Factors Associated with the Duration of Moderate-to-Severe Diarrhea among Children in Rural Western Kenya Enrolled in the Global Enteric Multicenter Study, 2008–2012

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Abstract. Diarrheal disease is a leading cause of death among young children worldwide. As rates of acute diarrhea (AD; 1–6 days duration) have decreased, persistent diarrhea (PD; > 14 days duration) accounts for a greater proportion of the diarrheal disease burden. We describe factors associated with the duration of moderate-to-severe diarrhea in Kenyan children < 5 years old enrolled in the Global Enteric Multicenter Study. We found 587 (58%) children experienced AD, 360 (35%) had prolonged acute diarrhea (ProAD; 7–13 days duration), and 73 (7%) had PD. We constructed a Cox proportional hazards model to identify factors associated with diarrheal duration. Risk factors independently associated with longer diarrheal duration included infection with *Cryptosporidium* (hazard ratio [HR]: 0.868, $P = 0.035$), using an unimproved drinking water source (HR: 0.87, $P = 0.035$), and being stunted at enrollment (HR: 0.026, $P < 0.0001$). Diarrheal illness of extended duration appears to be multifactorial; given its association with adverse health and development outcomes, effective strategies should be implemented to reduce the duration and severity of diarrheal illness. Effective treatments for *Cryptosporidium* should be identified, interventions to improve drinking water are imperative, and nutrition should be improved through exclusive breastfeeding in infants ≤ 6 months and appropriate continued feeding practices for ill children.

INTRODUCTION

Globally, diarrheal disease is a leading cause of death among young children.¹ It is responsible for approximately 580,000 deaths among children < 5 years of age each year.² To explore the burden, etiologies, risk factors, and complications of moderate-to-severe diarrhea (MSD), the Global Enteric Multicenter Study (GEMS) was conducted. GEMS was a case-control study of MSD in children < 5 years old in sub-Saharan Africa and south Asia. The clinical and epidemiological methods used in GEMS have been described in detail elsewhere.³

One subobjective of GEMS was to assess persistent diarrhea (PD) as an outcome of MSD.³ PD has been used to describe diarrhea lasting 14 days or longer.¹ As rates of acute diarrhea (1–6 days duration) (AD) have decreased over the years, PD has become a greater proportion of the diarrheal disease burden in children.⁴ Of additional importance, higher rates of death have been reported among infants presenting with PD than among those with AD.⁵ Furthermore, PD can lead to a number of health consequences including delays in growth,⁶ nutritional deficiencies,⁷ and decreased cognitive function over time.^{7,8} Risk factors for PD have been documented; however, many of the studies are quite old, dating back 10–20 years. From previous research, prominent risk factors include age,^{9,10} malnutrition,^{11–16} the enteric etiologic agent that the child is infected with,^{13,17} maternal education level,^{10,17,18} previous diarrheal illness,^{7,11} breastfeeding

practices,¹⁸ having bloody diarrhea,^{14,19,20} antibiotic or antimicrobial use,^{14–16} poor sanitary conditions within the home,^{9,15,21} and the age of a child when he/she first experiences diarrhea.¹⁸

More recently, it has been established that diarrhea lasting 7–13 days, also known as prolonged acute diarrhea (ProAD), has been associated with future PD episodes and consequences.¹⁷ Moore and others¹⁷ evaluated diarrheal illness in a cohort of young Brazilian children over a span of 10 years, specifically exploring risk factors for and effects of ProAD and PD. They not only identified ProAD as a risk factor for future PD events, but also identified a number of factors associated with ProAD including the mother's level of education, two enteric etiologic agents (*Cryptosporidium* and *Shigella* spp.), age at weaning, being stunted before the ProAD event, and being stunted and underweight after the diarrheal event.¹⁷ Others have noted age, nutritional status, breastfeeding practices, health of the child at diarrheal onset, and the time of the year in which the diarrheal event occurs as factors associated with diarrhea lasting ≥ 7 days.^{22,23} Limited research has focused on ProAD; however, due to the important characteristics and apparent consequences of this duration other researchers have suggested focusing on "prolonged diarrhea" lasting more than 5–7 days, but less than 14 days.^{4,17} Research on how to define the end of a diarrheal episode is also limited and fairly inconsistent^{24–28}; however, a recent study describing ProAD used a definition of two consecutive diarrhea-free days as the end of a diarrheal episode.¹⁷ This definition is also supported by a World Health Organization (WHO) memorandum, which defines an episode of diarrhea as ending when the child experiences at least two consecutive diarrhea-free days.⁷

PD and ProAD remain major global health problems among young children; however, these health problems are often not

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specifically addressed in the management, treatment, and prevention of diarrheal diseases.²⁹ A better understanding of the key risk factors for ProAD and PD can help identify the most appropriate interventions and strategies to reduce their burden. In this article, we describe the characteristics of and factors associated with the duration of MSD among GEMS-Kenya case children < 5 years old.

MATERIALS AND METHODS

The Global Enteric Multicenter Study. To conduct this analysis, we used data from children who were enrolled as cases into the GEMS. GEMS is a multi-site, case-control study to estimate the burden, etiology, risk factors, and complications of MSD in children < 5 years old in sub-Saharan Africa and south Asia.³ Seven countries participated in GEMS: India, Bangladesh, Pakistan, The Gambia, Mozambique, Mali, and Kenya. This article focuses on data from the GEMS-Kenya site specifically. The GEMS-Kenya study site has been described elsewhere. In brief, the Kenya Medical Research Institute (KEMRI) in collaboration with the U.S. Centers for Disease Control and Prevention (CDC) has been operating a health and demographic surveillance system (HDSS) in these communities since 2001.³⁰ This site, located in rural Nyanza Province in western Kenya, had six sentinel health centers which served a population of about 135,000 of whom nearly 21,000 were children < 5 years old.^{3,31}

The sampling frame for each study site was an HDSS. The HDSS enumerated all persons living within the regional bounds of the surveillance system thrice yearly, and captured births, deaths, pregnancies, and in- and out-migrations.³⁰ Children were eligible to be enrolled into GEMS as a case with MSD if they were < 5 years old and presented to select HDSS sentinel health centers with ≥ 3 loose stools per day, for ≤ 7 days, and one or more of the following signs indicative of dehydration: sunken eyes, loss of skin turgor, intravenous rehydration administered or prescribed; or dysentery; or were hospitalized with diarrhea or dysentery. Using the HDSS census database, well children with similar characteristics were randomly identified and enrolled as controls at their home within 2 weeks of case enrollment. Controls were matched on age (i.e., for cases 0–11 months control children had to be within ± 2 months and for cases 12–59 months controls had to be within ± 4 months and within the same age strata [0–11, 12–23, and 24–59]), sex, and geographic location (i.e., the same/nearby village).³ Children were not eligible to be controls if they experienced diarrhea within the past 7 days. Children were not eligible for reenrollment if they were currently enrolled in GEMS. The GEMS enrollment period lasted until the 60-day follow-up interview was conducted, after which time reenrollment could occur.

At enrollment, stool specimens were collected from all cases and controls. Specimens were tested for a full spectrum of known infectious bacterial, viral, and parasitic enteric pathogens.³² In addition, clinical examinations were conducted on case children by trained clinical staff, and anthropometric measurements were collected on both cases and controls. Questionnaires were used to collect demographic information, household level characteristics, and to assess risk factors for diarrheal disease. Between 50 and 90 days after enrollment, all cases and controls received a follow-up home visit during which anthropometric

measurements were repeated and a questionnaire was administered on demographic and household level characteristics, risk factors for diarrheal disease, and the child's health status since enrollment including diarrheal duration. Additional information collected within GEMS included data on human immunodeficiency virus (HIV) status for a subset of cases, controls, and their biological parents.

Study area and study population. In Kenya, children were enrolled between January 31, 2008 and January 29, 2011 and again starting on October 31, 2011 through September 30, 2012. During the first enrollment period, the study was conducted in the areas of Gem and Asembo, and during the second enrollment period, in the areas of Asembo and Karemo because the KEMRI/CDC Kenya HDSS had moved to neighboring Karemo.

This region of Kenya is plagued with high rates of child mortality (infants: 27 per 1,000 live births; children < 5 years old: 73 per 1,000 live births), HIV/acquired immune deficiency syndrome, and malaria.^{33,34} These rural areas are located near Lake Victoria, about 35 miles outside Kisumu, the third largest city in Kenya. Most people living in this region are of Luo descent, and the primary occupations are fishing and farming.³¹

Definitions. For the purposes of this study, the following case definitions for diarrheal duration were used: diarrhea lasting 1–6 days was termed AD; diarrhea lasting 7–13 days was considered ProAD; and diarrhea lasting ≥ 14 days was termed PD. The end of a diarrheal episode was defined by two consecutive diarrhea-free days. Improved and unimproved water and sanitation were defined according to WHO/UNICEF Joint Monitoring Program for Water Supply and Sanitation definitions.³⁵ For the purposes of this study, a traditional pit latrine was considered an improved sanitation facility as we did not know whether the latrine had a slab or not. Wealth Index Quintiles were defined in five categories and were constructed following the methodology proposed by The World Bank Development Research Group.³⁶

Data sources for diarrheal duration. Diarrhea duration was determined using two data sources. First, for cases, we obtained the number of days of diarrhea during the week before enrollment as recounted by the caregiver. Between 1 and 7 days could have been reported during this period (we considered the days of diarrhea reported to be consecutive—children with > 7 consecutive days of diarrhea were ineligible for enrollment as acute MSD cases). Second, we extracted data reported by the caregiver on a form called the Memory Aid, a tool used to collect data on the nature of the child's stool in the 14 days after the child was enrolled (Figure 1).

On enrollment, each caretaker was given a blank Memory Aid and was instructed on how to properly complete the form. Caretakers were asked to recall each morning whether their child had diarrhea or normal stool on the previous day. Diarrhea was defined as ≥ 3 loose or watery stools in the previous day, not usual for that child. Normal stool was defined as stool that was typical for that child, having one or two abnormally loose stools, or having no stools. A day was defined as the period of time beginning when the child awoke in the morning and ending when the child awoke the next morning. The Memory Aid was designed by the Malian Office of Literacy for all reading levels, including populations who may be illiterate. Each site conducted focus groups and field tested the form.

CRF 9A- Memory Aid to Record the Presence of Diarrhea

Site Center Child ID Day Month Year

Please complete this form every day for each of the next 14 days.

- Each morning when you wake up, decide whether your child had diarrhea during the previous day. *Diarrhea* means that your child passed 3 or more loose or watery stools that were not normal for him or her on that day.
- Go to the correct day. "○" means today, "○○" means tomorrow, and so on. A day begins when you wake up in the morning and ends when you wake up the next morning.
- If your child had diarrhea that day, mark "X" in the dark box for that day ☒. If your child did not have diarrhea, mark "X" in the white box for that day ☐. Each day, make only one "X".
- If you forget for a few days, try to start again on the correct day.
- Keep this form in a safe place. We will come to your house to collect it in 60 days.

	DIARRHEA	NORMAL

(1) ○ (today)	☒	☐
(2) ○○	☒	☐
(3) ○○○	☒	☐
(4) ○○○○	☒	☐
(5) ○○○○○	☒	☐
(6) ○○○○○○	☒	☐
(7) ○○○○○○○	☒	☐
(8) ○○○○○○○○	☒	☐
(9) ○○○○○○○○○	☒	☐
(10) ○○○○○○○○○○	☒	☐
(11) ○○○○○○○○○○○	☒	☐
(12) ○○○○○○○○○○○○	☒	☐
(13) ○○○○○○○○○○○○○	☒	☐
(14) ○○○○○○○○○○○○○○	☒	☐

FIGURE 1. Memory Aid form used to record diarrhea for 14 days after enrollment into Global Enteric Multicenter Study, Kenya. This figure appears in color at www.ajtmh.org.

Combined recommendations from all sites were used to create one generic form.

Caregivers were asked to monitor the child's stool and to record whether the child had "diarrhea" or "normal stool" for the previous day by marking "X" in the appropriate

column and box, for 14 days (see Figure 1). If at any point the caregiver missed a day they were told to resume recording on the correct day. Caregivers were asked to place the form in a safe place at the end of the 14-day period, when it should have been complete, until the 60-day

follow-up interview. During the follow-up interview, field staff reviewed the form with the caretaker for any discrepancies or missing information before collecting them. Completed forms were returned to GEMS Kenya data management personnel and filed along with the case report forms for each child.

Calculating the duration of diarrhea. Using these two sources, we were able to calculate the duration of diarrhea reported for the 7 days before and the 14 days after enrollment. A total of 20 days were captured during this reporting period as the day of enrollment was captured in both the diarrhea reported at enrollment and on the Memory Aid. When counting diarrheal days after enrollment, we took into account days in which diarrhea was not reported. As noted, once a child experienced two consecutive days of normal stools, the episode was considered over. If the child subsequently experienced diarrhea, this was considered a new episode.

Eligibility for analysis. For the purposes of this study, only case children experiencing a single episode of diarrhea during the 20-day reporting period with complete data were included. We excluded children whose Memory Aid form was incomplete or missing.

Statistical analysis. In this article, we provide descriptive statistics, unadjusted analysis, and a multivariable, time-to-event analysis using a stratified Cox proportional hazards (PHs) model to examine factors associated with diarrheal disease duration. Our main outcome variable was diarrheal disease duration. The event was the end of a diarrheal episode. Children who continued to have diarrhea at the end of the reporting period on the Memory Aid were censored. In this article, for the purposes of descriptive statistics, we present diarrhea as a categorical variable (AD, ProAD, or PD); however, in the context of survival analysis it was treated as a continuous variable (1–20 days).

Crude analysis involved an exploration of factors that might influence diarrheal duration using Kaplan–Meier (KM) survival analysis. Clinical and biological factors within this analysis included: the child's age and gender, identified enteric pathogens, and clinical characteristics such as the presence of bloody diarrhea, treatments given before or during the enrollment visit to the health facility, and anthropometric measures (weight-for-height z-score [WHZ], weight-for-age z-score [WAZ], height-for-age z-score [HAZ]). We also examined household factors including the amount of food or drink the child was offered while ill, breastfeeding practices, household demographics, socioeconomic factors, and household water, sanitation, and hygiene (WASH) characteristics.

Any variable with a P value ≤ 0.10 in univariable analysis was considered for inclusion in the multivariable Cox PH model. Before multivariable modeling, we checked the correlation between variables to be considered within the Cox PH model using Spearman correlation coefficients.³⁷ Variables with a Spearman correlation coefficient > 3 were considered correlated. One variable from each correlated pair was removed based on epidemiological significance to our study.

Two variables violated the PHs assumption: age group and whether the child was stunted at enrollment. We thus stratified the model by age group and created a time-dependent

variable for being stunted at enrollment. To do the latter, a “change-point” approach was used.³⁸ This method involves identifying the point in time when the relative risk in children who were stunted versus those who were not stunted changed between the two groups. To identify the “change-point” we created two variables for each possible event time, one to indicate children who were stunted before the event time and one to indicate children who were stunted after the event time. We then fit models for each pair and chose the event time with the best fit based on which pair minimized the log likelihood.

A manual stepwise selection process was used for multivariable analysis.³⁹ All variables in the final model were assessed for interactions. Children who were enrolled more than once as a case into GEMS were included in this analysis; we conducted a sensitivity analysis to assess how our results differed when we excluded children enrolled more than once. Hazard ratios, confidence intervals (CIs), and P values are presented for the final model. Data were analyzed using SAS 9.3 (SAS Institute Inc., Cary, NC).

Scientific ethics. Written informed consent was collected from parents or guardians of all children who participated in GEMS. The GEMS protocol was approved by the KEMRI Scientific and Ethical Review Committees and the Institutional Review Board (IRB) at the University of Maryland, School of Medicine, Baltimore, MD. The CDC, Atlanta, GA, formally deferred to the IRB at the University of Maryland for review.

RESULTS

Study enrollment and background characteristics. A total of 1,778 children were enrolled as cases into GEMS-Kenya. Of these, 117 (6.6%) had missing Memory Aids and 83 (4.7%) had incomplete or ineligible data reported on the Memory Aid and were excluded from the analysis, leaving 1,578 case children with complete data. Of these, 1,020 (65%) had one episode of diarrhea, 448 (28%) had two episodes of diarrhea, and 110 (7%) had three episodes of diarrhea (based on the definition of an episode, described earlier). For the purposes of this analysis, we focused on the 1,020 case children with a single episode of diarrhea.

Among the 1,020 cases included in our analysis, 480 (47%) were 0–11 months, 264 (26%) were 12–23 months, and 276 (27%) were 24–59 months old; 427 (42%) were females (see Table 1). Approximately, 46% of primary caretakers had less than a primary school education. Nearly half (46%) of respondents reported having four or more people sleeping in the home, and 62% of respondents reported having more than two children < 5 years old living in the home. When ranking respondents according to their wealth index quintile, 18% were categorized as being in the “poorest” quintile, 20% were “poor,” 27% were in the “middle,” 17% were “wealthy,” and 19% were categorized in the “wealthiest” quintile.

Descriptive statistics. We examined demographics, clinical characteristics, socioeconomic factors, and laboratory-confirmed enteric infections for associations with the duration of diarrhea (Table 2). In our study sample, 587 (58%) children experienced AD, 360 (35%) ProAD, and 73 (7%) PD. One child had diarrhea for the entire 20-day reporting

TABLE 1
Factors associated with acute, ProAD, and PD among cases ($N = 1,020$) enrolled in GEMS, western Kenya, 2008–2012

Characteristic	Children with AD ($N = 587$) n (%)	Children with ProAD ($N = 360$) n (%)	Children with PD ($N = 73$) n (%)	All children ($N = 1,020$) n (%)
Number of times enrolled as a case into GEMS*				
1	498 (86.9)	300 (84.3)	59 (83.1)	857 (85.7)
2	68 (11.9)	47 (13.2)	11 (15.5)	126 (12.6)
3	6 (1.1)	6 (1.7)	1 (1.4)	13 (1.3)
4	1 (0.2)	3 (0.8)	0 (0.0)	4 (0.4)
Caretakers education level				
Less than primary school	259 (44.1)	174 (48.3)	37 (50.7)	470 (46.1)
Primary caregiver is mother	552 (94.0)	351 (97.5)	70 (95.9)	973 (95.4)
Number of young children living in home (> 2)	358 (61.0)	234 (65.0)	43 (58.9)	635 (62.3)
Number of people sleeping in home (> 4)	263 (44.8)	178 (49.4)	29 (39.7)	470 (46.1)
Home has a finished floor	123 (21.0)	62 (17.2)	14 (19.2)	199 (19.5)
Wealth Index Quintile				
Poorest	109 (18.6)	65 (18.1)	10 (13.7)	184 (18.0)
Poor	125 (21.3)	56 (15.6)	20 (27.4)	201 (19.7)
Middle	136 (23.2)	117 (32.5)	23 (31.5)	276 (27.1)
Wealthy	98 (16.7)	62 (17.2)	8 (11.0)	168 (16.5)
Wealthiest	119 (20.3)	60 (16.7)	12 (16.4)	191 (18.7)
WASH characteristics				
Unimproved main water source	203 (35.6)	160 (44.4)	35 (48.0)	398 (39.0)
Effective treatment method used†	358 (94.2)	206 (94.1)	38 (92.7)	602 (94.0)
Washes hands with water only	20 (3.4)	27 (7.5)	3 (4.1)	50 (4.9)
Uses shared sanitation facility				
No facility	112 (19.1)	73 (20.3)	9 (12.3)	194 (19.0)
Private facility	107 (18.2)	54 (15.0)	8 (11.0)	169 (16.6)
Shared facility	368 (62.7)	233 (64.7)	56 (76.7)	657 (64.4)
Unimproved sanitation facility‡	113 (19.3)	73 (20.3)	9 (12.3)	195 (19.1)
Blood in stool	16 (2.7)	11 (3.1)	0 (0.0)	27 (2.7)
Maximum number of stools > 7	154 (26.2)	101 (28.1)	13 (17.8)	268 (26.3)
Breastfeeding practices§				
No breastfeeding	192 (38.9)	75 (26.3)	19 (30.7)	286 (34.0)
Partial breastfeeding	288 (58.3)	197 (69.1)	40 (64.5)	525 (62.4)
Exclusive breastfeeding	14 (2.8)	13 (4.6)	3 (4.8)	30 (3.6)
Anthropometry at enrollment				
Wasting at enrollment (WHZ < -2)	59 (10.1)	41 (11.4)	11 (15.1)	111 (10.9)
Underweight at enrollment (WAZ < -2)	131 (22.3)	69 (19.2)	25 (35.3)	225 (22.1)
Stunted at enrollment (HAZ < -2)	151 (25.7)	83 (23.1)	30 (41.1)	264 (25.9)
Child is HIV-infected	11 (3.3)	6 (2.7)	1 (2.6)	18 (3.0)
Food or drink offerings				
Offered less than usual to drink	248 (42.3)	167 (46.4)	40 (54.8)	455 (44.6)
Offered less than usual to eat	455 (77.5)	295 (81.9)	59 (80.8)	809 (79.3)
Treatments given before visiting health facility				
ORS	73 (12.4)	55 (15.3)	7 (9.6)	135 (13.2)
Zinc	19 (3.2)	9 (2.5)	4 (5.5)	32 (3.1)
Treatments given at health facility				
ORS	569 (96.9)	352 (97.8)	70 (95.9)	991 (97.2)
Zinc	58 (9.9)	39 (10.8)	9 (12.3)	106 (10.4)
IV treatment	63 (10.7)	49 (13.6)	9 (12.3)	121 (11.9)
Antibiotics	50 (8.5)	43 (11.9)	7 (9.6)	100 (9.8)

AD = acute diarrhea; GEMS = Global Enteric Multicenter Study; HAZ = height-for-age z-score; HIV = human immunodeficiency virus; IV = intravenous; ORS = oral rehydration solution; PD = persistent diarrhea; ProAD = prolonged acute diarrhea; WASH = water, sanitation, and hygiene; WHZ = weight-for-height z-score.

* $N = 1,000$ as 20 children were missing the unique identification number that was used to determine whether child was enrolled more than once; hence, we were unable to determine the number of times these children were enrolled into GEMS.

† Among those who reported usually treating their drinking water: AD, $N = 380$; ProAD, $N = 219$; PD, $N = 41$; all children, $N = 640$.

‡ Traditional pit latrines considered improved sanitation facility as we did not know whether the latrine had a slab or not.

§ Represents only children in first 3 years of GEMS ($N = 841$) as questions related to breastfeeding practices were not compatible during the fourth year of GEMS.

period. The median number of diarrhea days was 6 (range: 1–20; mean: 6.7 days). Infants accounted for 47.1%, and males for 58.1%, of all cases; these remained the predominant age group and gender across all three diarrheal duration categories.

The number of enteric pathogens identified in a child's stool ranged from 0 to 5; 184 (18%) cases had no pathogen identified, 409 (40%) had a single pathogen identified, and 427 (42%) had more than one pathogen identified. The number of pathogens identified in a child's stool was not associated with diarrheal duration and therefore the

numbers reported here include children who had no pathogen, a single pathogen, or multiple pathogens identified. All etiologies identified in those children with multiple pathogens are reported. The most common pathogens identified in children with AD were *Giardia* (19%), rotavirus (17%), enteroaggregative *Escherichia coli* (EAEC) (14%), enterotoxigenic *E. coli* (ETEC) (10%), and typical enteropathogenic *E. coli* (8%) (Table 2). For children experiencing ProAD, the most common pathogens identified were EAEC (19%), rotavirus (18%), *Giardia* (16%), followed by *Cryptosporidium* (14%) and *Campylobacter*

TABLE 2

Characteristics of and etiologic agents identified by acute, ProAD, and PD among cases ($N = 1,020$) enrolled in GEMS, western Kenya, 2008–2012

Characteristic	Children with AD ($N = 587$) n (%)	Children with ProAD ($N = 360$) n (%)	Children with PD ($N = 73$) n (%)	All children ($N = 1,020$) n (%)
Age stratum (months)				
0–11	252 (42.9)	188 (52.2)	40 (54.8)	480 (47.1)
12–23	143 (24.4)	101 (28.1)	20 (27.4)	264 (25.9)
24–59	192 (32.7)	71 (19.7)	13 (17.8)	276 (27.1)
Gender, female	245 (41.7)	153 (42.5)	29 (39.7)	427 (41.9)
Etiology*				
Number of pathogens				
No pathogens	112 (19.1)	61 (16.9)	11 (15.1)	184 (18.0)
One pathogen	243 (41.4)	131 (36.4)	35 (48.0)	409 (40.1)
More than one pathogen	232 (39.5)	168 (46.7)	27 (37.0)	427 (41.9)
<i>Giardia</i>	111 (18.9)	56 (15.6)	12 (16.4)	179 (17.6)
Rotavirus	98 (16.7)	66 (18.3)	8 (11.0)	172 (16.9)
Enteropathogenic <i>E. coli</i>	83 (14.1)	69 (19.2)	14 (19.2)	166 (16.3)
<i>Cryptosporidium</i>	45 (7.7)	50 (13.9)	17 (23.3)	112 (11.0)
<i>Campylobacter jejuni</i>	46 (7.8)	36 (10.0)	12 (16.4)	94 (9.2)
ST-Enterotoxigenic <i>E. coli</i> (ST-only or LT/ST)	58 (9.9)	31 (8.6)	3 (4.1)	92 (9.0)
<i>Shigella</i> spp.	43 (7.3)	30 (8.3)	5 (6.9)	78 (7.7)
Typical EPEC	48 (8.2)	24 (6.7)	3 (4.1)	75 (7.4)
Atypical EPEC	35 (6.0)	20 (5.6)	3 (4.1)	58 (5.7)
Nontyphoidal <i>Salmonella</i>	30 (5.1)	24 (6.7)	4 (5.5)	58 (5.7)
LT-Enterotoxigenic <i>E. coli</i>	32 (5.5)	21 (5.8)	3 (4.1)	56 (5.5)
<i>Campylobacter coli</i>	31 (5.3)	18 (5.0)	5 (6.9)	54 (5.3)
Norovirus GII	25 (4.3)	17 (4.7)	0 (0.0)	42 (4.1)
Norovirus GI	13 (2.2)	18 (5.0)	2 (2.7)	33 (3.2)
Sapovirus	20 (3.4)	10 (2.8)	3 (4.1)	33 (3.2)
Adenovirus non-40/41	15 (2.6)	11 (3.1)	2 (2.7)	28 (2.8)
Adenovirus 40/41	15 (2.6)	11 (3.1)	1 (1.4)	27 (2.7)
Astrovirus	11 (1.9)	5 (1.4)	1 (1.4)	17 (1.7)
<i>Entamoeba histolytica</i>	5 (0.85)	5 (1.4)	0 (0.0)	10 (0.98)

AD = acute diarrhea; *E. coli* = *Escherichia coli*; EPEC = enteropathogenic *E. coli*; GEMS = Global Enteric Multicenter Study; LT = heat-labile enterotoxin; PD = persistent diarrhea; ProAD = prolonged acute diarrhea; ST = heat-stable enterotoxin.

* Not included are pathogens identified in less than 10 patients: *Vibrio cholerae* O1 ($N = 5$), *Aeromonas* ($N = 1$), enterohaemorrhagic *E. coli* ($N = 0$), *Salmonella typhi* ($N = 0$).

jejuni (10%). The most commonly identified pathogens among children experiencing PD included *Cryptosporidium* (23%), EAEC (19%), *C. jejuni* (16%), *Giardia* (16%), and rotavirus (11%).

Approximately 39% of all households reported using an unimproved water source; a higher proportion of these homes had children who experienced PD as compared with children with ProAD or AD (Table 1). Also, a higher proportion of households with children experiencing PD reported they shared their reported sanitation facility with one or more households (PD: 77%, ProAD: 65%, AD: 63%). A high proportion, 45%, of all children were offered less than usual to drink or eat during their diarrheal episode. Among children with PD, a higher proportion (54.8%) were given less than usual to drink while ill as compared with children with ProAD (46.4%) or AD (42.3%). A larger percentage (79%) of all children regardless of diarrhea duration category was given less than usual to eat while ill. Children who were stunted (HAZ < -2) (PD: 41%, ProAD: 23%, AD: 25.7%), wasted (WHZ < -2) (PD: 15%, ProAD: 11%, AD: 10%), or underweight (WAZ < -2) (PD: 35%, ProAD: 19%, AD: 22%) at the time of enrollment had PD more frequently as compared with children with ProAD or AD.

Factors associated with diarrhea of extended duration.

Thirteen variables with P value < 0.1 in KM analysis were considered for multivariable modeling. KM analysis shows a difference within the group but not where the difference lies. As shown in Table 3, four etiologic agents appeared to be associated with extended diarrheal

duration (based on $P < 0.1$). These were *Cryptosporidium* spp. ($P < 0.0001$), *C. jejuni* ($P = 0.04$), enterotoxigenic *E. coli* that produces heat-stable enterotoxin (log-rank $P = 0.07$), and EAEC ($P = 0.08$). Other factors potentially

TABLE 3

Results of bivariate Kaplan–Meier analysis exploring factors associated with acute, prolonged acute, and persistent diarrhea among cases ($N = 1,020$) enrolled in GEMS, western Kenya, 2008–2012

Characteristic	Log-rank test P value
Enteric pathogen*	
<i>Cryptosporidium</i>	< 0.0001
<i>Campylobacter jejuni</i>	0.04
ST-Enterotoxigenic <i>E. coli</i> (ST-only or LT/ST)	0.07
Enteropathogenic <i>E. coli</i>	0.08
Other factors	
Child's age	< 0.0001
Caretakers education level: less than primary school	0.06
Main drinking water source considered unimproved	0.004
Sanitation facility: no facility, private facility, or shared facility	0.02
Offered less than usual while ill (drink)	0.01
Offered less than usual while ill (eat)	0.02
Anthropometry at enrollment	
Stunted at enrollment (HAZ < -2)	0.04
Wasting at enrollment (WHZ < -2)	0.08
Underweight at enrollment (WAZ < -2)	0.09

GEMS = Global Enteric Multicenter Study; HAZ = height-for-age z-score; ST = heat-stable enterotoxin; WHZ = weight-for-height z-score.

* Multiple enteric pathogens possible per child.

associated with longer diarrheal duration included age group ($P < 0.0001$), whether the child was stunted ($P = 0.04$), wasted ($P = 0.08$), or underweight ($P = 0.09$) at enrollment, whether the child was exclusively breastfed, partially breastfed, or not breastfed at all ($P = 0.003$), whether the child was offered less than usual to eat ($P = 0.02$) or drink ($P = 0.01$) while ill, the primary caregivers education level ($P = 0.06$), having an unimproved drinking water source ($P = 0.004$), or having a shared sanitation facility ($P = 0.02$) (Table 3). We assessed for correlation between these variables and found the following correlations: age and breastfeeding (Spearman correlation coefficient: -0.73), being offered less than usual to eat and being offered less than usual to drink while ill (Spearman correlation coefficient: 0.32), being stunted or underweight at enrollment (Spearman correlation coefficient: 0.56), and being wasted or underweight (Spearman correlation coefficient: 0.52). We chose to remove breastfeeding, being offered less than usual to eat while ill, and being wasted or underweight at enrollment from any further multivariable modeling.

Since the age variable and stunted at enrollment both violated the proportionality of hazards assumption, we used both a stratified Cox PH modeling approach and a time-dependent variable for stunted at enrollment, based on the optimal cutoff point (14 days). Some children continued to have diarrhea through the end of the Memory Aid reporting period. Thus, in this analysis 57 children were right censored (diarrhea persisted through the period of observation [the 20th day] as we were unable to determine when the child's diarrhea ceased). We evaluated our model excluding the 143 children who were enrolled more than once as a case into GEMS. The final multivariable Cox PH model was very similar to the final model obtained when those 143 children were excluded in the analysis (Supplemental Table 1). Therefore, we present in Table 4 the model with all case children who had a single episode of diarrhea. The final model includes being stunted at enrollment defined as HAZ < -2 , having a main drinking water source that is considered unimproved, or having an infection with *Cryptosporidium*. The adjusted hazards ratio (HR) for children infected with *Cryptosporidium* is 0.75, CI: 0.61, 0.93 ($P = 0.009$) suggesting that children infected with *Cryptosporidium*, when holding all other variables in the model constant, were at a greater risk for experiencing longer duration diarrhea as compared with children who were not infected with *Cryptosporidium*. In

other words, the risk (hazard rate) of end-of-diarrhea for children infected with *Cryptosporidium* is 75% the hazard rate in children not affected with *Cryptosporidium*. We also found that children whose main drinking water source was considered unimproved (HR: 0.87, CI: 0.76, 0.99, $P = 0.035$) were at greater risk for experiencing longer duration diarrhea. Further we found that, for duration of diarrhea up to 14 days there is no evidence of a difference between (survival curves of) children who were stunted at enrollment and those who were not (adjusting for other factors), whereas after 14 days diarrheal duration children who were not stunted at enrollment did significantly better compared with children who were stunted (relative risk or HR = $1/0.03 = 33.3$, CI: 10, 100).

DISCUSSION

The GEMS study confirmed that ProAD and PD remain important global health problems, and identified factors associated with extended diarrheal duration that should be addressed in strategies to reduce their burden and consequences. Among GEMS-Kenya cases, $> 40\%$ suffered acute moderate-to-severe diarrheal illness lasting 7 days or longer. In this study, children infected with *Cryptosporidium* had longer duration diarrhea. We also found that, after 14 days of diarrhea children who were not stunted at enrollment did significantly better compared with children who were stunted. In addition, children whose household's main drinking water came from an unimproved source had longer duration diarrhea.

Etiologic agent. Children infected with *Cryptosporidium* had an increased risk for longer duration diarrhea, confirming its association with ProAD and PD in earlier studies.^{13,17,40} Cryptosporidiosis is characterized by watery diarrhea often lasting ≥ 4 weeks in previously healthy individuals; illness can be more severe in individuals with weakened immune systems.⁴¹ *Cryptosporidium* is commonly spread through drinking contaminated water,⁴² and is resistant to routine drinking water chlorination as practiced at home or in some water treatment plants.^{42,43} Treatments are not highly effective and vaccines for *Cryptosporidium* are not available.⁴⁴ *Cryptosporidium* was found to be a major cause of MSD in children < 5 years old in all seven GEMS sites.⁴⁵ In children 12–23 months old with MSD across the seven GEMS sites combined, *Cryptosporidium* was associated with an increased risk of death.⁴⁵ As a result, efforts to find water quality interventions that are effective against *Cryptosporidium* and well suited for low resource settings, as well as effective treatments and vaccines are imperative.

Although not significant in multivariable analysis, we noted other pathogens that were associated with diarrheal duration in bivariate analysis including EAEC, enterotoxigenic *E. coli* that produces heat-stable enterotoxin, and *C. jejuni*. Other studies have also noted the association between these pathogens and longer diarrheal duration.^{17,46}

WASH characteristics. To our knowledge, no other studies have identified using an unimproved water source as an independent factor associated with longer diarrheal duration. In a Bangladesh study, using an unimproved water source was associated with PD on bivariate analysis; however, when adjusting for other factors this association was no

TABLE 4

Results of the Multivariate Stratified Cox Proportional Hazards Model exploring factors associated with acute, prolonged acute, and persistent diarrhea among cases ($N = 1,020$) enrolled in GEMS, western Kenya, 2008–2012

Characteristic	Hazards ratio (CI)	P value
Risk factors		
Stunted		
Children with > 14 days of diarrhea	0.03 (0.01, 0.10)	< 0.0001
Children with ≤ 14 days of diarrhea	1.14 (0.98, 1.32)	0.085
Main drinking water source considered unimproved	0.87 (0.76, 0.99)	0.035
Enteric pathogen*		
<i>Cryptosporidium</i>	0.75 (0.61, 0.93)	0.009

CI = confidence interval; GEMS = Global Enteric Multicenter Study.

* Multiple enteric pathogens possible per child.

longer significant.¹⁵ Drinking water storage practices have also reportedly been associated with diarrhea of extended duration. For example, in Kenya it was found that using uncovered storage containers for drinking water was associated with PD.²¹ We explored whether water treatment practices influenced the duration of diarrhea, but found no differences between those who reported treating their water with one of five proven household water treatment methods⁴⁷ compared with those who used ineffective treatment methods. Respondents may have overreported water treatment or may not have been treating it sufficiently well to eliminate all pathogens.

In our study, we also noted that shared sanitation facilities appeared to be a factor associated with longer diarrheal duration; one study in Guatemala found the presence of feces either on the ground, in the household compound or in the yard to be risk factors for longer duration of diarrhea.⁹ The relationship between sanitation and longer duration diarrhea warrants further investigation, especially in light of the proposed reclassification of shared sanitation (adequate if shared with ≤ 30 people) as no longer unimproved.⁴⁸

Inadequate water and sanitation facilities have long been documented as risk factors for diarrheal disease. Our study suggests that they could also be associated with longer diarrheal events. Although universal access to improved water sources and sanitation infrastructure may not be a reality in the near future for our rural study population, an interim solution to improving water quality could be through simple-to-use, low-cost, proven household water treatment interventions particularly those that are effective against *Cryptosporidium*.⁴⁹ Furthermore, safe sanitation practices and promotion of handwashing with soap should be encouraged.

Nutritional deficiencies. Malnutrition has previously been noted as one of the most significant risk factors for PD.^{11–16,50} Our results corroborate this relationship, as we found that children who were stunted (HAZ < -2) at enrollment experienced longer diarrheal events. The relationship between malnutrition and diarrhea of extended duration is two way.⁵¹ A malnourished child is less able to fight off infection which leads to more severe, longer duration illness.⁵¹ Furthermore, a child with diarrhea, particularly PD, may be eating less than usual and the body's capacity to absorb nutrients may be diminished, leading to poorer nutritional status.⁵¹ Educating parents on feeding practices, before, during, and after the child's illness, and making sure that supplemental feeding programs are available for malnourished children, may help break this cyclic process.

Other nutritional interventions for infants and older children include the promotion of exclusive breastfeeding up to 6 months of age, continued feeding during diarrheal illness, and zinc supplementation for diarrheal prevention and treatment.^{52,53} Further, administering oral rehydration solution during diarrheal illness to prevent dehydration is important. In our study, among infants aged 0–6 months enrolled in the first 3 years of GEMS, 15% of mothers reported exclusively breastfeeding their infant, 83% reported partial breastfeeding, and 3% reported not breastfeeding at all. On bivariate analysis, there was a significant association between these three categories and diarrheal duration, but we were unable to explore the relationship further due to its

correlation with age. A meta-analysis conducted by Patel and others⁵⁴ showed that higher levels of zinc supplementation were associated with diarrhea of shorter duration, and zinc treatment has been shown to shorten the duration of diarrhea in children with PD and those with cholera.^{55,56} We found no significant differences in diarrheal duration among children reportedly treated with zinc before ($N = 32$) or after visiting the health facility ($N = 106$), and children who were not treated with zinc. Possible explanations for this include low numbers of children treated with zinc and correspondingly little power to detect a difference in diarrheal duration, and insufficient dosage or duration of treatment. The WHO recommends that 20 mg of zinc should be given to a child with diarrhea for 10–14 days (10 mg for children < 6 months old); however, GEMS did not collect information on the dose or the length of time of zinc administration; therefore, we were unable to include it in the analysis or make inferences regarding zinc.⁵³

This study is subject to a number of other limitations. First, we limited data analysis to cases with a single episode of diarrhea during the 20-day period of data collection. Second, the quality of Memory Aid data may vary even though steps were taken throughout the study to ensure data quality. Although only a small proportion of the forms had missing or illegible entries, we have no way of validating that forms were completed correctly by caregivers. Furthermore, the diarrhea days reported before enrollment were collected retrospectively so are subject to recall bias. However, the recall period of 7 days is considered an acceptable period of recall for caregivers to report child illnesses.⁵⁷ Regarding the finding that after 14 days of diarrhea, children who were not stunted at enrollment did significantly better compared with children who were stunted, the large HR and wide CIs associated with this result are due to the small number of individuals in this group. Third, in light of a recent reanalysis of a subset of GEMS microbiologic data obtained across all seven study sites, the laboratory results presented here within may be underestimated for a number of enteric pathogens.⁵⁸ The reanalysis used more sensitive methods, quantitative molecular diagnostic techniques; however, the results for rotavirus and *Cryptosporidium* spp. specifically were found to be comparable with the original conventional methods.⁵⁸ Finally, although our results align well with what other investigators have reported, they may not be generalizable to children living in other parts of Kenya or globally.

In summary, diarrhea of extended duration appears to be multifactorial. In this subset of GEMS case children living in rural western Kenya, these factors include infection with *Cryptosporidium*, the nutritional status of the child at presentation to the health center, and the household's drinking water source. Identifying strategies to reduce the length and severity of diarrheal illness and incorporating these strategies into global, national, and local guidelines for diarrhea prevention and management is critical.²⁹ We recommend increased emphasis on finding effective treatments for *Cryptosporidium* that can be implemented in resource-limited settings, increasing access to improved drinking water sources and private, improved sanitation facilities. We also support recommendations for exclusive breastfeeding for the first 6 months of life, improved nutrition for the first 5 years of life, increased handwashing with soap,

encouragement of appropriate feeding practices for ill children, and increased use of zinc supplementation.⁵³ To gain a broader, more global understanding of longer duration diarrhea, similar analyses should be conducted using the data from the other GEMS study sites.

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REFERENCES

- World Health Organization, 2013. *Diarrhoeal Disease Fact Sheet*. Geneva, Switzerland: World Health Organization. Available at: <http://www.who.int/mediacentre/factsheets/fs330/en/>. Accessed May 1, 2015.
- Walker CL, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta ZA, O'Brien KL, Campbell H, Black RE, 2013. Global burden of childhood pneumonia and diarrhoea. *Lancet* 381: 1405–1416.
- Kotloff KL, Blackwelder WC, Nasrin D, Nataro JP, Farag TH, van Eijk A, Adegbola RA, Alonso PL, Breiman RF, Faruque AS, Saha D, Sow SO, Sur D, Zaidi AK, Biswas K, Panchalingam S, Clemens JD, Cohen D, Glass RI, Mintz ED, Sommerfelt H, Levine MM, 2012. The Global Enteric Multicenter Study (GEMS) of diarrheal disease in infants and young children in developing countries: epidemiologic and clinical methods of the case/control study. *Clin Infect Dis* 55 (Suppl 4): S232–S245.
- Bhutta ZA, Nelson EA, Lee WS, Tarr PI, Zablach R, Phua KB, Lindley K, Bass D, Phillips A. Persistent Diarrhea Working Group, 2008. Recent advances and evidence gaps in persistent diarrhea. *J Pediatr Gastroenterol Nutr* 47: 260–265.
- Victora CG, Huttly SR, Fuchs SC, Nobre LC, Barros FC, 1992. Deaths due to dysentery, acute and persistent diarrhoea among Brazilian infants. *Acta Paediatr Suppl* 381: 7–11.
- Lima AA, Moore SR, Barboza MS Jr, Soares AM, Schleupner MA, Newman RD, Sears CL, Nataro JP, Fedorko DP, Wuhib T, Schorling JB, Guerrant RL, 2000. Persistent diarrhea signals a critical period of increased diarrhea burdens and nutritional shortfalls: a prospective cohort study among children in northeastern Brazil. *J Infect Dis* 181: 1643–1651.
- World Health Organization, 1988. Persistent diarrhoea in children in developing countries: memorandum from a WHO meeting. *Bull World Health Organ* 66: 709–717.
- Niehaus MD, Moore SR, Patrick PD, Derr LL, Lortz B, Lima AA, Guerrant RL, 2002. Early childhood diarrhea is associated with diminished cognitive function 4 to 7 years later in children in a northeast Brazilian shantytown. *Am J Trop Med Hyg* 66: 590–593.
- Bartlett AV, Hurtado E, Schroeder DG, Mendez H, 1992. Association of indicators of hygiene behavior with persistent diarrhea of young children. *Acta Paediatr Suppl* 381: 66–71.
- Kermani NA, Jafari F, Mojarad HN, Hoseinkhan N, Zali R, 2010. Prevalence and associated factors of persistent diarrhoea in Iranian children admitted to a paediatric hospital. *East Mediterr Health J* 16: 831–836.
- Black RE, 1993. Persistent diarrhea in children of developing countries. *Pediatr Infect Dis J* 12: 751–761.
- Thanh PN, Ly DT, Dung PT, Le PD, 1992. Clinical aspects of acute vs persistent diarrhea in Ho Chi Minh City, Vietnam. *Acta Paediatr Suppl* 381: 121–123.
- Lima AA, Guerrant RL, 1992. Persistent diarrhea in children: epidemiology, risk factors, pathophysiology, nutritional impact, and management. *Epidemiol Rev* 14: 222–242.
- Das SK, Faruque AS, Chisti MJ, Malek MA, Salam MA, Sack DA, 2012. Changing trend of persistent diarrhoea in young children over two decades: observations from a large diarrhoeal disease hospital in Bangladesh. *Acta Paediatr* 101: e452–e457.
- Karim AS, Akhter S, Rahman MA, Nazir MF, 2001. Risk factors of persistent diarrhea in children below five years of age. *Indian J Gastroenterol* 20: 59–61.
- Umamaheswari B, Biswal N, Adhisivam B, Parija SC, Srinivasan S, 2010. Persistent diarrhea: risk factors and outcome. *Indian J Pediatr* 77: 885–888.
- Moore SR, Lima NL, Soares AM, Oria RB, Pinkerton RC, Barrett LJ, Guerrant RL, Lima AA, 2010. Prolonged episodes of acute diarrhea reduce growth and increase risk of persistent diarrhea in children. *Gastroenterology* 139: 1156–1164.
- Fraser D, Dagan R, Porat N, el-On J, Alkrinawi S, Deckelbaum RJ, Naggan L, 1998. Persistent diarrhea in a cohort of Israeli Bedouin infants: role of enteric pathogens and family and environmental factors. *J Infect Dis* 178: 1081–1088.
- Lanata CF, Black RE, Gilman RH, Lazo F, Del Aguila R, 1991. Epidemiologic, clinical, and laboratory characteristics of acute vs. persistent diarrhea in periurban Lima, Peru. *J Pediatr Gastroenterol Nutr* 12: 82–88.
- Bhan MK, Bhandari N, Sazawal S, Clemens J, Raj P, Levine MM, Kaper JB, 1989. Descriptive epidemiology of persistent

- diarrhoea among young children in rural northern India. *Bull World Health Organ* 67: 281–288.
21. Mirza NM, Caulfield LE, Black RE, Macharia WM, 1997. Risk factors for diarrheal duration. *Am J Epidemiol* 146: 776–785.
 22. Patel AB, Ovung R, Badhoniya NB, Dibley MJ, 2012. Risk factors for predicting diarrheal duration and morbidity in children with acute diarrhea. *Indian J Pediatr* 79: 472–477.
 23. Strand TA, Sharma PR, Gjessing HK, Ulak M, Chandyo RK, Adhikari RK, Sommerfelt H, 2012. Risk factors for extended duration of acute diarrhea in young children. *PLoS One* 7: e36436.
 24. Baqui AH, Black RE, Yunus M, Hoque AR, Chowdhury HR, Sack RB, 1991. Methodological issues in diarrhoeal diseases epidemiology: definition of diarrhoeal episodes. *Int J Epidemiol* 20: 1057–1063.
 25. Morris SS, Cousens SN, Lanata CF, Kirkwood BR, 1994. Diarrhoea—defining the episode. *Int J Epidemiol* 23: 617–623.
 26. Pickering H, Hayes RJ, Tomkins AM, Carson D, Dunn DT, 1987. Alternative measures of diarrhoeal morbidity and their association with social and environmental factors in urban children in The Gambia. *Trans R Soc Trop Med Hyg* 81: 853–859.
 27. Wright J, Gundry SW, Conroy RM, 2007. A review of changing episode definitions and their effects on estimates of diarrhoeal morbidity. *J Health Popul Nutr* 25: 448–455.
 28. Wright JA, Gundry SW, Conroy R, Wood D, Du Preez M, Ferro-Luzzi A, Genthe B, Kirimi M, Moyo S, Mutisi C, Ndamba J, Potgieter N, 2006. Defining episodes of diarrhoea: results from a three-country study in sub-Saharan Africa. *J Health Popul Nutr* 24: 8–16.
 29. Rahman AE, Moinuddin M, Molla M, Worku A, Hurt L, Kirkwood B, Mohan SB, Mazumder S, Bhutta Z, Raza F, Mrema S, Masanja H, Kadobera D, Waiswa P, Bahl R, Zangenberg M, Muhe LPersistent Diarrhoea Research Group, 2014. Childhood diarrhoeal deaths in seven low- and middle-income countries. *Bull World Health Organ* 92: 664–671.
 30. Adazu K, Lindblade KA, Rosen DH, Odhiambo F, Ofware P, Kwach J, van Eijk AM, Decock KM, Amornkul P, Karanja D, Vulule JM, Slutsker L, 2005. Health and demographic surveillance in rural western Kenya: a platform for evaluating interventions to reduce morbidity and mortality from infectious diseases. *Am J Trop Med Hyg* 73: 1151–1158.
 31. Omore R, O'Reilly CE, Williamson J, Moke F, Were V, Farag TH, van Eijk AM, Kotloff KL, Levine MM, Obor D, Odhiambo F, Vulule J, Laserson KF, Mintz ED, Breiman RF, 2013. Health care-seeking behavior during childhood diarrheal illness: results of health care utilization and attitudes surveys of caretakers in western Kenya, 2007–2010. *Am J Trop Med Hyg* 89: 29–40.
 32. Robins-Browne RM, Levine MM, 2012. Laboratory diagnostic challenges in case/control studies of diarrhea in developing countries. *Clin Infect Dis* 55: S312–S316.
 33. Kenya National Bureau of Statistics and ICF Macro, 2012. *Kenya Demographic and Health Survey 2008–09*. Calverton, MD: KNBS and ICF Macro.
 34. UNICEF, 2013. *Statistics*. Kenya. Available at: https://www.unicef.org/infobycountry/kenya_statistics.html. Accessed May 3, 2015.
 35. UNICEF/WHO Joint Monitoring Programme, 2015. *Definitions and Methods*. Available at: <https://www.wssinfo.org/definitions-methods>. Accessed May 3, 2015.
 36. Filmer D, Pritchett L, 2001. *Estimating Wealth Effects without Expenditure Data—or Tears: An Application to Educational Enrollments in States of India*. *Demography*, 38: 115–132.
 37. Smith TS, Smith B, 2003. *Kaplan Meier And Cox Proportional Hazards Modeling: Hands on Survival Analysis*. San Diego, CA: Department of Defense Center for Deployment Health Research, Naval Health Research Center.
 38. Klein JP, Moeschberger ML, 2005. *Survival Analysis: Techniques for Censored and Truncated Data*, 2nd edition. New York, NY: Springer.
 39. Collett D, 2003. Models for binary and binomial data: strategy for model selection. Chatfield CL, Tanner M, Zidek J, eds. *Modelling Binary Data*. Boca Raton, FL: Chapman and Hall/CRC, Taylor & Francis Group.
 40. Nataro JP, Sears CL, 2001. Infectious causes of persistent diarrhea. *Pediatr Infect Dis J* 20: 195–196.
 41. Centers for Disease Control and Prevention, 2015. *Cryptosporidium Illness and Symptoms*. Centers for Disease Control and Prevention. Available at: <https://www.cdc.gov/parasites/crypto/illness.html>. Accessed May 15, 2015.
 42. Baldursson S, Karanis P, 2011. Waterborne transmission of protozoan parasites: review of worldwide outbreaks: an update 2004–2010. *Water Res* 45: 6603–6614.
 43. Keegan A, Daminato D, Saint CP, Monis PT, 2008. Effect of water treatment processes on Cryptosporidium infectivity. *Water Res* 42: 1805–1811.
 44. Ryan U, Hijawi N, 2015. New developments in Cryptosporidium research. *Int J Parasitol* 45: 367–373.
 45. Kotloff KL, Nataro JP, Blackwelder WC, Nasrin D, Farag TH, Panchalingam S, Wu Y, Sow SO, Sur D, Breiman RF, Faruque AS, Zaidi AK, Saha D, Alonso PL, Tamboura B, Sanogo D, Onwuchekwa U, Manna B, Ramamurthy T, Kanungo S, Ochieng JB, Omere R, Oundo JO, Hossain A, Das SK, Ahmed S, Qureshi S, Quadri F, Adegbola RA, Antonio M, Hossain MJ, Akinsola A, Mandomando I, Nhamposha T, Acácio S, Biswas K, O'Reilly CE, Mintz ED, Berkeley LY, Muhsen K, Sommerfelt H, Robins-Browne RM, Levine MM, 2013. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. *Lancet* 382: 209–222.
 46. McAuliffe JF, Shields DS, Auxiliadora de Sousa M, Sakell J, Schorling J, Guerrant RL, 1986. Prolonged and recurring diarrhea in the northeast of Brazil: examination of cases from a community-based study. *J Pediatr Gastroenterol Nutr* 5: 902–906.
 47. World Health Organization, 2015. *Household Water Treatment and Safe Storage: Treatment Technologies*. Geneva, Switzerland: World Health Organization.
 48. UNICEF/WHO Joint Monitoring Programme, 2012. *Post-2015 WASH Targets and Indicators*. Available at: https://www.unicef.org/wash/files/4_WSSCC_JMP_Fact_Sheets_4_UK_LoRes.pdf. Accessed May 20, 2015.
 49. Mintz E, Bartram J, Lochery P, Wegelin M, 2001. Not just a drop in the bucket: expanding access to point-of-use water treatment systems. *Am J Public Health* 91: 1565–1570.
 50. Bhutta ZA, Ghishan F, Lindley K, Memon IA, Mittal S, Rhoads JMCommonwealth Association of Paediatric Gastroenterology and Nutrition, 2004. Persistent and chronic diarrhea and malabsorption: working group report of the second World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 39 (Suppl 2): S711–S716.
 51. Nel E, 2010. Diarrhoea and malnutrition. *South Afr J Clin Nutr* 23: S15–S18.
 52. Das JK, Bhutta ZA, 2015. 3.6 Reducing the burden of acute and prolonged childhood diarrhea. *World Rev Nutr Diet* 113: 168–172.
 53. UNICEF/WHO, 2004. *Clinical Management of Acute Diarrhoea*. Available at: http://apps.who.int/iris/bitstream/10665/68627/1/WHO_FCH_CAH_04.7.pdf. Accessed May 2, 2015.
 54. Patel A, Mamtani M, Dibley MJ, Badhoniya N, Kulkarni H, 2010. Therapeutic value of zinc supplementation in acute and persistent diarrhea: a systematic review. *PLoS One* 5: e10386.
 55. Roy SK, Tomkins AM, Akramuzzaman SM, Chakraborty B, Ara G, Biswas R, Islam KE, Khatun W, Jolly SP, 2007. Impact of zinc supplementation on subsequent morbidity and growth in Bangladeshi children with persistent diarrhoea. *J Health Popul Nutr* 25: 67–74.
 56. Roy SK, Hossain MJ, Khatun W, Chakraborty B, Chowdhury S, Begum A, Mah-e-Muneer S, Shafique S, Khanam M, Chowdhury R, 2008. Zinc supplementation in children with cholera in Bangladesh: randomised controlled trial. *BMJ* 336: 266–268.

57. Arnold BF, Galiani S, Ram PK, Hubbard AE, Briceno B, Gertler PJ, Colford JM Jr, 2013. Optimal recall period for caregiver-reported illness in risk factor and intervention studies: a multicountry study. *Am J Epidemiol* 177: 361–370.
58. Liu J, Platts-Mills JA, Juma J, Kabir F, Nkeze J, Okoi C, Operario DJ, Uddin J, Ahmed S, Alonso PL, Antonio M, Becker SM, Blackwelder WC, Breiman RF, Faruque ASG, Fields B, Gratz J, Haque R, Hossain A, Hossain MJ, Jarju S, Qamar F, Iqbal NT, Kwambana B, Mandomando I, McMurtry TL, Ochieng C, Ochieng JB, Ochieng M, Onyango C, Panchalingam S, Kalam A, Aziz F, Qureshi S, Ramamurthy T, Roberts JH, Saha D, Sow SO, Stroup SE, Sur D, Tamboura B, Taniuchi M, Tennant SM, Toema D, Wu Y, Zaidi A, Nataro JP, Kotloff KL, Levine MM, Houpt ER, et al., 2016. Use of quantitative molecular diagnostic methods to identify causes of diarrhoea in children: a reanalysis of the GEMS case-control study. *Lancet* 388: 1291–1301.