KDH with a history of diarrhoea between 01 January 2002 and 31 December 2004 were eligible for inclusion in the study. These children are termed "cases." Diarrhoea was defined as passing three or more loose stools during the preceding 24 h. To estimate the prevalence of GARV infection in the absence of diarrhoeal disease we studied a group of children who were admitted to the ward but who did not have a history of diarrhoea; these patients are termed "controls" in the study. Controls were contemporaneous to cases, randomly selected in a ratio of one control to each three cases of diarrhoea, with frequency matching to diarrhoea cases by age class. Stool samples were collected as soon as possible after completion of the recruitment process. To prevent possible confusion from nosocomial transmission, diarrhoea cases and nondiarrhoea controls became ineligible for recruitment 24 h after admission.

HIV diagnostic counselling and testing were not established in the wards at the time of this study and approval was not sought to determine the HIV status of the study patients. Written informed consent was obtained from the parent or caretaker of each participant. Ethical approval was granted for the study by the Kenyan National Research Ethical Committee and by the Coventry Research Ethics Committee, UK.

Laboratory Analysis

Stool samples were stored at −80 °C until shipment on dry ice for screening at the MRC Diarrhoeal Pathogens Research Unit, South Africa. GARV antigen testing was conducted using an enzyme immunoassay (IDEIA Rotavirus, DakoCytomation) according to the manufacturers instructions. GARV-positive samples from controls were tested for viral genome pattern by PAGE as described previously [19].

Data Analysis

Analyses were performed by use of STATA v8.2 (StataCorp). Incidence was defined as the number, among residents, of cases per 100,000 person-years of observation within age and location strata, with Poisson-based 95% confidence intervals (CIs). Person-years of observation were defined as the midstudy resident population multiplied by the number of years of linked surveillance (2.71 y, i.e., 16 April 2002 to 31 December 2004). The resident population of the DSS at the

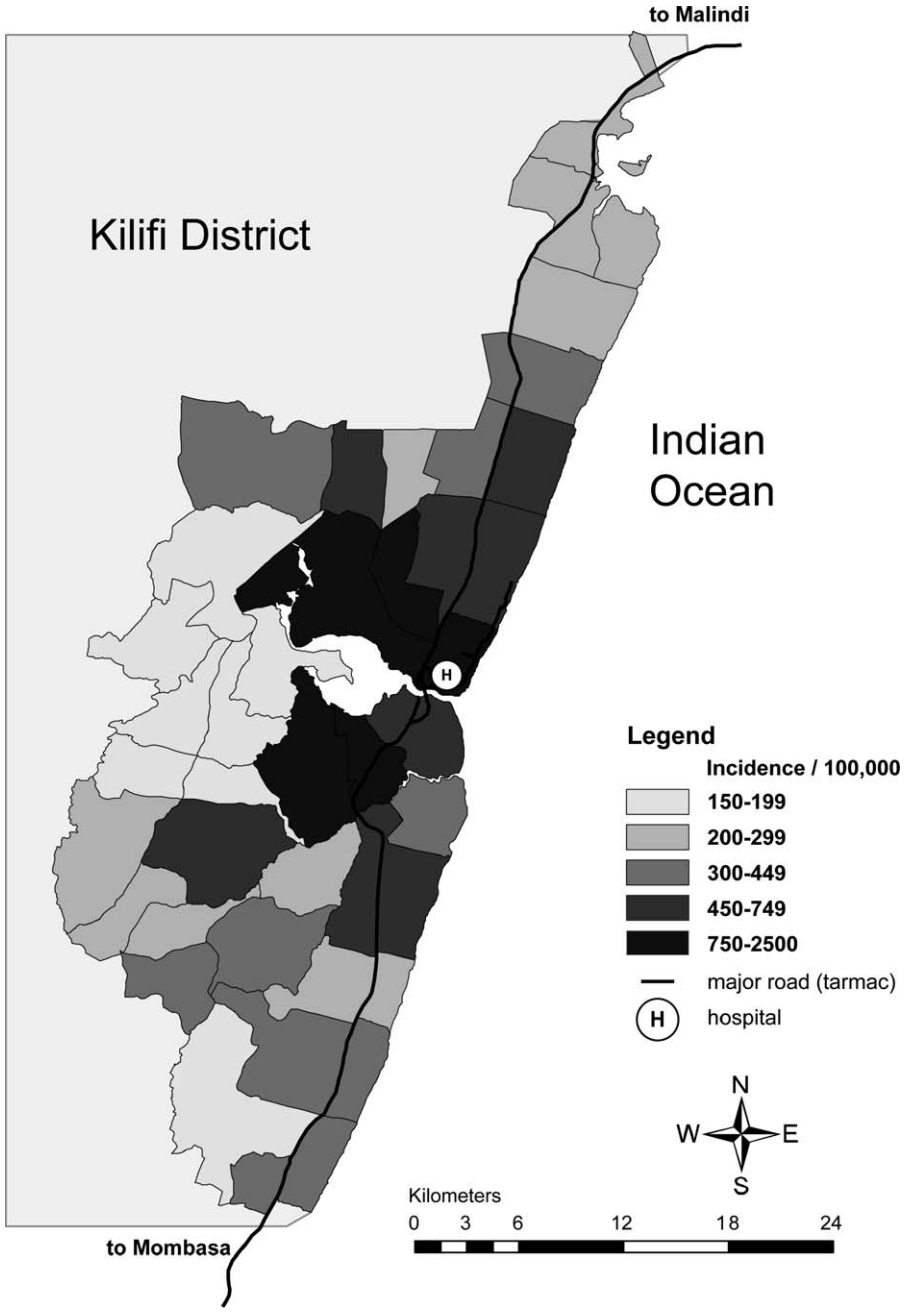

Figure 1. Map of Kilifi Demographic Surveillance System (DSS), Showing the Under-5-Year-Old Incidence (Per 100,000 Per Year) by Sublocation of GARV-Positive Diarrhoea Admissions to Kilifi District Hospital (H), 2002–2004

Sublocation data was pooled with nearest neighbour data where diarrhoea admissions in children under 5 y was less than 20 cases over the period of surveillance. (Using DSS data from Figure 2 of reference [34].)

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midpoint of the study (24 August 2003) was interpolated from the linear equation determined by regressing population size ($\log_{10}$) for all ten enumeration rounds against the mid-date of each round. The midstudy population size for a sublocation was estimated as the midpoint resident population weighted by the fraction of individuals within that sublocation at the enumeration round with mid-date 30 May 2003. A sublocation was defined as near to the district hospital if part of its boundary fell within a circle of 5 km radius with KDH at its centre. The population of resident under-5-y-olds within this area represented 42% of the total in the DSS, and accounted for 43% of all resident diarrhoea admissions. Among patients with diarrhoea we examined the association between rotavirus infection and a range of clinical signs and symptoms, and coexisting illnesses. We defined severe malnutrition using a combination of mid-upper arm circumference (MUAC), visible severe wasting, and bipedal oedema [20]. The diagnosis of severe pneumonia, very severe pneumonia, and shock followed modified WHO definitions [21,22]. Further categorisations on the basis of clinical and laboratory findings were as described previously [23,24]. Proportions were compared using the Fisher exact test (two-tailed) with exact 95% CIs and

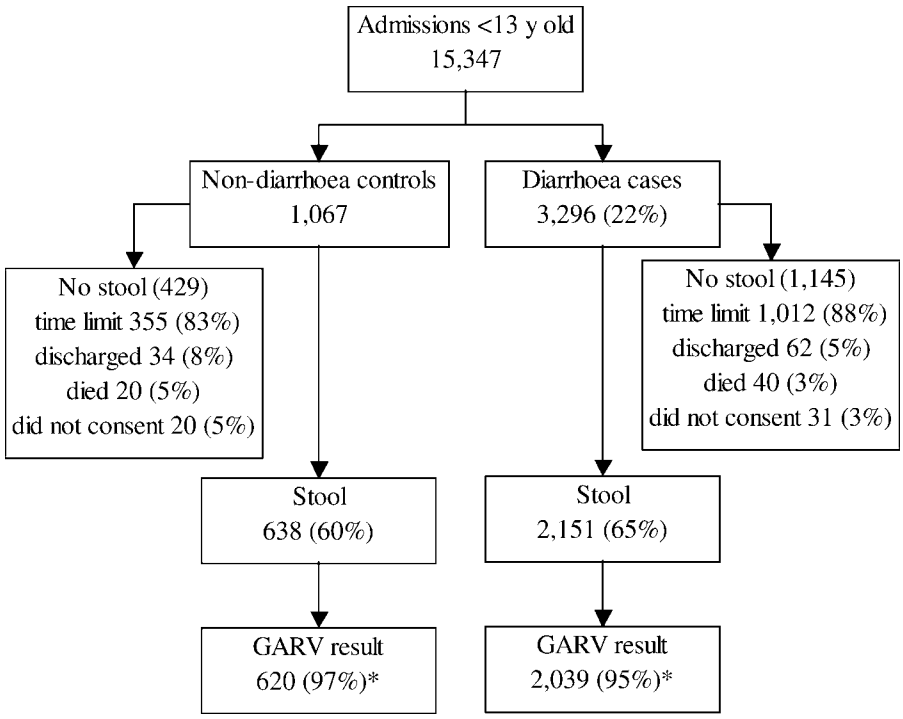

Figure 2. Flow Diagram Summarising Case and Control Sampling from Childhood Admissions to Kilifi District Hospital, 2002–2004

Percentages within a box refer to the proportion sampled from the preceding box, except where describing the breakdown of reasons why stools were not collected (entitled "No stool"). "Time limit" indicates children who ceased to be eligible because they failed to provide a stool sample within 24 hours of admission. Absence of laboratory results for stool samples collected (*) was due to insufficient sample or mismatch of laboratory and admission numbers. In total 1,257 children with diarrhoea were not tested (NT) for GARV.

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equality of distributions evaluated using the Wilcoxon rank-sum test. Adjusted odds ratios (ORs) were determined using logistic regression.

Results

Over the 3-y period 15,347 children aged < 13 y of age were admitted to KDH. There were 3,296 diarrhoea cases with a median age of 13 mo (interquartile range [IQR] 8–23 mo); 1,397 (42%) were female. For 35% (1,145) of cases a stool sample was not collected, for the reasons detailed in Figure 2, with the most important being a failure to provide a sample within the 24 h time limit postadmission. Relative to those who did provide a stool specimen, those who did not were more likely to be admitted directly to the high-dependency ward (15% versus 4%, $p < 0.001$) and to die before discharge (13% versus 7%, $p < 0.001$). One hundred twelve diarrhoea cases who provided a stool sample had no GARV test results. An analysis of the possible bias upon rotavirus incidence and severity characteristics from omission of the 1,257 eligible cases who were not GARV tested, provided evidence that the influence was not substantial (see Table S1 and Text S1). There were 12,051 patients admitted without diarrhoea, of whom 1,067 were selected as controls. The median age of the control group was 11 mo (IQR 4–22 mo); 455 (43%) were female. Reasons for failure to collect a stool sample from controls were in similar proportions to cases (Figure 2). The severity differential in sampled and nonsampled controls was also similar to that of cases. Among children tested for GARV antigen in the diarrhoea and control groups, the age (median 12.5 versus 12.2 mo, $p = 0.219$) and sex (proportion female 43% versus 42%, $p = 0.926$) distributions were very similar.

GARV-Associated Diarrhoea: Seasonality and Age Distribution

Twenty-nine percent (588/2,039) of stool samples tested positive for GARV antigen (Table 1). This proportion did not vary significantly by calendar year ($p = 0.686$) or by sex ($p = 0.199$). Variation in the monthly GARV-positive cases mirrored approximately the pattern of diarrhoea admissions but had no clear seasonal pattern or obvious association with weather indicators (see Figure S1). Of all diarrhoea cases 83% were aged 3–17 mo (Table 2) and the proportion of cases GARV positive was higher in this age group (37%) than among other children (14%). While 19% of cases under 3 mo old were GARV positive, only 3% of all GARV positives were found in this age group.

GARV in Children Admitted without Diarrhoea

Of the 620 control specimens, 19 (3.1%; 95% CI 1.9%–4.7%) tested positive for GARV. This proportion did not vary by calendar year or by sex. PAGE analysis identified GARV RNA in 14 (74%) of the 19 positives. A review of the clinical records confirmed that none of the GARV-positive controls gave a history of diarrhoea in the week prior to admission.

The Community Burden of GARV-Associated Diarrhoea

The incidence rates for admission to KDH with diarrhoea and with GARV-associated diarrhoea are shown in Table 1. We assume to be negligible the proportion of GARV-positive children whose diarrhoea was not the result of rotavirus

Table 1. The Incidence (Per 100,000 Per Year) of Severe Diarrhoea and GARV-Positive Severe Diarrhoea Estimated from Surveillance of Admissions to Kilifi District Hospital, Kenya 2002–2004

Age Group	% Cases GARV Positive	Resident Diarrhoea Admissions	Person-Years of Observation	Incidence of Diarrhoea (95% CI)	Incidence of GARV-Positive Diarrhoea[a] (95% CI)
Infants (<1 y)	38.1 (372/976)[b]	807	21,529	3,748 (3,494–4,016)	1,431 (1,275–1,600)
Young children (<5 y)	30.0 (587/1,954)	1,706	107,224	1,591 (1,516–1,668)	478 (437–521)
All ages (<13 y)	28.8 (588/2,039)	1,797	253,505	709 (676–742)	204 (187–223)

[a] % cases GARV positive × resident diarrhoea admissions/person-years of observation × 100,000. Estimated number of resident GARV cases rounded to nearest integer. Estimates are unadjusted for the suspected proportion (3%) of GARV positive cases for which the disease is not due to the GARV infection. It is assumed that the prevalence of GARV in diarrhoea cases not tested in this study is equivalent to that in the cases tested.
[b]Number of group A rotavirus–positive samples/total number of specimens tested between 01 January 2002 to 31 December 2004.
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infection, and as a consequence make no adjustment to these incidence figures to account for potential false-positive results. Incidence estimates assume that the proportion GARV positive in cases tested applies to all diarrhoea admissions whether or not tested. For children under 5 y of age, the incidence (per 100,000 per annum) of GARV-positive diarrhoea admissions was estimated at 478. For comparison, during the same period the incidence rates for admissions of under-5-y-olds with severe or very severe pneumonia, bacteraemia, or a final diagnosis that included malaria were 2,125, 325, and 2,639, respectively. Variation between sublocations of the DSS in the incidence of GARV-positive diarrhoea for children under 5 y is shown in Figure 1. For residents living near KDH the annual incidence of GARV-positive diarrhoea admissions in children < 5 y was estimated at 839 (95% CI 779–901) as opposed to 354 (95% CI 332–377) for residents from further away.

Severity of Diarrhoea and Concurrent Illness by Rotavirus Status

The clinical and laboratory features of GARV-positive and GARV-negative cases are compared in Table 3. Relative to GARV-negative cases, GARV-positive children presented with acute nonbloody diarrhoea or vomiting more frequently, and had a higher prevalence of life-threatening complications at admission including severe dehydration (sunken eyes), deep breathing (a correlate of metabolic acidosis), and severely perturbed biochemical parameters (hypernatraemia, hypokalaemia, severe metabolic acidosis, or elevated creatinine, but not hyponatraemia), all of which require prompt intravenous correction. Compared to the GARV-negative cases, GARV-positive children had a lower prevalence of concomitant illnesses including clinical pneumonia, malnutrition, and laboratory-confirmed malaria or bacterial infection (Table 3). The median age of GARV-positive cases (10 mo, IQR 7–15 mo) was significantly lower than that of GARV-negative cases (14 mo, IQR 9–25 mo) ($p < 0.001$). ORs for each feature, adjusted for potential confounding by age, retain the pattern described above (Table 3). The effect on this analysis of adjusting for distance from KDH (near versus far) was negligible and is not included.

Bacterial pathogens were isolated from the blood of 13/588 (2%) GARV-positive cases and 96/1451 (6.6%) GARV-negative cases (Table 3). Isolates from GARV-positive patients included group A β-haemolytic streptococci (2), *Staphylococcus aureus* (1), *Acinetobacter* sp. (5), *Pseudomonas* sp. (2), *Klebsiella* sp. (2), and *Salmonella* sp. (1). Those from GARV-negative cases included *Streptococcus pneumoniae* (22), *Escherischia coli* (21), and *Salmonella* sp. (21), the remainder comprising group A β-haemolytic streptococci (9), *Haemophilus influenzae* (7), *Acinetobacter* sp. (6), *S. aureus* (5), *Pseudomonas* sp. (4), *Campylobacter* sp. (2), *Klebsiella* sp. (1), *Shigella* sp. (1) and a gram-negative coccus (1). In four GARV-negative cases two species were coinfecting.

Table 2. Age Distribution of Paediatric Cases of Diarrhoea Tested for GARV and Those Found GARV-Positive from Admissions to KDH, Kenya between 01 January 2002 and 31 December 2004

Age Group (Years)	Diarrhoea Cases Tested	GARV Cases	Proportion GARV Positive	
			Within Age Group	Out of Total GARV
0–2	84	16	19%	3%
3–5	224	92	41%	16%
6–8	318	130	41%	22%
9–11	350	134	38%	23%
12–17	405	130	32%	22%
18–23	229	50	22%	9%
24–35	219	25	11%	4%
36+	210	11	5%	2%
Total	2,039	588	29%	100%

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Table 3. Clinical, Laboratory, and Outcome Characteristics, Stratified by GARV Status, in Paediatric Diarrhoea Admissions to Kilifi District Hospital, Kenya 2002 to 2004

Category	Feature	GARV-Positive Cases[a] (%), $n = 588$	GARV-Negative Cases[a] (%) $n = 1,451$	*p*-Value for Positive Versus Negative[b]	Adjusted OR (95% CI)[c]
Gastroenteric history	Acute diarrhoea (<14 d)	576 (98)	1,264/1,435 (88)	<0.001	5.38 (2.94–9.82)[d]
	Bloody diarrhoea	20 (3)	118 (8)	<0.001	0.49 (0.30–0.81)[e]
	Vomiting	515 (88)	882 (61)	<0.001	4.10 (3.09–5.35)[d]
Respiratory	Indrawing	90 (15)	277 (19)	0.048	0.65 (0.50–0.86)[e]
	Deep "acidotic" breathing	147 (25)	218 (15)	<0.001	1.53 (1.19–1.96)[d]
	Hypoxia (O_2 sat <90%)[f]	11 (2)	55 (4)	0.027	0.54 (0.27–1.7)
Cardiovascular and hydration	Decreased skin turgor	191 (32)	406 (28)	0.047	1.07 (0.87–1.34)
	Sunken eyes	343 (58)	536 (37)	<0.001	1.99 (1.62–2.44)[d]
	Capillary refill time ≥3 s	72 (12)	198 (14)	0.428	0.87 (0.65–1.18)
	Weak pulse volume	86 (15)	182 (13)	0.219	1.15 (0.86–1.54)
	Shock[g]	210 (36)	496 (34)	0.538	1.07 (0.86–1.31)
Neurological	Lethargy	120 (20)	197 (14)	<0.001	1.60 (1.23–2.08)[d]
	Prostration or coma	19 (3)	67 (5)	0.181	0.87 (0.50–1.50)
Laboratory	Acidosis (base deficit >15 mmol/l)	248/541 (46)	226/1,298 (17)	<0.001	3.41 (2.69–4.32)[d]
	Hypernatraemia (>145 mmol/l)	34/494 (7)	19/1,140 (2)	<0.001	3.53 (1.93–6.46)[d]
	Hyponatraemia (<125 mmol/l)	14/494 (3)	84/1,140 (7)	<0.001	0.42 (0.23–0.76)[e]
	Hypokalaemia (<3 mmol/l)	221/494 (45)	376/1,141 (33)	<0.001	1.53 (1.22–1.92)[d]
	Elevated creatinine (>80 μmol/l)[h]	87/482 (18)	156/1,116 (14)	0.040	2.29 (1.66–3.18)[d]
	Hypoglycaemia (<2.5 mmol/l)	11/548 (2)	60/1,321 (5)	0.008	0.86 (0.43–1.71)
	Leucocytosis (WBC $>12 \times 10^9$/l)[i]	210/575 (37)	711/1,420 (50)	<0.001	0.60 (0.48–0.74)[e]
Coexisting illness	Severe pneumonia[j]	54 (9)	205 (14)	0.002	0.51 (0.36–0.70)[e]
	Very severe pneumonia[k]	16 (3)	71 (5)	0.029	0.54 (0.31–0.96)[e]
	Malnutrition[l]	82 (14)	537 (37)	<0.001	0.35 (0.27–0.46)[e]
	Severe anaemia (Hb <5 g/dl)	6/575 (1)	89/1,420 (6)	<0.001	0.18 (0.08–0.41)[e]
	Malaria parasitaemia	65 (11)	386 (27)	<0.001	0.38 (0.28–0.51)[e]
	Bacteraemia (blood culture positive)	13 (2)	96 (7)	<0.001	0.37 (0.20–0.68)[e]
Outcome	Death	10 (2)	132 (9)	<0.001	0.23 (0.12–0.45)[e]
	Inpatient duration >12 d	20 (3)	229 (16)	<0.001	0.26 (0.16–0.41)[e,m]

[a]Number with characteristic and percentage (%) presented; denominator is *n* unless otherwise specified in column.
[b]Comparison of GARV-positive and -negative proportions, with probability *p*-value of Fisher exact test.
[c]Odds of feature in GARV-positive divided by odds in GARV-negative cases, adjusted for age class.
[d]Significant positive association.
[e]Significant negative association.
[f]Oxygen saturation measured by pulse oxymeter (Nelcor).
[g]Temperature gradient, capillary refill > 3 s, or weak pulse volume.
[h]Creatinine > 110 μmol/l if age < 12 mo.
[i]WBC > 15×10^9/l if age < 12 mo.
[j]History of acute cough or difficulty in breathing, and subcostal recession.
[k]History of acute cough or difficulty in breathing, and impaired consciousness or hypoxia.
[l]Small MUAC for age, bipedal oedema or visible severe wasting. Small MUAC was defined as ≤ 10th percentile calculated for all KDH admissions 2002–2004 generating the following cut-off values by age: 0–5 mo ≤ 7.7 cm, 6–23 mo ≤ 11.0 cm, 24–35 mo ≤ 11.6 cm, 36–59 mo ≤ 12.2 cm, ≥ 60 mo ≤ 12.8 cm (for comparable age classes these show close similarity to those previously defined [20]).
[m]Adjusted for age class and discharge status.
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Mortality and Duration of Hospital Inpatient Stay by GARV Status

The proportion of GARV-positive cases remaining in hospital for more than 12 d (3%) was significantly lower than that in GARV-negatives (16%) (Table 3). Mean durations of hospital stay were 5.2 d and 7.5 d, respectively. In-hospital mortality in GARV-positive cases was 2%, significantly lower than in GARV-negative cases (9%) (Table 3). Relative to GARV-negatives, the age-adjusted OR of death in GARV-positives was 0.21 (95% CI 0.11–0.41; $p < 0.001$). The differential in mortality is primarily attributable to the high prevalence of severe malnutrition amongst the GARV-negative group compared to GARV-positives (37% versus 14%, $p < 0.001$, Table 3), and concomitant higher case fatality in the GARV-negative, compared to GARV-positive, malnourished children (21% versus 6%, $p = 0.001$). Further analyses of factors associated with in-hospital mortality in diarrhoea cases are presented in Table S2 and Text S2.

Four of the GARV-positive children with diarrhoea who died had malnutrition and one had a lower respiratory tract infection. The mean annual number of in-hospital deaths among resident diarrhoea cases under 5 y old was 48, of which 3.6% were GARV positive. Similarly, the annual number of deaths in resident infant diarrhoea cases was 18, of which 4.9% were GARV positive. These data yield estimated rates (per 100,000 per year) of hospital deaths attributable to diarrhoea of 120 (95% CI 100–143) in children under 5 y, and 228 (168–301) in infants, and corresponding estimates of hospital deaths attributable to GARV-positive diarrhoea of 5 (2–11) and 9 (1–34), respectively (note that these are based on small numbers of deaths).

Discussion

In our study, conducted in a rural district hospital in Kenya over a 3-y period, GARV was identified in 29% of children admitted with diarrhoea. The prevalence was highest in the youngest children: 38% in those < 1 y of age and 30% in under-5-y-olds. We estimated the annual incidence (per 100,000 population) of GARV-associated hospitalisations with acute severe diarrhoea at 1,275–1,600 in children under 1 y of age, 437–521 in children under 5 y, and 187–223 in those under 13 y, similar figures to those reported in industrialised nations with greater access to health care and diagnostic facilities [1]. Our data suggest that in the area served by our hospital, over 1% of infants are hospitalised with severe GARV-associated diarrhoea each year. By 5 y of age, over 2% of children will have been hospitalised with GARV diarrhoea (Table 1); by extrapolation, therefore, given the under-5-y population of Kenya (5.98 million in 2005 [25]), in the nation as a whole an effective rotavirus vaccine could prevent in excess of 28,000 hospital admissions in this age group every year. Our incidence estimates include only the children who present to hospital with diarrhoea; the under-ascertainment implicit in this method is reflected by the fact that the estimated incidence was over 70% higher for the population immediately served by KDH than for the DSS as a whole. It is likely that our current study represents a conservative estimate of the true burden of rotavirus disease.

External validity of these data is an important consideration in making extrapolations. KDH paediatric care is unusually well resourced for a Kenyan district hospital. However, apart from mortality and in-patient stay, the characteristics of the study participants (detailed in Table 3) are determined at admission, and uninfluenced by in-patient management. Furthermore, there is no evidence that local knowledge of the high quality care at KDH influences admission rates. At the time of this study demographic and health indicators for Kilifi District were not dissimilar to much of Kenya [26].

Only a small proportion (3%) of children without diarrhoea (controls) were found to be GARV positive. This provides assurance that the vast majority of the observed GARV-associated severe diarrhoea is potentially GARV-vaccine preventable. Few studies have investigated the prevalence of rotavirus shedding in the absence of disease [27], and yet asymptomatic rotavirus infection [27–29] and prolonged excretion have both been reported in children [27,30,31], in particular in neonates. It is of interest that five of 19 positive controls in this study were less than 2 wk old, because subclinical infection and associated prolonged virus shedding, particularly within young infants, may play an important role in the spread of GARV infection. Consistent with previous studies [8] we found that the major burden (85%) of GARV diarrhoea fell on children under 18 mo of age, and over 60% of cases were in infants. Of importance to the delivery of a vaccine within the current immunization schedule, the proportion of cases in children under 3 mo old was only 3% and in those under 6 mo was 18%.

From the clinical perspective, we found that relative to GARV-negative cases, the GARV-positive children with diarrhoea were more ill on admission, but their clinical signs and symptoms were mainly reflections of fluid loss and electrolyte imbalance and, therefore, readily corrected with the good supportive care available at this hospital. The GARV-negative children admitted with diarrhoea were less acutely unwell at admission but had a higher incidence of coexisting illnesses, such as malnutrition, that were less readily treated and consequently had worse outcomes. Compared with early work in the US [32] we identify a similar clinical picture of higher prevalence of dehydration and vomiting, and short in-hospital stay, in rotavirus-infected relative to uninfected children, with similar age distribution of children with GARV infection but of lower prevalence. However, our findings of a marked differential in the degree of acidosis and electrolyte imbalance between the two groups were not previously identified. While we consider it unlikely that there was a substantial systematic bias in the distribution of severity characteristics (Table 3) attributable to the group of diarrhoea patients admitted who were not tested for GARV, or to patterns of admission related to distance, these are uncertainties that urge caution in the interpretation of the data.

A limitation with the present study is the bias inevitable with hospital-based surveillance in estimating community incidence of GARV severe diarrhoea and associated mortality. Such estimates are rooted in parental interpretation of what constitutes disease severe enough to warrant hospital attendance. Clearly, this will be linked to factors related to health care utilisation such as ease of access. Possible distortion of the distribution of severity in relation to distance, for example, resulting from children arriving from greater distances representing the more severe cases within their home areas, could lead to overestimation of GARV-positive diarrhoea severity relative to GARV-negative diarrhoea. A further limitation results from the failure to test around one-third of eligible children, and although its effect on the profile of GARV severe disease presented must be considered uncertain, we present some evidence that suggests it is not substantial.

Despite its importance in defining the need for rotavirus vaccines, data on GARV-associated mortality from developing countries are limited [33]. The low mortality reported for cases in the current study may well reflect the fact that these children were ostensibly healthy individuals, and the acute life-threatening metabolic derangements we commonly recorded were readily reversed in the well-functioning setting of KDH. In the majority of African hospitals, which do not provide immediate fluid and electrolyte resuscitation, it seems likely that mortality from GARV would be very much higher.

Supporting Information

Figure S1. GARV-Positive Diarrhoea Admissions to Kilifi District Hospital, Kenya, 2002–2004

Shown are monthly cases of diarrhoea (solid line), tests for GARV (dashed line), and GARV-positives (filled area), with corresponding mean daily rainfall (bars), maximum temperature (°C) (open diamonds), and relative humidity (closed triangles). Climate data was obtained from the national meteorological station Kilifi Institute of Agriculture, Kilifi, Kenya.

Found at doi:10.1371/journal.pmed.0050153.sg001 (23 KB PDF).

Table S1. Characteristics of Patients with Diarrhoea Who Were Tested or Not Tested (NT) for GARV, for Children with a Final Diagnosis That Includes Gastroenteritis (GE) at Kilifi District Hospital, Kenya, 2002–2004

Found at doi:10.1371/journal.pmed.0050153.st001 (49 KB DOC).

Table S2. Fatality Proportions in Paediatric Diarrhoea Admissions to Kilifi District Hospital, Kenya, with or without a Range of Clinical and Biochemical Features

Found at doi:10.1371/journal.pmed.0050153.st002 (46 KB DOC).

Text S1. Implications of the Failure to Collect and Test a Proportion of Diarrhoea Cases

Found at doi:10.1371/journal.pmed.0050153.sd001 (27 KB DOC).

Text S2. Indicators of High Risk of In-Hospital Mortality in Diarrhoea Cases

Found at doi:10.1371/journal.pmed.0050153.sd002 (26 KB DOC).

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Author contributions. DJN, AP, and TNW designed the study. JA and JKM undertook laboratory analysis, with training and guidance by IP and JD. Implementation, ward supervision and clinical data interpretation were undertaken by AP and KM. JAGS and TNW established the epidemiological DSS, which is coordinated by EB, and DSS data management is undertaken by HG. DJN led the statistical analysis with support from HG, JAGS, and TNW. DJN wrote the paper with critical revisions by JAGS, KM, and TNW. All authors made critical comments on the manuscript content, and all have approved the final submitted version.

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Editors' Summary

Background. Rotavirus is a leading global cause of diarrhea in babies and young children. Indeed, most children become infected at least once with this virus before their fifth birthday. Rotavirus is usually spread by children or their caregivers failing to wash their hands properly after going to the toilet and then contaminating food or drink. The symptoms of rotavirus infection—diarrhea, vomiting, and fever—are usually mild, but if the diarrhea is severe it can quickly lead to dehydration. Mild to moderate dehydration can be treated at home by providing the patient with plenty of fluids or with a special rehydration drink that replaces lost water and salts. However, for infants or toddlers who become severely dehydrated, rehydration with intravenous fluids (fluids injected directly into a vein) in hospital may be essential. Unfortunately, in developing countries in sub-Saharan Africa and elsewhere, this treatment is not widely available and every year more than half a million young children die from rotavirus infections.

Why Was This Study Done? Two rotavirus vaccines that could reduce this burden of disease are currently undergoing clinical trials to determine their effectiveness in sub-Saharan Africa. However, very little is known about the incidence of severe rotavirus infections among children living in this region (that is, how many children develop severe disease every year) or about the clinical characteristics of the disease here. Public-health officials need this baseline information before they can make informed decisions about the mass introduction of rotavirus vaccination and to help them judge whether the intervention has been successful if it is introduced. In this study, the researchers examine the incidence and clinical characteristics of rotavirus infections (specifically, group A rotavirus [GARV] infections; there are several different rotaviruses but GARV causes most human infections) among children admitted to the district hospital in Kilifi, Kenya.

What Did the Researchers Do and Find? During the 3-year study, more than 15,000 children under the age of 13 years were admitted to Kilifi District Hospital, a little under a quarter of whom had severe diarrhea. Nearly a third of the patients admitted with diarrhea who were tested had a GARV-specific protein in their stools (faeces); by contrast, only three in 100 children admitted without diarrhea showed any evidence of GARV infection. Two-thirds of the GARV-positive children were infants (under 1 year old). Using these figures and health surveillance data (records of births, deaths, and causes of death) collected in the area around the hospital, the researchers calculated that the annual incidence (per 100,000 children) of GARV-positive hospital admissions in the region was 1,431 for infants and 478 for children under age 5 years. Children with GARV-positive diarrhea were less likely to have other illnesses (for example, malnutrition) than those admitted with GARV-negative diarrhea, the researchers report, but were more likely to have life-threatening complications such as severe dehydration and salt imbalances in their blood. However, despite being more ill on admission, only 1 in 50 children with GARV-positive diarrhea died, compared to nearly 1 in 10 of the children with GARV-negative diarrhea; the GARV-positive children also left hospital quicker than those who were GARV-negative.

What Do These Findings Mean? These findings indicate that severe GARV-positive diarrhea is a major cause of hospital admission among otherwise healthy young children in the Kilifi region of Kenya. By the time they are 5 years old, the researchers estimate that 1 in 50 of the children living in this region will have been admitted to hospital with severe GARV-positive diarrhea. Because rotavirus vaccines prevent virtually all severe rotavirus-associated disease (at least in developed countries where their effectiveness has been extensively tested), the researchers estimate that vaccination might prevent more than 28,000 hospitalizations annually across Kenya; however, this prediction assumes that it is valid to extrapolate from the data obtained from this one district hospital to the entire country.

Additional Information. Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.0050153.

- The US Centers for Disease Control and Prevention provides information about rotavirus infections, surveillance, and vaccination (in English and Spanish)
- The UK National Health Service Direct health encyclopedia provides information on rotavirus infections
- MedlinePlus also provides links to information on rotavirus (in English and Spanish)
- The African Rotavirus Surveillance Network is working to improve knowledge about rotavirus infections in Africa
- The Rotavirus Vaccine Program aims to reduce child illness and death from diarrhea by increasing the availability of rotavirus vaccines in developing countries (in English and Spanish)
- PATH, a nonprofit international organization that aims to create sustainable, culturally relevant solutions to global health problems, also provides detailed information on rotavirus surveillance and disease burden