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

Katharine A. Schilling, Centers for Disease Control and Prevention
Richard Omore, Kenya Medical Research Institute
Gordana Derado, Emory University
Tracy Ayers, Centers for Disease Control and Prevention
John B. Ochieng, Kenya Medical Research Institute
Tamer H. Farag, University of Maryland
Dilruba Nasrin, University of Maryland
Sandra Panchalingam, University of Maryland
James P. Nataro, University of Maryland
Karen L. Kotloff, University of Maryland

Only first 10 authors above; see publication for full author list.

Journal Title: American Journal of Tropical Medicine and Hygiene
Volume: Volume 97, Number 1
Publisher: American Society of Tropical Medicine and Hygiene | 2017-01-01, Pages 248-258
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.4269/ajtmh.16-0898
Permanent URL: https://pid.emory.edu/ark:/25593/t4t58

Final published version: http://dx.doi.org/10.4269/ajtmh.16-0898

Copyright information:
© The American Society of Tropical Medicine and Hygiene

Accessed February 1, 2019 7:54 AM EST
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

Katharine A. Schilling,1* Richard Omore,2,3 Gordana Derado,1 Tracy Ayers,1 John B. Ochieng,2,3 Tamer H. Farag,4 Dilruba Nasrin,5 Sandra Panchaligam,6 James P. Nataro,7,8 Karen L. Kotloff,9 Myron M. Levine,4 Joseph Oundo,6 Michelle B. Parsons,1 Cheryl Bopp,1 Kayla Laserson,2,7 Christine E. Stauber,8 Richard Rothenberg,8 Robert F. Breiman,6,9 Ciara E. O’Reilly,1 and Eric D. Mintz1

1Division of Foodborne, Waterborne, and Environmental Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; 2Kenya Medical Research Institute/Centers for Disease Control and Prevention, Kisumu, Kenya; 3Centre for Global Health Research, Kenya Medical Research Institute, Kisumu, Kenya; 4Center for Vaccine Development, School of Medicine, University of Maryland, Baltimore, Maryland; 5Department of Pediatrics, University of Virginia School of Medicine, Charlottesville, Virginia; 6Centers for Disease Control and Prevention, Nairobi, Kenya; 7Centers for Disease Control and Prevention, Delhi, India; 8School of Public Health, Georgia State University, Atlanta, Georgia; 9Emory Global Health Institute, Emory University, Atlanta, Georgia

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 inconsistent4–26; 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
specifically addressed in the management, treatment, and prevention of diarrheal diseases. 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. 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. 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.

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. 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). 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. 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. 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.

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. 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.

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.
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. 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. 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. 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
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*.
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 2**

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Children with AD ($N = 587$) n (%)</th>
<th>Children with ProAD ($N = 360$) n (%)</th>
<th>Children with PD ($N = 73$) n (%)</th>
<th>All children ($N = 1,020$) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age stratum (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–11</td>
<td>252 (42.9)</td>
<td>188 (52.2)</td>
<td>40 (54.8)</td>
<td>480 (47.1)</td>
</tr>
<tr>
<td>12–23</td>
<td>143 (24.4)</td>
<td>101 (28.1)</td>
<td>20 (27.4)</td>
<td>264 (25.8)</td>
</tr>
<tr>
<td>24–59</td>
<td>192 (32.7)</td>
<td>71 (19.7)</td>
<td>13 (17.8)</td>
<td>276 (27.1)</td>
</tr>
<tr>
<td>Gender, female</td>
<td>245 (41.7)</td>
<td>153 (42.5)</td>
<td>29 (39.7)</td>
<td>427 (41.9)</td>
</tr>
<tr>
<td>Etiology*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of pathogens</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No pathogens</td>
<td>112 (19.1)</td>
<td>61 (16.9)</td>
<td>11 (15.1)</td>
<td>184 (18.0)</td>
</tr>
<tr>
<td>One pathogen</td>
<td>243 (41.4)</td>
<td>131 (36.4)</td>
<td>35 (48.0)</td>
<td>409 (40.1)</td>
</tr>
<tr>
<td>More than one pathogen</td>
<td>232 (39.5)</td>
<td>168 (46.7)</td>
<td>27 (37.0)</td>
<td>427 (41.9)</td>
</tr>
<tr>
<td>Giardia</td>
<td>111 (18.9)</td>
<td>56 (15.6)</td>
<td>12 (16.4)</td>
<td>179 (17.6)</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>98 (16.7)</td>
<td>66 (18.3)</td>
<td>8 (11.0)</td>
<td>172 (16.9)</td>
</tr>
<tr>
<td>Enteroaggregative E. coli</td>
<td>83 (14.1)</td>
<td>69 (19.2)</td>
<td>14 (19.2)</td>
<td>166 (16.3)</td>
</tr>
<tr>
<td>Cryptosporidum</td>
<td>45 (7.7)</td>
<td>50 (13.9)</td>
<td>17 (23.3)</td>
<td>112 (11.0)</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td>46 (7.8)</td>
<td>36 (10.0)</td>
<td>12 (16.4)</td>
<td>94 (9.2)</td>
</tr>
<tr>
<td>ST-Enterotoxigenic E. coli (ST-only or LT/ST)</td>
<td>58 (9.9)</td>
<td>31 (8.6)</td>
<td>3 (4.1)</td>
<td>92 (9.0)</td>
</tr>
<tr>
<td>Shigella spp.</td>
<td>43 (7.3)</td>
<td>30 (8.3)</td>
<td>5 (6.9)</td>
<td>78 (7.7)</td>
</tr>
<tr>
<td>Typical EPEC</td>
<td>48 (8.2)</td>
<td>24 (6.7)</td>
<td>3 (4.1)</td>
<td>75 (7.4)</td>
</tr>
<tr>
<td>Atypical EPEC</td>
<td>35 (6.0)</td>
<td>20 (5.6)</td>
<td>3 (4.1)</td>
<td>58 (5.7)</td>
</tr>
<tr>
<td>Nontyphoidal Salmonella</td>
<td>30 (5.1)</td>
<td>24 (6.7)</td>
<td>4 (5.5)</td>
<td>58 (5.7)</td>
</tr>
<tr>
<td>LT-Enterotoxigenic E. coli</td>
<td>32 (5.5)</td>
<td>21 (5.8)</td>
<td>3 (4.1)</td>
<td>56 (5.5)</td>
</tr>
<tr>
<td>Campylobacter coli</td>
<td>31 (5.3)</td>
<td>18 (5.0)</td>
<td>5 (6.9)</td>
<td>54 (5.3)</td>
</tr>
<tr>
<td>Norovirus GII</td>
<td>25 (4.3)</td>
<td>17 (4.7)</td>
<td>0 (0.0)</td>
<td>42 (4.1)</td>
</tr>
<tr>
<td>Norovirus GI</td>
<td>13 (2.2)</td>
<td>18 (5.0)</td>
<td>2 (2.7)</td>
<td>33 (3.2)</td>
</tr>
<tr>
<td>Sapovirus</td>
<td>20 (3.4)</td>
<td>10 (2.8)</td>
<td>3 (4.1)</td>
<td>33 (3.2)</td>
</tr>
<tr>
<td>Adenovirus non-40/41</td>
<td>15 (2.6)</td>
<td>11 (3.1)</td>
<td>2 (2.7)</td>
<td>28 (2.8)</td>
</tr>
<tr>
<td>Adenovirus 40/41</td>
<td>15 (2.6)</td>
<td>11 (3.1)</td>
<td>1 (1.4)</td>
<td>27 (2.7)</td>
</tr>
<tr>
<td>Astrovirus</td>
<td>11 (1.9)</td>
<td>5 (1.4)</td>
<td>1 (1.4)</td>
<td>17 (1.7)</td>
</tr>
<tr>
<td>Enteroheastlytica</td>
<td>5 (0.85)</td>
<td>5 (1.4)</td>
<td>0 (0.0)</td>
<td>10 (0.98)</td>
</tr>
</tbody>
</table>

* Multiple enteric pathogens possible per child.

**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

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

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

* Not included are pathogens identified in less than 10 patients: Vibrio cholerae O1 (N = 5), Aeromonas (N = 1), enterohaemorrhagic E. coli (N = 3), Salmonella typhi (N = 3).
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 enrolment 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 diarrheal duration 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>
<thead>
<tr>
<th>Table 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
</tr>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Risk factors</td>
</tr>
<tr>
<td>Stunted</td>
</tr>
<tr>
<td>Children with &gt; 14 days of diarrhea</td>
</tr>
<tr>
<td>Children with ≤ 14 days of diarrhea</td>
</tr>
<tr>
<td>Main drinking water source</td>
</tr>
<tr>
<td>considered unimproved</td>
</tr>
<tr>
<td>Enteric pathogen*</td>
</tr>
<tr>
<td>Cryptosporidium</td>
</tr>
</tbody>
</table>

\( CI = \) confidence interval; GEMS = Global Enteric Multicenter Study.

* Multiple enteric pathogens possible per child.
longer significant. 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.\textsuperscript{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 methods\textsuperscript{47} 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.\textsuperscript{3} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{51} A malnourished child is less able to fight off infection which leads to more severe, longer duration illness.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 others\textsuperscript{54} 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.\textsuperscript{55,56} We found no significant differences in diarrheal duration among children reported 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.\textsuperscript{57}

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.\textsuperscript{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.\textsuperscript{58} The re-analysis 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.\textsuperscript{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.\textsuperscript{58} 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. To gain a broader, more global understanding of longer duration diarrhea, similar analyses should be conducted using the data from other GEMS study sites.

Received November 12, 2016. Accepted for publication January 31, 2017.

Note: Supplemental table appears at www.ajtmh.org.

Acknowledgments: This study includes data generated by the Kenya Medical Research Institute/Centers for Disease Control and Prevention (KEMRI/CDC) Health and Demographic Surveillance System (HDSS), which is a member of the International Network for the Demographic Evaluation of Populations and their Health (INDEPTH). We acknowledge the contributions of and thank the KEMRI/CDC HDSS team; the Global Enteric Multicenter Study (GEMS) Kenya staff for supporting the data collection and processing; the GEMS Kenya laboratory staff; the GEMS Data Coordinating Center, Perry Point Veterans Administration Medical Center, Perry Point, MD. We are grateful to the caretakers in the Asembo, Gem and Karemo communities who participated in this work. This manuscript is published with the approval of the director of KEMRI.

Financial support: The Global Enteric Multicenter Study (GEMS) was funded by the Bill & Melinda Gates Foundation through the University of Maryland, School of Medicine, Center for Vaccine Development, Baltimore, MD. Additional support for technical assistance with GEMS in Kenya was provided by the U.S. Agency for International Development through an Inter-Agency Agreement with the U.S. Centers for Disease Control and Prevention.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the U.S. Centers for Disease Control and Prevention.

Authors’ addresses: Katharine A. Schilling, Gordana Derado, Tracy Ayers, Michele B. Parsons, Cheryl Bopp, Clara E. O’Reilly, and Eric D. Mintz, Centers for Disease Control and Prevention, Atlanta, GA; E-mails: schillka@gmail.com, uwx8@cdc.gov, eyk6@cdc.gov, zcp9@cdc.gov, cabor4@cdc.gov, bxrf1@cdc.gov, and edm1@cdc.gov. Richard Omore and John B. Ochieng, Kenya Medical Research Institute/Centers for Disease Control and Prevention, Kisumu, Kenya, and Centre for Global Health Research, Kenya Medical Research Institute, Kisumu, Kenya, E-mails: omorerichard@gmail.com and bochieng@kemricdc.org. Tamer H. Farag, Dilruba Nasrin, Sandra Panchalingam, James P. Nataro, Karen L. Kotloff, and Myron M. Levine, Center for Vaccine Development, School of Medicine, University of Maryland, Baltimore, MD, E-mails: faragt@uw.edu, dnaarins@medicine.umaryland.edu, 7lingam@gmail.com, jpn2r@virginia.edu, kktolfo@medicine.umaryland.edu, and mlevine@medicine.umaryland.edu. Joseph Oundo, Centers for Disease Control and Prevention, Nairobi, Kenya, E-mail: joundo@kr.cdc.gov. Kayla Laserson, Centers for Disease Control and Prevention, New Delhi, India, and Kenya Medical Research Institute/Centers for Disease Control and Prevention, Kisumu, Kenya, E-mail: kle4@cdc.gov. Christine E. Slauber and Richard Rothenberg, School of Public Health, Georgia State University, Atlanta, GA, E-mails: cstauber@gsu.edu and rothenberg@gsu.edu. Robert F. Breiman, Emory Global Health Institute, Emory University, Atlanta, GA, and Centers for Disease Control and Prevention, Nairobi, Kenya, E-mail: rbreiman@emory.edu.

REFERENCES


