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Risk Factors for Mortality Among Children Younger Than Age 5 Years With Severe Diarrhea in Low- and Middle-income Countries: Findings From the World Health Organization-coordinated Global Rotavirus and Pediatric Diarrhea Surveillance Networks

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Background. Diarrhea is the second leading cause of death in children younger than 5 years of age globally. The burden of diarrheal mortality is concentrated in low-resource settings. Little is known about the risk factors for childhood death from diarrheal disease in low- and middle-income countries.

Methods. Data from the World Health Organization (WHO)-coordinated Global Rotavirus and Pediatric Diarrhea Surveillance Networks, which are composed of active, sentinel, hospital-based surveillance sites, were analyzed to assess mortality in children <5 years of age who were hospitalized with diarrhea between 2008 and 2018. Case fatality risks were calculated, and multivariable logistic regression was performed to identify risk factors for mortality.

Results. This analysis comprises 234 781 cases, including 1219 deaths, across 57 countries. The overall case fatality risk was found to be 0.5%. Risk factors for death in the multivariable analysis included younger age (for <6 months compared with older ages, odds ratio [OR] = 3.54; 95% confidence interval [CI], 2.81–4.50), female sex (OR = 1.18; 95% CI, 1.06–1.81), presenting with persistent diarrhea (OR = 1.91; 95% CI, 1.01–3.25), no vomiting (OR = 1.13; 95% CI, .98–1.30), severe dehydration (OR = 3.79; 95% CI, 3.01–4.83), and being negative for rotavirus on an enzyme-linked immunosorbent assay test (OR = 2.29; 95% CI, 1.92–2.74). Cases from the African Region had the highest odds of death compared with other WHO regions (OR = 130.62 comparing the African Region with the European Region; 95% CI, 55.72–422.73), whereas cases from the European Region had the lowest odds of death.

Conclusions. Our findings support known risk factors for childhood diarrheal mortality and highlight the need for interventions to address dehydration and rotavirus-negative diarrheal infections.

Keywords. rotavirus; pediatric; diarrhea; diarrheal mortality; global surveillance.

Diarrheal diseases are the second leading cause of death in children younger than 5 years of age worldwide, accounting for approximately 1.7 billion cases and 525 000 deaths each year [1]. Diarrheal deaths disproportionately affect those living in low- and middle-income countries (LMICs), with approximately 90% of diarrheal deaths occurring in sub-Saharan Africa and South Asia [2]. Diarrheal deaths have been decreasing over time largely because of advancements in treatment and introduction of rotavirus vaccines, improvements in nutrition, and improvements in water, sanitation, and hygiene [3]. Known risk factors for pediatric diarrheal mortality include malnutrition, wasting, early cessation of or not breastfeeding, not receiving

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any dose or the full dose of rotavirus vaccines, poor access to healthcare, and poor sanitation and hygiene [4–7].

The cause of diarrhea may be associated with mortality, and the causes of severe and fatal diarrhea are similar. There are many different pathogens that cause diarrheal infection, including viruses, bacteria, and parasites. Two landmark studies provided insight to the leading etiologies causing pediatric diarrheal disease in LMICs. The Global Enteric Multicenter Study found that the leading pathogens causing moderate-to-severe diarrhea in children <5 years of age were rotavirus, *Cryptosporidium*, *Shigella*, and enterotoxigenic *Escherichia coli* [8]. The Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health found that norovirus, rotavirus, *Campylobacter*, astrovirus, *Cryptosporidium*, and *Shigella* were the leading pathogens causing diarrhea in the first 2 years of life [9].

In this paper, we describe case fatality risks and risk factors for mortality from pediatric diarrhea in hospitalized children using data from the World Health Organization (WHO)-coordinated Global Rotavirus Surveillance Network (GRSN) and Global Pediatric Diarrhea Surveillance (GPDS).

METHODS

GRSN and GPDS comprise active, sentinel, hospital-based surveillance of children younger than age 5 years [10, 11]. GRSN, which has been in place since 2008, collects data on children hospitalized with acute watery diarrheal presentation. Diarrhea is defined as more than 3 loose stools in a 24-hour period. Stool specimens are collected within 48 hours of admission and are tested by enzyme-linked immunosorbent assay (ELISA) for rotavirus. All cases meeting the eligibility criteria, who were hospitalized with diarrhea at a sentinel surveillance site, are included in the surveillance network. As of 2018, there were 54 countries participating in GRSN, though the number of countries fluctuates year by year. Beginning in 2017, sites in 28 countries expanded the case definition from acute watery presentation to include bloody and persistent diarrhea to collect information on all pediatric diarrhea cases as part of GPDS. Children with previous hospitalization at the sentinel hospital, or children who transferred from other facilities, were excluded to omit nosocomial diarrhea infections and re-enrollment of ongoing/chronic infections. Because GRSN and GPDS are part of routine public health surveillance, they do not require human subjects ethical review.

The outcome of interest was death before discharge from the hospital. Discharge outcomes of transferred, left hospital, unknown, or missing were treated as missing.

An analysis dataset was created using data from both GRSN and GPDS as follows (Figure 1). For each site in a given year, the site-year data were excluded if more than 10% of the discharge status variable was missing, or if the site had fewer than 100 cases per year and/or cases were not collected in all 12 months of the year. Any cases with the outcome variable missing were excluded.

Case fatality risk (CFR) was defined as the number of cases that died divided by the number of cases with known vital status at discharge. Cases missing the outcome variable were excluded under the assumption that they were missing at random. Rotavirus cases were defined as being ELISA positive. Cases with indeterminate or missing rotavirus ELISA results were excluded for CFR calculations based on rotavirus

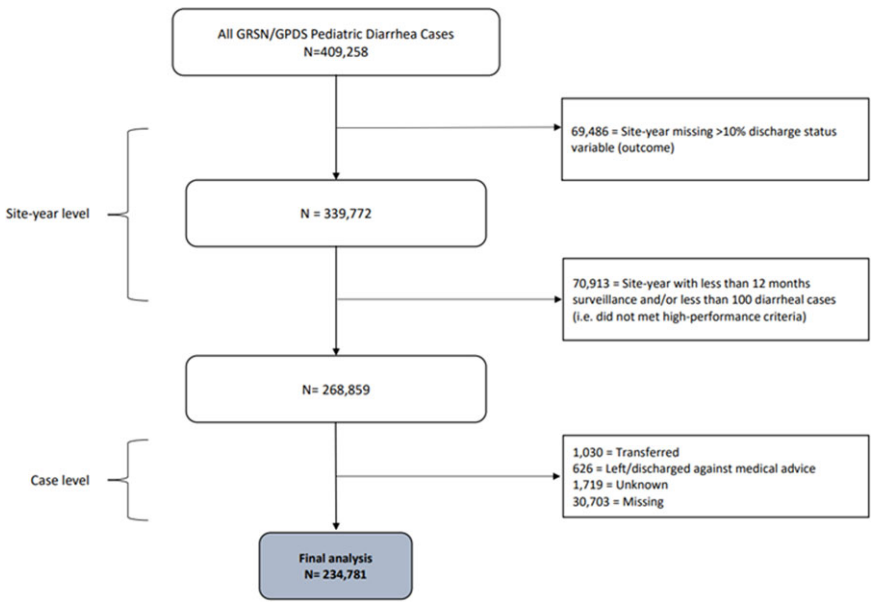

Figure 1. Schematic showing creation of dataset used for analysis.

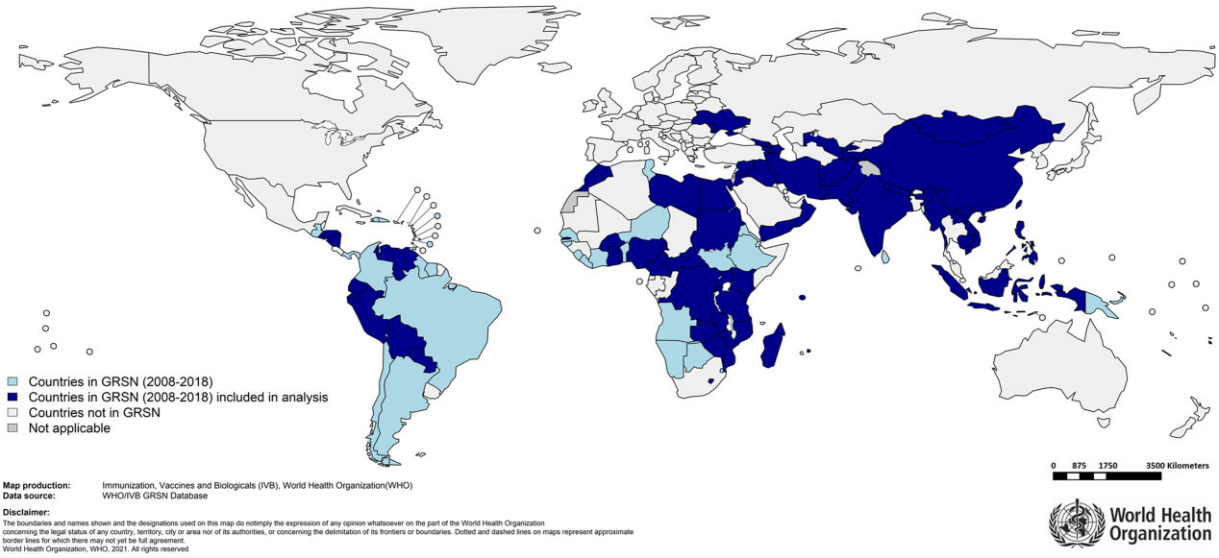

Figure 2. Countries that conducted surveillance through the World Health Organization-coordinated Global Rotavirus Surveillance Network (2008–2018) and those that have been included in the analysis.

positivity but not for CFR calculations based on all-cause diarrhea.

For regression analyses, cases with unknown vital status at discharge were excluded, under the assumption that they are missing at random. Simple logistic regressions were performed between each covariate of interest and the outcome variable, discharge status. The year variable was treated as linear to adjust for changes in mortality rate because of secular trends.

A multivariable logistic model with vital status at discharge as the outcome was created. Covariates were selected based on scientific and clinical evidence of their association with diarrheal mortality. Acute diarrhea is diarrhea that lasts less than 14 days, whereas persistent diarrhea lasts 14 or more days. Model testing for collinearity (using multiple linear regression to calculate the variance inflation factor), Akaike information criterion (using stepwise regression), and clinically relevant interaction terms (using likelihood ratio tests) was performed. None of the covariates showed collinearity in the model. The final model included the covariates mentioned previously as well as an interaction term between acute/persistent presentation and bloody/watery presentation. Variables with a P value $\leq .05$ were considered statistically significant.

Several subanalyses were performed: cases with acute watery presentation only, 2017 and 2018 cases only because the GPDS expanded case definition was introduced in those 2 years, and rotavirus positive cases only. Additionally, a stratified analysis by WHO region was performed to evaluate if there were differences in risk factor by region.

Demographic and clinical features for cases missing the outcome variable were evaluated to see if they were different from cases with the outcome variable. All analyses were performed using R version 3.5.3 software [12].

RESULTS

This analysis comprises 234 781 cases, including 1219 deaths, in 57 countries as shown in Figure 2. The total number of cases and years that countries in the analysis dataset contributed data are shown in Supplementary Table 1. The median time from hospital admission to death was 2 days. Children dying within 1 day of admission were similar in characteristics to children dying more than 1 day after admission (Supplementary Table 2).

The overall CFR for any pediatric diarrhea was 0.52% (1219 deaths among 234 781 total cases; 95% confidence interval [CI], .49–.55). The CFR for rotavirus-positive cases was 0.28% (177 deaths among 63 736 total cases; 95% CI, .24–.32). The CFR for pediatric diarrhea cases that were rotavirus negative was 0.61% (1042 deaths among 171 045 total cases; 95% CI, .57–.65). CFRs were highest in the younger ages, female cases, cases from the African Region, cases with persistent and watery presentation, cases with severe dehydration and without vomiting, and cases that tested rotavirus negative by ELISA (Table 1).

Use of rotavirus vaccine in the countries included in the analysis increased over time from 9% in 2008 to 68% in 2018. Rotavirus vaccine use in the countries included in this analysis is described in Supplementary Tables 3 and 4 [14]. Individual-level vaccination data were not available for most cases. To examine the effect of rotavirus vaccination, the

Table 1. Demographic and Clinical Characteristics of Cases

Variable	Died (n = 1219)	Alive (n = 233 562)	Case Fatality Risk
Age			
<6 mo	313	38 476	0.81%
6 mo–1 y	522	90 769	0.58%
1–2 y	295	65 638	0.45%
2–5 y	89	38 679	0.23%
Sex			
Male	663	136 354	0.49%
Female	555	97 038	0.57%
WHO region			
African Region (19 countries)	811	57 619	1.41%
Region of the Americas (8 countries)	139	14 364	0.97%
Eastern Mediterranean Region (12 countries)	162	47 132	0.34%
European Region (7 countries)	15	66 123	0.02%
South East Asia Region (4 countries)	7	5491	0.13%
Western Pacific Region (7 countries)	85	42 833	0.20%
Acute vs persistent			
Persistent (≥14 d)	28	1578	1.77%
Acute (<14 d)	1191	23 1984	0.51%
Bloody vs watery			
Watery	1156	22 7821	0.51%
Bloody	5	1726	0.29%
Vomiting			
Not vomiting	341	51 529	0.66%
Vomiting	804	173 332	0.46%
Dehydration type[a]			
None	99	21 689	0.46%
Some	338	105 913	0.32%
Severe	646	48 928	1.32%
Rotavirus positivity (using ELISA)			
Rotavirus positive	177	63 559	0.28%
Rotavirus negative	1042	170 003	0.61%
Year			
2008	37	5387	0.69%
2009	72	8733	0.82%
2010	167	13 914	1.20%
2011	111	13 368	0.83%
2012	46	14 958	0.31%
2013	86	21 617	0.40%
2014	177	30 682	0.58%
2015	162	35 749	0.45%
2016	166	37 387	0.44%
2017	122	29 810	0.41%
2018	73	21 957	0.33%

Abbreviation: ELISA, enzyme-linked immunosorbent assay.

[a]Dehydration severity is categorized based on WHO classification [13].

analysis was stratified by whether rotavirus vaccination had been introduced into the country in the year when the case was enrolled (Supplementary Table 5). Age was identified as a risk factor only for mortality in countries with rotavirus vaccination, but other risk factors were found to be similar regardless of rotavirus vaccine introduction.

Risk factors for death in the multivariable analysis included being of younger age (for <6 months, OR = 3.54; 95% CI, 2.81–4.50), female (OR = 1.18; 95% CI, 1.06–1.81), presenting with persistent diarrhea (OR = 1.91; 95% CI, 1.01–3.25), no vomiting (OR = 1.13; 95% CI, .98–1.30), severe dehydration (OR = 3.79; 95% CI, 3.01–4.83), and being negative for rotavirus on an ELISA test (OR = 2.29; 95% CI, 1.92–2.74; Table 2). Additionally, cases from the African Region had the highest odds of death (OR = 130.62 comparing the African Region with the European Region; 95% CI, 55.72–422.73), whereas cases from the European Region had the lowest odds of death. Increasing year was associated with decreased odds of death (OR = 0.94; 95% CI, .92–.96); however, when included in the model as a categorical variable, year was not statistically significant.

Subanalyses gave similar results to those observed in the full analysis (Supplementary Tables 6 and 7); therefore, the full model (as described previously) was used.

Multivariable logistic regression odds ratios stratifying by region were performed for 4 of the regions (Supplementary Table 8); analysis could not be performed for the South East Asia Region or the European Region individually because there were too few deaths in those regions. Across all regions, severe dehydration and a rotavirus-negative ELISA test were significantly associated with increased odds of dying. Younger age was significantly associated with increased odds of dying in the African Region, Region of the Americas, and the Eastern Mediterranean Region. Female sex was significantly associated with increased odds of dying in the Region of the Americas. Not vomiting was significantly associated with an increased odds of dying in the African Region and the Western Pacific Region. The trend of decreasing odds of death over time (years of study) was observed in the Region of the Americas, the Eastern Mediterranean Region, and the Western Pacific Region.

DISCUSSION

Despite advancements in diarrheal treatments, global use of rotavirus vaccines, and general sanitation, diarrhea remains a major contributor to childhood mortality across the globe, especially in LMICs. This analysis characterizes the burden of diarrheal mortality among children that reach care. The overall CFR for children hospitalized with all-cause diarrhea was 0.52%, or 1 in 200 children hospitalized with diarrhea. In low-income countries, where children <3 years of age have an average of 3 diarrheal episodes yearly, this CFR translates to a large absolute number of deaths [1]. We found that younger age, female sex, persistent diarrheal presentation, severe dehydration, and rotavirus-negative ELISA test were all statistically significantly associated with mortality. These findings highlight important risk factors for childhood diarrheal mortality

Table 2. Simple and Multivariable Logistic Regression Analysis of Covariates Association With Mortality

Variable	Crude		Adjusted[a]	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	…	<.001	…	<.001
<6 mo	3.54 (2.81–4.50)		2.07 (1.59, 2.73)	…
6 mo–1 y	2.50 (2.01–3.15)		1.52 (1.19–1.98)	…
1–2 y	1.95 (1.55, 2.49)		1.38 (1.06–1.81)	…
2–5 y	Ref		Ref	…
Sex	…	.005	…	.01
Male	Ref		Ref	…
Female	1.18 (1.05–1.32)		1.18 (1.04–1.34)	…
WHO region	…	<.001	…	<.001
European Region	Ref		Ref	…
African Region	62.05 (38.70–108.26)		130.62 (55.75–422.73)	…
Region of the Americas	42.65 (25.91–75.82)		91.03 (38.31–296.76)	…
Eastern Mediterranean Region	15.20 (9.24–26.84)		39.44 (16.54–128.84)	…
South East Asia Region	5.62 (2.14–13.33)		31.33 (9.24–120.01)	…
Western Pacific Region	8.75 (5.21–15.76)		24.12 (9.44–81.62)	…
Acute vs persistent	…	<.001	…	.03
Persistent (≥14 d)	3.46 (2.31–4.94)		1.91 (1.01–3.25)	…
Acute (<14 d)	Ref		Ref	…
Bloody vs watery	…	.24	…	.95
Watery	Ref		Ref	…
Bloody	.59 (.21–1.27)		.97 (.24–2.55)	…
Vomiting	…	<.001	…	.10
Not vomiting	1.43 (1.26–1.62)		1.13 (.98–1.30)	…
Vomiting	Ref		Ref	…
Dehydration type[b]	…	<.001	…	<.001
None	Ref		Ref	…
Some	.71 (.56–.91)		.93 (.72–1.20)	…
Severe	3.12 (2.50–3.96)		3.79 (3.01–4.83)	…
Rotavirus positivity (using ELISA)	…	<.001	…	<.001
Rotavirus positive	Ref		Ref	…
Rotavirus negative	2.20 (1.88–2.59)		2.29 (1.92–2.74)	…
Year	.90 (.88–.92)	.001	.94 (.92–.96)	<.001

The adjusted model includes an interaction term between acute/persistent presentation and watery/bloody presentation.

Abbreviations: CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; OR, odds ratio.

[a]Adjusted for all variables.

[b]Dehydration severity is categorized based on WHO classification [13].

globally, demonstrating the critical need to address dehydration, age- and sex-specific vulnerabilities, and causes of diarrhea other than rotavirus with clinical and public health interventions.

Children younger than 6 months of age had the highest odds of death, being more than twice as likely to die compared with children between 2 and 5 years of age. This is consistent with the literature [5, 8, 15]. Female sex was also associated with increased likelihood of death. This could be due to sex differences in how children are raised and brought to care. Female children may be more likely to have their nutrition neglected, increasing their risk of death [16, 17]. Studies in Bangladesh, Brazil, and Burkina Faso have shown that caregivers are more likely to bring male children to care, so it is plausible that caregivers also are waiting longer to bring female children to care, increasing their likelihood of death from diarrhea [18–20]. Indeed, a study in Ethiopia found that caregivers of female children were almost 2 times more likely to delay care seeking than caregivers of male children [21].

Our finding that the African Region had the highest odds of death and highest burden of deaths is consistent with the literature [2]. For children hospitalized with all-cause diarrhea in the African Region, the CFR was 1.39%, or 1 in 72 children hospitalized with diarrhea. The Region of the Americas, Eastern Mediterranean Region, South-East Asia Region, and Western Pacific Region all had lower odds of death compared with the African Region, but statistically significantly increased odds of death compared with the European Region. Differences by region are hard to interpret because of regional heterogeneity, but variation in mean income level, quality of care, cultural

norms including delays in seeking care and discontinuing breastfeeding or feeding, and distance to the closest hospital could explain the large differences in mortality rates between regions.

Persistent diarrheal cases are almost twice as likely to die as acute diarrheal cases. It may be that persistent cases are more commonly associated with malnutrition, which has been shown to be strongly correlated with a higher likelihood of death in studies done in Mozambique and Bangladesh [5, 22]. Additionally, different pathogens cause different presentations, so pathogens causing persistent diarrhea may also cause problems that lead to an increased risk of death. For example, studies have found that enteropathogenic *E coli* and *Clostridium difficile* are pathogens commonly associated with persistent diarrhea in LMICs and that these pathogens are also associated with an increased risk of death [23–25].

Severe dehydration was found to be a risk factor for diarrheal death. This finding was not surprising given that dehydration is often the reason of death for children with diarrhea [5, 26].

Mortality from rotavirus is well described in the literature [27]. However, the lower likelihood of death in cases with rotavirus may reflect the successful treatment with hydration in children with diarrhea that reach medical care or reflect the increasing use of rotavirus vaccines in LMICs [5]. A previous analysis of this surveillance network has shown a decrease in hospitalized rotavirus cases after introduction of rotavirus vaccine [28]. Pathogens causing death in ways other than dehydration, for example hemolytic urea syndrome from *E coli* or complications from *Shigella*, may be more difficult to treat, leading to higher CFRs [29]. Additionally, these pathogens require treatment with antibiotics, which may not be administered soon enough. As rotavirus vaccines are implemented in more countries and reach more children, it will be increasingly important to shift focus to other diarrheal pathogens that are causing mortality in healthcare facilities.

There are some differences in risk factors for diarrheal death by region. Although dehydration and a rotavirus-negative ELISA test were significant risk factors for death across all regions, female sex was a significant risk factor for death only in the Region of the Americas. Differences in risk factors for diarrheal death by region may be due to variability in diarrheal pathogen etiologies, cultural practices relating to healthcare, or health system capacity. There are several limitations of this analysis. First, the estimated CFRs may be an underestimate. Slightly more than 10% of the cases in the original dataset were missing the outcome variable, vital status at discharge, and were therefore excluded from the analysis. Cases missing the outcome variable are more likely to be younger, be from the African Region or the South East Asia Region, have bloody presentation, have no vomiting, have more severe dehydration, and be rotavirus positive. All of these factors are associated with increased likelihood of death, except for being rotavirus positive, which is associated with a lower likelihood of death. If cases missing vital status at discharge are more likely to have more severe diarrhea, and therefore more likely to have died, then excluding them in the calculation of CFRs and in the regression analysis may bias our estimates toward underestimation.

A second limitation is that the use of WHO region as a covariate ignores heterogeneity within regions and gives higher weight to countries with more cases. WHO regions are based on geography of countries instead of grouping countries with similar characteristics together. Third, there may be other variables that affect likelihood of death that were not collected by the network. For example, continued feeding and breastfeeding before hospital admission, nutritional status, access to healthcare facilities, and concomitant disease such as pneumonia or sepsis, may impact the likelihood of death [30]. Last, given the small proportion of cases with individual-level vaccination data available, we could not draw conclusions regarding vaccination status and rotavirus mortality.

There are also several notable strengths of this analysis. First, the analysis has a large sample size, which allows for the ability to identify risk factors for the rare event of diarrheal death. Second, the population included in the analysis is geographically diverse, allowing for a global perspective of diarrheal disease in LMICs. Third, the data collected from GRSN and GPDS use standardized protocols and laboratory testing, allowing the cases to be readily compared across sites.

Our results show that despite progress, mortality from diarrhea in hospitalized children remains an important public health issue. Knowledge of risk factors of diarrheal mortality will help identify important preventive measures and best interventions for treating children who present to care with diarrhea. The association of severe dehydration with death underscores the importance of hydration in the treatment of children with diarrhea. Furthermore, the association of rotavirus negativity with death suggests the need to broaden the attention from rotavirus to other pathogens causing diarrheal disease, especially those implicated in persistent diarrheal cases. More research is needed to identify the reasons for death of children hospitalized with diarrhea so that interventions can be implemented to save lives.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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