Exploring Leading Causes of Childhood Morbidity using the Global Enterics Multicenter Study (GEMS), Rural Western Kenya, 2008-2012

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Exploring Leading Causes of Childhood Morbidity using the Global Enterics Multicenter Study (GEMS), rural western Kenya, 2008-2012

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ABSTRACT

Diarrhea, malnutrition, and human immunodeficiency virus (HIV) are three leading causes of childhood morbidity and mortality. All of these conditions impact children living in sub-Saharan Africa disproportionately to the rest of the world. This dissertation outlines three papers in which these three childhood health problems are explored in greater detail in one low-income country in sub-Saharan Africa (Kenya) using data from the Global Enteric Multicenter Study (GEMS). In particular the three papers will explore further: 1) risk factors for the duration of diarrhea, 2) water, sanitation, and hygiene (WASH) practices among people living with HIV (PLHIV), and 3) a methodological paper exploring distribution and outlier analysis from anthropometric data documenting stunting. As evidenced here the burden of diarrhea, malnutrition, and HIV/AIDS is significant within this population in rural western Kenya. It’s likely that in many countries in sub-Saharan Africa similar health problems and challenges are being experienced in young children. These studies contribute to the epidemiology of diarrheal duration. They add to the knowledge about the water, sanitation, and hygiene practices (WASH) practices and behaviors among HIV infected individuals. And, they contribute to the methodological processes for cleaning anthropometric data. Based on findings from our studies, stunting, a signal of long-term nutritional deficiencies and malnutrition is a serious health problem within this population. We found that a high proportion of both case and control children were stunted. In addition, children who were stunted at enrollment tended to have longer duration diarrhea. Improving overall nutritional status among young children in rural western Kenya is imperative. Furthermore, a more standardized approach to dealing with extreme values within anthropometric data is important so that these measures can be better understood and interpreted. Another key finding was the importance of the main drinking water source. We found using an unimproved water source to be a risk factor for diarrheal duration. We found no differences in drinking water sources among HIV-positive households as compared to HIV-negative households. However, a large proportion of HIV-positive and HIV-negative households were using unimproved water sources. Due to the increased adverse consequences among PLHIV and the increased risk for longer duration diarrhea improving access to adequate water sources is especially important among children living in this region of rural western Kenya. Our studies also highlighted differences in WASH practices among HIV-positive households who were aware of their status for at least one month prior to enrollment into GEMS as compared to households who found out their status more recently. Further investigation should identify what is contributing to these results so they can be applied at a larger scale in similar populations. Last, the etiologic agent with which the child is infected seemed to be an important factor in diarrheal duration. Prevention and treatment methods for pathogens causing severe illness, such as Cryptosporidium are warranted.
Chapter 1: Introduction and Statement of Purpose
Diarrhea, malnutrition, and human immunodeficiency virus (HIV) are three leading causes of childhood morbidity and mortality. All of these conditions impact children living in sub-Saharan Africa disproportionately to the rest of the world. This dissertation outlines three papers in which these three childhood health problems are explored in greater detail in one low-income country in sub-Saharan Africa (Kenya) using data from the Global Enteric Multicenter Study (GEMS). In particular the three papers will explore further: 1) risk factors for the duration of diarrhea, 2) water, sanitation, and hygiene (WASH) practices among people living with HIV (PLHIV), and 3) a methodological paper exploring distribution and outlier analysis from anthropometric data documenting stunting.

Three Leading Childhood Health Problems

Diarrhea, malnutrition, and HIV cause significant illness on their own, but when a child is suffering from two or more these health issues in combination the consequences to the child’s health and life can be devastating. For example, when a child is malnourished he is less able to fight off infection and therefore diarrhea can cause more severe illness that tends to last longer (Nel, 2010). On the other hand if the child has diarrhea, particularly persistent diarrhea the child may be eating less than usual and the body may be unable to absorb nutrients as it would if the child were healthy, in turn leading to poorer nutritional status (Nel, 2010). Among children living with HIV, common co-morbidities include malnutrition and diarrheal illness. Outside of the physiological complications, other risk factors that may influence these relationships and consequences of these illnesses include many social and economic factors such as socioeconomic status, access to healthcare, infant and young child feeding practices, access to improved water source(s), adequate sanitation, and hygiene facilities, and caregiver’s education level, to name a few. Figure 1.1 diagrams the relationship between these three childhood health problems described here within, identifies potential risk factors for and effects of these co-morbidities, and presents a number of factors that may influence these relationships.
GEMS is a large international, epidemiological study on diarrheal diseases conducted in sub-Saharan Africa and south Asia. The purpose of GEMS was to explore the burden, etiologies, risk factors, and complications of moderate-to-severe diarrhea (MSD) in children less than 5 years of age. Although the primary outcome of interest in GEMS was MSD, the GEMS Kenya study site collected data on prolonged and persistent diarrhea, HIV, and malnutrition. This provides us a unique opportunity to explore these three childhood health problems in one low-income country in sub-Saharan Africa. The purpose of this dissertation will be to further explore three leading childhood health problems among children and their families using data collected in Kenya as part of GEMS. The purpose of the three papers presented within this dissertation is briefly described below:
• The first paper focuses on examining the duration of MSD in Kenyan children less than 5 years old whom were enrolled as cases in GEMS. This paper describes the risk factors for the duration of MSD.
• The second paper examines water, sanitation, and hygiene practices among HIV-positive and HIV-negative households.
• The third paper is a methodological paper that explores various criteria for excluding extreme height and height-for-age z-scores values. It demonstrates how these methods can be applied to anthropometric data and the influence that each has on the data in terms of the measures of location and dispersion.

Duration of Diarrhea

Globally, diarrheal disease is a leading cause of death amongst young children (WHO, 2009). It is responsible for approximately 580,000 deaths among children under 5 years of age each year (Walker, 2013). Diarrhea is often a result of ingesting enteric pathogens either through drinking or eating contaminated water or food, present in the environment because of poor water and sanitation facilities (Lim et al., 2012).

Persistent diarrhea (PD) has been used to describe diarrhea lasting 14 days or longer (Lim et al., 2012). As rates of acute diarrhea (≤6 days) (AD) have decreased over the years, PD has become a larger percentage of the diarrheal disease burden in children (Kotloff et al., 2012). Of additional importance, higher rates of death have been reported amongst infants presenting with PD as compared to those with AD (Victora et al., 1992). Furthermore, PD can lead to a number of health consequences including delays in growth (Lima et al., 2000), nutritional deficiencies (WHO, 1988), and decreased cognitive function over time (Victora, Huttly, Fuchs, Nobre, & Barros, 1992; Lima et al., 2000). The risk factors for
PD have been documented; however, many of the studies are quite old dating back 10 to 20 years. From the previous research, prominent risk factors include: age (Kermani, Jafari, Mojarad, Hoseinkhan & Zali, 2010; Bartlett, Hurtado, Schroeder & Mendez, 1992), malnutrition (Niehaus et al., 2002; Bartlett et al., 1992; Kermani et al., 2010; Black, 1993; Das, Faruque, Chisti, Malek, Salam, & Sack, 2012; Karim, Akhter, Rahman, & Nazir, 2001; Umamaheswari, Biswal, Adhisivam, Parija, & Srinivasa, 2010), etiologic agent in which the child is infected, maternal education level (Kermani et al., 2010; Black, 1993; Thanh, Ly, Dung & Le, 1992), previous diarrheal illness (Victora et al., 1992; Niehaus et al., 2002; Moore et al., 2010), breastfeeding practices (Thanh et al., 1992), bloody diarrhea (Lima & Guerrant, 1992; Das et al., 2012), antibiotic or antimicrobial use (Das et al., 2012; Umamaheswari et al., 2010; Karim et al., 2001), sanitary conditions within the home (Bartlett et al., 1992; Mirza, Caulfield, Black & Macharia, 1997; Karim et al., 2001) and the age of a child when they first experience diarrhea (Black, 1993).

More recently, it has been established that diarrhea lasting 7 to 13 days, also known as prolonged acute diarrhea (ProAD) is an important diarrhea durational length since it has been seen to be predictive of future PD episodes and the consequences thereof (WHO, 1988). Moore and colleagues (2010) evaluated diarrheal illness in a cohort of young Brazilian children over a span of 10 years, specifically exploring risks factor 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 etiologic agents Cryptosporidium and Shigella, time of weaning, and being stunted prior to the ProAD event as well as being stunted and underweight after the diarrheal event (WHO, 1988). Others have noted age, nutritional status, breastfeeding practices, health of the child at diarrheal onset, and the time of year in which the diarrheal event occurs to be associated with diarrhea lasting more than 7 days (Strand et al., 2012; Patel, Ovung, Badhoniya & Dibley, 2012). Limited research has focused on this diarrheal length; however, due to the seemingly important characteristics and possibly predictive nature of this durational length other researchers have suggested focusing on
“prolonged diarrhea” or diarrhea lasting longer than 5 to 7 days, but not exceeding 14 days (Kotloff et al., 2012; WHO, 1988).

Research on how to define a diarrheal episode is also limited and fairly inconsistent (Wright, Gundry, & Conroy, 2007; Wright et al., 2006; Morris, Cousens, Lanata, & Kirkwood, 1994; Bacqui, Black, Hoque, Chowdhury, & Sack, 1991; Pickering, Hayes, Tomkins, Carson, & Dunn, 1986); however, the recent study describing prolonged acute diarrhea employed a definition of two consecutive diarrhea-free days as the end of a diarrheal episode (Moore et al., 2010). 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 2 consecutive diarrhea-free days (WHO, 1988).

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 (Rahman, 2014). A better understanding of the key risk factors for these types of diarrheal disease of prolonged duration is warranted in order to identify the most appropriate interventions and strategies to reduce the burden of ProAD and PD.

Water, sanitation, and hygiene practices among people living with HIV/AIDS

Worldwide, it’s estimated 35.3 million people are infected with HIV (WHO, 2013a). The greatest burden of people living with HIV/AIDS (PLHIV) is concentrated in sub-Saharan Africa (WHO, 2013a). Approximately, 3.34 million children are infected with HIV. Every day about 700 new infections occur among children (WHO, 2013b). In Kenya, approximately 5.6% of adults are infected with HIV (UNAIDS, 2013). HIV prevalence is higher in women (6.9%) as compared to men (5.6%). It is estimated that more than 190,000 children aged 0-14 years are living with HIV in Kenya (UNAIDS, 2013).

HIV attacks and weakens the immune system of infected persons making them more susceptible to illness and death. As a result, diarrheal illness is often a common infection among PLHIV. Diarrhea is
frequently a consequence of ingesting contaminated food or water. Food and water typically become contaminated because of insufficient water or sanitation facilities and poor hygiene practices (WHO, 2013b). Certain enteric pathogens, especially intestinal parasites, have been more commonly identified among people living with HIV (Nkenfou, Nana, & Payne, 2013; Kipyegam, Sivairo, & Odhiambo, 2012; Gumbo et al., 1999). In healthy persons these infections can cause significant illness, but in PLHIV illness is typically more severe and lasts longer (Lule et al., 2005; Mermin et al., 2005). Furthermore, PLHIV often have an increased need for water as they usually use more for hygienic purposes and keeping themselves healthy and away from opportunistic infections (Ngwenya, 2006; WHO, 2010).

Owing to the increased adverse consequences among PLHIV, improving access to adequate water and sanitation facilities is especially important (8). It has been found that improving water, sanitation, and hygiene (WASH) practices can have positive health benefits among PLHIV (Peletz et al., 2013; Peletz et al., 2012; Yates, Lantagne, Mintz, & Quick, 2015). A recent systematic review examining studies reporting on the health effects of WASH interventions implemented among PLHIV (Peletz et al., 2013) found that water quality interventions reduced morbidity among PLHIV by 43% (RR=0.57, 95% CI:0.38-0.86) when pooling the data from 7 studies (Lule et al., 2005; Peletz et al., 2013; Barzilay et al., 2011; Abebe et al., 2014; Colford et al., 2005; Harris et al., 2009; Huang & Zhou, 2007). Only one study included within the review reported on a hand washing intervention; however, it found that morbidity was reduced by 58% (RR=0.42, 95% CI: 0.33-0.54) (Peletz et al., 2013; Huang & Zhou, 2007). Shortly thereafter, another review article examining the health impact of WASH interventions on PLHIV (Yates et al, 2015) concluded that both water quality and hand washing interventions reduced morbidity. Furthermore, they found that households with improved water supplies had less diarrheal morbidity, especially as a result of intestinal parasites (Yates et al, 2015). They also noted that having a household sanitation facility as compared to open defecation or sharing a sanitation facility reduced the risk of diarrhea among PLHIV.
The evidence suggests improved WASH is important for PLHIV; however, numerous barriers limiting access to these services and facilities have been identified. Knowledge, attitudes, cost and increased illness have all been noted as factors to inhibit one’s ability to utilize or have access to improved WASH facilities among PLHIV (Mugambe, Tumwesigye, Larkan, 2013; Yallew et al., 2012). Discrimination and stigma have also contributed to inadequate access to WASH (Mugambe et al., 2013; Yallew et al., 2012; WaterAid, 2010). Accounts report that PLHIV have been prevented from using certain water sources and sanitation facilities and have been made to travel farther distances to both water sources and sanitation facilities (Yallew et al., 2012; WaterAid, 2010; Nkongo, 2009).

**Malnutrition in young children**

Malnutrition is a leading cause of morbidity and mortality in young children globally (Black et al., 2008). Worldwide, approximately 2.2 million children under five years old die as a result of being malnourished (Black et al., 2008). Malnutrition can lead to delays in physical and cognitive development among other health complications (Black et al., 2008). A common way of assessing malnutrition in young children is to collect anthropometric data or body measurements such as height, weight, mid-upper arm circumference, or head circumference. These values along with the gender and age of the child are used to compute indicators, typically expressed as z-scores, such as weight-for-age z-scores (WAZ), height-for-age z-scores (HAZ), or weight-for-height z-scores (WHZ) (O’Donnell, van Doorlaer, Wagstaff, & Lindelow, 2010). These indicators can then be compared to a standardized reference population from a healthy, ethnically-diverse population of children (WHO, 2006). Z-scores below certain thresholds are indicative of the level and severity of nutritional deficiencies. Three commonly well-known and well-accepted indicators include a HAZ < -2 which is indicative of stunting, a WAZ < -2 indicates being underweight, and a WHZ < -2 is considered wasting (WHO, 1995). Being stunted is a
long-term indicator of malnutrition whereas wasting is an indicator of short-term malnutrition (WHO, 1995).

The relationship between malnutrition and diarrheal duration is well established; it’s been noted as one of the most significant risk factors for PD (Bhutta et al., 2004). Our results corroborate this relationship as well, we found that children who were stunted (HAZ < -2) at enrollment experienced longer diarrheal events. Many other studies identified malnutrition as important risk factors as well (Black, 1993; Thanh et al., 1992; Lima & Guerrant, 1992; Das et al., 2012; Karim et al., 2010; Umamaheswari et al., 2010). The relationship between malnutrition and diarrheal duration is two-way (Nel, 2010). When a child is malnourished he is less able to fight off infection and therefore diarrhea can cause more severe illness that tends to last longer (Nel, 2010). On the other hand if the child has diarrhea, particularly PD, the child may be eating less than usual and the body may be unable to absorb nutrients as it would if the child were healthy, in turn leading to poorer nutritional status (Nel, 2010).

There’s a strong relationship between malnutrition and HIV/AIDS (WHO, 2005). The nutritional requirements of a child infected with HIV/AIDS are greater than those of a healthy child (WHO, 2005). Children living with HIV/AIDS often experience growth faltering and are malnourished (WHO, 2005). HIV infected children may experience growth faltering for a number of reasons some of which may be a result of the HIV virus, or due to infections that occur more frequently and with greater severity as a result of their weakened immune system, or due to a decrease in appetite because of the medications a child may be taking (Sint et al., 2013). Socioeconomic factors such as poverty and/or insufficient food supplies may also contribute to poor nutritional intake, in turn lead to inadequate growth (Sint et al., 2013). As a result of being malnourished, the HIV-infected child’s immune system is further weakened (Anabwani & Navario, 2005). Furthermore, children who are malnourished and infected with HIV/AIDS have an increased risk of death compared to children infected with HIV/AIDS (Callens et al, 2009; WHO, 2005).
Anthropometric measures are good predictors of the nutritional status at both the individual and population level (Suchdev, 2006). Furthermore, they can be obtained economically and can be collected in a reasonable amount of time (Cogill, 2003). In order to obtain accurate measures, however, data must be collected methodically since there are numerous ways error can be introduced. Moreover, the analysis of anthropometric data is important in order to obtain an accurate interpretation of the nutritional status of an individual or a population. Often, anthropometric data will contain values that are outside of what would seem biologically plausible. Guidance on how best to deal with extreme values within anthropometric data is limited (Cogill, 2003; WHO, 1995; PANDA, n.d.). The criteria that do exist are very liberal, and do not focus on the change in growth over time.

Results from these papers will be useful to those working in the field of child health, specifically those working on diarrheal disease, HIV, or malnutrition. The data from these studies will help to inform future public health interventions and methodologies for future research.

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Diarrheal disease is a leading cause of death among young children worldwide. As rates of acute diarrhea (AD) (1-6 days) have decreased, persistent diarrhea (PD) (>14 days) 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 Enterics Multicenter Study. We constructed a Cox Proportional Hazards Model to identify factors associated with diarrheal duration. We found, 587 (58%) children experienced AD, 360 (35%) had prolonged acute diarrhea (ProAD) or diarrhea lasting 7-13 days, and 73 (7%) had PD. Risk factors independently associated with longer diarrheal duration included infection with Cryptosporidium (Hazard Ratio [HR]: 0.868, \( p \)-value: 0.035), using an unimproved drinking water source (HR: 0.87, \( p \)-value: .035), and being stunted at enrollment (HR: 0.026, \( p \)-value: <.0001). Diarrheal illness of extended duration appears to be multifactorial. To reduce the length and severity of diarrheal illness effective strategies should be implemented. 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 feeding practices for ill children.
INTRODUCTION

Globally, diarrheal disease is a leading cause of death among young children. It is responsible for approximately 580,000 deaths among children under 5 years of age each year. Diarrhea is often a result of ingesting enteric pathogens through drinking or eating contaminated water or food, as a result of poor water, sanitation and hygiene conditions. To explore the burden, etiologies, risk factors, and complications of moderate-to-severe diarrhea (MSD) the largest ever, international, epidemiological study on diarrheal diseases was conducted. The Global Enteric Multicenter Study (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.

One sub-objective of GEMS was to assess persistent diarrhea (PD) as an outcome of MSD. PD has been used to describe diarrhea lasting 14 days or longer. As rates of acute diarrhea (1-6 days) (AD) have decreased over the years, PD has become a greater proportion of the diarrheal disease burden in children. Of additional importance, higher rates of death have been reported among infants presenting with PD than among those with AD. Furthermore, PD can lead to a number of health consequences including delays in growth, nutritional deficiencies, and decreased cognitive function over time. Risk factors for PD have been documented; however, many of the studies are quite old dating back 10 to 20 years. From previous research, prominent risk factors include: age, malnutrition, the etiologic agent that the child is infected with, maternal education level, previous diarrheal illness, breastfeeding practices, bloody diarrhea, antibiotic or antimicrobial use, poor sanitary conditions within the home, and the age of a child when they first experience diarrhea.

More recently, it has been established that diarrhea lasting 7 to 13 days, also known as prolonged acute diarrhea (ProAD), is an important category as it has been associated with future PD episodes and the consequences thereof. Moore and colleagues 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 etiologic agents (Cryptosporidium and Shigella), age at weaning, and being stunted before the ProAD event and being stunted and underweight after the diarrheal event. Others have noted age, nutritional status, breastfeeding practices, health of the child at diarrheal onset, and the time of year in which the diarrheal event occurs as factors associated with diarrhea lasting ≥7 days. Limited research has focused on prolonged acute diarrhea; however, due to the important characteristics and apparent consequences of this durational length other researchers have suggested focusing on “prolonged diarrhea” lasting between 5 to 7 days, but less than 14 days. Research on how to define a diarrheal episode is also limited and fairly inconsistent; however, a recent study describing prolonged acute diarrhea employed a definition of 2 consecutive diarrhea-free days as the end of a diarrheal episode. 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 2 consecutive diarrhea-free days.

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 paper we describe the characteristics of and factors associated with the duration of moderate-to-severe diarrhea among GEMS-Kenya case children <5 years old.

**METHODS AND MATERIALS**

The Global Enterics Multicenter Study.
GEMS is a multi-site, case-control study to estimate the burden, etiology, risk factors, and complications of moderate-to-severe diarrhea (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 paper focuses on data from the GEMS-Kenya site. The study site was coordinated in partnership with the Centers for Disease Control and Prevention (CDC) and the Kenya Medical Research Institute (KEMRI). This site 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 a Health and Demographic Surveillance System (HDSS) implemented within each country. The HDSS enumerated all persons living within the regional bounds of the surveillance system on a routine basis. Children were eligible to be enrolled into GEMS as a case with MSD if they were <5 years old and presented to select DSS sentinel health centers. MSD was defined as ≤3 loose stools per day, for ≤7 days, with one or more of the following signs indicative of dehydration: sunken eyes, loss of skin turgor, intravenous rehydration administered or prescribed; or dysentery; or hospitalized with diarrhea or dysentery. Using the HDSS, children with similar characteristics were identified and enrolled as controls at their home within 2 weeks of case enrollment. Controls were matched on age, sex, and geographic location (i.e. the same/nearby village). Children were not eligible for re-enrollment if they were currently enrolled in GEMS. The GEMS enrollment period lasted until the 60-day follow-up interview was conducted, after which time re-enrollment 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. Questionnaires were used to collect demographic information, household level characteristics, and to assess risk factors for diarrheal disease. A follow-up
home visit was conducted between 49 and 91 days for all cases and controls during which time 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 HIV status for a sub-set 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. The GEMS-Kenya study site was located in rural western Kenya in Nyanza Province. During the first enrollment period the study was conducted in the districts of Gem and Asembo, and during the second enrollment period in the districts of Asembo and Karemo because the KEMRI/CDC Kenya HDSS had moved to a neighboring area.

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/AIDS, and malaria. These 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 acute diarrhea; diarrhea lasting 7 - 13 days was considered prolonged acute diarrhea, and; diarrhea lasting ≥14 days was persistent diarrhea. The end of a diarrheal episode was defined by 2 consecutive diarrhea-free days.

**Data Sources for Diarrheal Duration.**

Diarrhea duration was determined using two data sources. First, 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 time period (we considered the days of diarrhea reported to
be consecutive -- children with more than 7 consecutive days of diarrhea were ineligible for enrollment).

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).

Upon 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. 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 CRFs 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
When counting diarrheal days after enrollment, we took into account days in which diarrhea was not reported. As noted, once a child experienced 2 consecutive days of normal stool the episode was considered over. If the child subsequently experienced diarrhea this was considered a new episode; however, for the purposes of this investigation we only included children who had a single episode of diarrhea.

**Eligibility for analysis.**

For the purposes of this study, only case children experiencing a single episode of diarrhea during a 20-day reporting period with complete data were included. Control children were not included as the primary outcome of interest was duration of diarrheal. We excluded children whose Memory Aid form was incomplete (4.7%) or missing (6.6%).

**Statistical Analysis.**

In this paper we provide descriptive statistics, unadjusted analysis, and a multivariable, time-to-event analysis using a stratified Cox Proportional Hazards (PH) Model to examine factors associated with diarrheal disease duration. Our main outcome variable of interest was diarrheal disease duration (in days). 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 paper, 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 survival analysis; a procedure used to test for differences in survival function for two or more groups without adjusting for other covariates. Factors likely to influence the duration of diarrhea were determined *a priori* based on previous research, biological plausibility, or established epidemiological links. Clinical and biological factors we explored 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 characteristics.

Any variable with a bivariate p-value ≤0.10 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 Pearson Correlation Coefficients. Variables with a Spearman Correlation Coefficient >.3 were considered for removal from further multivariable modeling. One variable from each correlated pair was removed based on epidemiological significance to our study.

One of the key assumptions in the Cox PH model (in addition to that of non-informative censoring) is that of proportional hazards. In a regression type setting this means that the survival curves for two strata must have hazard functions that are proportional over time (i.e. constant relative hazard).

In a multivariable model, each of the covariates needs to satisfy the proportionality assumption. If hazards are not proportional, that means that the linear component of the model varies with time in some manner. Proportionality assumption for the Cox PH model was assessed for each variable graphically through visual inspection of the survival curves and the ‘log of negative log of survival’ against the log of time curves. If the proportionality of hazard assumption is satisfied, the survival curves should not converge or cross, and the log-of-negative-log’ curves should be approximately parallel, i.e. the distance between them should be roughly the same. Two variables violated this assumption, age group and whether the child was stunted at enrollment. To deal with this we stratified the model by age group and we created time-dependent variables for being stunted at enrollment. To do this, 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 are 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 choose the event time with the best fit based on the which pair minimized the log likelihood.

After all variables were identified for inclusion in the multivariable model, a stepwise manual selection process was employed. The final model was assessed for fit by examining the log likelihood statistics of the null model as compared to the final model, by examining deviance statistics, and by visual inspection of standardized deviance residual plots. 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 differ when we exclude children multiply enrolled. Hazard ratios, confidence intervals, and p-values are presented for the final model.

Data were analyzed using SAS 9.3.

Scientific Ethics.

Written informed consent was collected from all parents of children who participated in GEMS before their participation in the study. The GEMS protocol was approved by the KEMRI Scientific and Ethical Review Committee and the Institutional Review Board (IRB) at University of Maryland, School of Medicine, Baltimore, MD, USA. The Centers for Disease Control and Prevention, Atlanta, GA, USA, 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. 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 female (see Table 2).

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 1). To present these data descriptively we use three diarrheal duration categories: AD (1-6 days), ProAD (7-13 days), or PD (≥14 days). In our study sample, 587 (58%) experienced AD, 360 (35%) had ProAD, and 73 (7%) had PD. Only one child had diarrhea for the entire 20-day reporting 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 case 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. When assessed, the number of pathogens identified in a child’s stool did not appear to influence 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 (E. coli) (14%),
enterotoxigenic E. coli (10%), and typical enteropathogenic E. coli (8%) (Table 1). For children
experiencing ProAD the most common pathogens identified were enteroaggregative E. coli (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%),
enteroaggregative E. coli (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 to children with ProAD or AD
(Table 2). Also a higher proportion of households with children experiencing PD reported using a shared
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 were given less than usual to drink. A larger percentage (79%) of all
children regardless of diarrhea duration type were given less than usual to eat. Children who were
stunted, wasted, or underweight at the time of enrollment had higher amounts of PD as compared to
children with ProAD or AD.

Factors Associated with Diarrhea of Extended Duration.

To identify factors associated with diarrheal duration we first conducted Kaplan-Meier survival
analysis. We used log-rank test from Kaplan-Meier analysis to identify potential factors associated with
longer diarrheal duration. Based on the long-rank test, 13 variables with p-value < 0.1 were considered in
multivariable modeling using Cox PH model. As shown in Table 3, four etiologic agents appeared to be
associated with extended diarrheal duration. These were ETEC (ST any) (log-rank p-value: 0.07), EAEC
(p-value: 0.08), Cryptosporidium spp. (p-value: <.0001), and C. jejuni (p-value: 0.04). Other factors
potentially associated with longer diarrheal duration, included the age group, 0-11 months, 12-23
months, or 24-59 months (p-value: <.0001), whether the child was stunted (p-value: 0.04), wasted (p-value: 0.08), or underweight (p-value: 0.09) at enrollment, whether the child was exclusively breastfed, partially breastfed, or not breastfed at all (p-value: 0.003), whether the child was offered less than usual to eat (p-value: 0.02) or drink (p-value: 0.01) while ill, the primary caregivers education level (p-value: 0.06), having an unimproved drinking water source (p-value: 0.004), or having a shared sanitation facility (p-value: 0.02) (see Table 3). We assessed for correlation between these variables and found the following correlated with one another: 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 choose to remove breastfeeding, being offered less than usual to eat while ill, and being wasted or underweight at enrollment from any further multivariable modeling, the other variables remained.

Since the age variable violated the proportionality of hazards assumption, we used a stratified Cox PH modeling approach. Another variable violated the PH assumption: being stunted at enrollment. A time-dependent variable was defined, based on the optimal cut-off point (14 days). In this analysis 57 children were right censored (diarrhea persisted through the period of observation and we were unable to determine when the child’s diarrhea ceased). When assessed for model fit, based on the fit statistics and examination of the residual plots, there was no indication of a significant lack of fit. We conducted a similar analysis 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 included 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-value: 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 to children who were not infected with
Cryptosporidium. We also found that children whose main drinking water source was considered
unimproved (HR: 0.87 [CI: 0.76, 0.99], p-value: 0.035) and those who were stunted at enrollment and
had diarrhea for more than 14 days (HR: 0.03 [CI: 0.01, 0.10], p-value: <.0001) were also at greater risk
for experiencing longer duration diarrhea.

DISCUSSION

This is the first study of persistent and prolonged acute diarrhea using the GEMS dataset. GEMS
conducted comprehensive risk factor assessments for diarrheal disease, all GEMS stool samples were
tested for a full spectrum of bacterial, viral, and protozoal enteric pathogens, and a memory aid was
used to help document diarrheal duration. GEMS 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 the burden and consequences of these health problems. Among
Kenyan children <5 years of age, we found that over half had acute diarrhea, about 35% had diarrhea
lasting 7 to 13 days, and 7% had diarrhea that lasted 14 or more days. In this study, factors associated
with longer duration diarrhea included the enteric pathogen identified in the child’s stool specimen, the
child’s nutritional status at enrollment, and the household’s drinking water source. Children infected
with Cryptosporidium had longer duration diarrhea as did children with MSD who were stunted at
enrollment. In addition children whose household’s main drinking water came from an unimproved
source had longer duration diarrhea.

Etiologic Agent
In our analysis of crude and adjusted factors associated with longer diarrheal duration we identified a number of etiologic agents associated with longer diarrheal duration including *Cryptosporidium*, EAEC, ETEC (ST any), and *C. jejuni*. Children infected with *Cryptosporidium* had longer duration diarrhea than children not infected with *Cryptosporidium*, confirming its association with ProAD and PD in earlier studies.\(^{14,18,40}\) Cryptosporidiosis is characterized by watery diarrhea lasting up to 4 or more weeks in 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 and vaccines for *Cryptosporidium* are not highly effective nor readily available.\(^{44}\) In addition to being a major cause of MSD in children <5 years old in all seven GEMS sites,\(^{45}\) *Cryptosporidium* was an important and independent factor associated with longer diarrhea duration in Kenyan children enrolled in GEMS. In children 12-23 months old with MSD, *Cryptosporidium* was associated with an increased risk of death.\(^{45}\) In Kenya, a GEMS site with high rates of HIV, it was identified in significantly more case children with MSD as compared to control children.\(^{45}\) As a result, efforts to find water quality interventions that are effective against *Cryptosporidium* 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, ETEC (ST any), and *C. jejuni*. Other studies have also noted the association between these pathogens and longer diarrheal duration.\(^{18,46}\)

**WASH characteristics**

Using an unimproved water source was associated with longer duration diarrhea in crude and adjusted analysis. To our knowledge no other studies have identified using an unimproved water source as an independent factor associated with longer diarrheal duration. In Bangladesh, using an unimproved water source was associated with PD upon bivariate analysis; however, when adjusting for other factors this association was no longer significant.\(^{16}\) 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{22} 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 over-reported 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; however, we choose not explore this association in multivariable analysis due to the variable violating the proportionality assumption of the Cox PH model. One study in Guatemala found sanitation practices to be associated with longer diarrheal duration. In this study, researchers found the presence of feces either on the ground, in the household compound or in the yard to be risk factors for longer duration diarrhea.\textsuperscript{10} The relationship between sanitation and longer duration diarrhea warrants further investigation, especially in light of the proposed reclassification of shared sanitation as no longer unimproved.

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. Furthermore, awareness about adequate sanitation and promotion of handwashing with soap should be encouraged.

\textit{Nutritional Deficiencies}

Malnutrition has been noted as one of the most significant risk factors for PD.\textsuperscript{12-17,48} 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. A malnourished child is less able to fight off infection which leads to more severe, longer duration illness. On the other hand, 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. 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 children include the promotion of exclusive breastfeeding up to 6 months of age, and administering oral rehydration solution, zinc supplementation for diarrheal prevention and treatment. In our study, among infants aged 0-6 months enrolled in the first three years of GEMS, 15% of mothers reported exclusively breastfeeding their infant, 83% reported partial breastfeeding, and 3% reported not breastfeeding at all. Upon bivariate analysis this was significantly associated with diarrheal duration, but we were unable to explore the relationship further due to its correlation between age strata. A meta-analysis conducted by Patel and colleagues showed that higher levels of zinc were associated with diarrhea of shorter duration, and zinc treatment has been shown to shorten the duration of diarrhea in children with persistent diarrhea and those with cholera. We found no significant differences in diarrheal duration among children 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 World Health Organization recommends that 20 mg of zinc is 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, and we were therefore unable to include it in the analysis.
This study is subject to a number of other limitations. For one, we limited data analysis to cases with a single episode of diarrhea. Secondly, 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 the form was completed correctly by the caregiver. Furthermore, the diarrhea days reported before enrollment was collected retrospectively and is subject to recall bias. However, the recall period was 7 days which has been determined by some as an acceptable period of recall for caregivers to report child’s illnesses.54 Lastly, 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 the world.

In summary, the diarrhea of extended duration appears to be multifactorial. In this subset of GEMS case children living in rural western Kenya, these factors include whether the child was infected with Cryptosporidium, the nutritional status of the child at presentation to the health center, and the household’s drinking water source. We also confirmed delayed linear growth as one of the consequences of longer diarrheal duration. 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 important.30 Based on our findings 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 recommend promotion of exclusive breastfeeding for the first 6 months of life, and improved nutrition for the first 5 years of life, increased handwashing with soap, encouragement of appropriate feeding practices for when children are ill, and increased use of zinc supplementation.51 To gain a broader, more global understanding of the longer duration diarrhea, similar analyses should be conducted using the data from the other GEMS study sites.
The Global Enterics Multicenter Study was funded by the Bill and Melinda Gates Foundation. It was coordinated by the University of Maryland, School of Medicine, Center for Vaccine Development, Baltimore, MD, USA.

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.

NAME:  
ADDRESS:  
AFFILIATION:  
CITY:  
COUNTRY:  
EMAIL ADDRESS:  
REFERENCES


Table 1. Characteristics of and etiologic agents identified by acute, prolonged acute, and persistent diarrhea amongst cases (n=1,020)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Children with AD (n=587)</th>
<th>Children with ProAD (n=360)</th>
<th>Children with PD (n=73)</th>
<th>All Children (n=1,020)</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 (25.9)</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 F</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>Pathogen</td>
<td>Incidence 1</td>
<td>Incidence 2</td>
<td>Incidence 3</td>
<td>Incidence 4</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Cryptosporidium</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>Enterotoxigenic E. coli any 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 any</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>
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<tr>
<td>Enterotoxigenic E. coli LT only</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</td>
<td>10 (2.8)</td>
<td>3 (4.1)</td>
<td>33 (3.2)</td>
</tr>
<tr>
<td></td>
<td>(3.4)</td>
<td></td>
<td></td>
<td></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>E. hystolytica</td>
<td>5 (0.85)</td>
<td>5 (1.4)</td>
<td>0 (0.0)</td>
<td>10 (0.98)</td>
</tr>
</tbody>
</table>

*Not included are pathogens identified in less than 10 patients: Vibrio cholerae O1(n=5), Aeromonas (n=1), EHEC (n=0), Salmonella Typhi (n=0)*
Table 2. Factors Associated with acute, prolonged acute, and persistent diarrhea amongst cases (n=1,020)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Children with</th>
<th>Children with</th>
<th>Children with</th>
<th>All Children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AD (n=587)</td>
<td>ProAD (n=360)</td>
<td>PD (n=73)</td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
</tbody>
</table>

**# of times enrolled as a case into GEMS**

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>ProAD</th>
<th>PD</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>498</td>
<td>300</td>
<td>59</td>
<td>857</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>47</td>
<td>11</td>
<td>126</td>
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<tr>
<td>3</td>
<td>6</td>
<td>6</td>
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<td>13</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

**Caretakers education level**

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>ProAD</th>
<th>PD</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than primary school</td>
<td>259</td>
<td>174</td>
<td>37</td>
<td>470</td>
</tr>
<tr>
<td>Primary caregiver is mother</td>
<td>552</td>
<td>351</td>
<td>70</td>
<td>973</td>
</tr>
<tr>
<td># of young children living in home (&gt;2)</td>
<td>358</td>
<td>234</td>
<td>43</td>
<td>635</td>
</tr>
<tr>
<td># of people sleeping in home (&gt;4)</td>
<td>263</td>
<td>178</td>
<td>29</td>
<td>470</td>
</tr>
<tr>
<td>Home has a finished floor</td>
<td>123</td>
<td>62</td>
<td>14</td>
<td>199</td>
</tr>
</tbody>
</table>

**WIQ**

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>ProAD</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorest</td>
<td>109</td>
<td>65</td>
<td>184</td>
</tr>
<tr>
<td>Poor</td>
<td>125</td>
<td>56</td>
<td>201</td>
</tr>
<tr>
<td>Middle</td>
<td>136</td>
<td>117</td>
<td>276</td>
</tr>
<tr>
<td>Characteristics</td>
<td>Wealthy</td>
<td>Wealthiest</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>---------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>98 (16.7)</td>
<td>119 (20.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>62 (17.2)</td>
<td>60 (16.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 (11.0)</td>
<td>12 (16.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>168 (16.5)</td>
<td>191 (18.7)</td>
<td></td>
</tr>
</tbody>
</table>

**WASH Characteristics**

<table>
<thead>
<tr>
<th>WASH Characteristic</th>
<th>Wealthy</th>
<th>Wealthiest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unimproved main water source</td>
<td>203 (35.6)</td>
<td>160 (44.4)</td>
</tr>
<tr>
<td></td>
<td>35 (48.0)</td>
<td>398 (39.0)</td>
</tr>
<tr>
<td>Effective treatment method used†</td>
<td>358 (94.2)</td>
<td>206 (94.1)</td>
</tr>
<tr>
<td></td>
<td>38 (92.7)</td>
<td>602 (94.0)</td>
</tr>
<tr>
<td>Washes hands with water only</td>
<td>20 (3.4)</td>
<td>7 (5.7)</td>
</tr>
<tr>
<td></td>
<td>3 (4.1)</td>
<td>50 (4.9)</td>
</tr>
</tbody>
</table>

**Uses shared sanitation facility**

<table>
<thead>
<tr>
<th>Facility Type</th>
<th>Wealthy</th>
<th>Wealthiest</th>
</tr>
</thead>
<tbody>
<tr>
<td>No facility</td>
<td>112 (19.1)</td>
<td>73 (20.3)</td>
</tr>
<tr>
<td>[Private Facility]</td>
<td>107 (18.2)</td>
<td>54 (15.0)</td>
</tr>
<tr>
<td>[Shared Facility]</td>
<td>107 (18.2)</td>
<td>54 (15.0)</td>
</tr>
<tr>
<td>Unimproved sanitation facility‡</td>
<td>107 (18.2)</td>
<td>54 (15.0)</td>
</tr>
<tr>
<td>Blood in stool</td>
<td>16 (2.7)</td>
<td>11 (3.1)</td>
</tr>
<tr>
<td>Maximum # of stools &gt; 7</td>
<td>154 (26.2)</td>
<td>101 (28.1)</td>
</tr>
</tbody>
</table>

**Breastfeeding practices§**

<table>
<thead>
<tr>
<th>Breastfeeding Practice</th>
<th>Wealthy</th>
<th>Wealthiest</th>
</tr>
</thead>
<tbody>
<tr>
<td>No breastfeeding</td>
<td>192 (38.9)</td>
<td>75 (26.3)</td>
</tr>
<tr>
<td>Partial breastfeeding</td>
<td>288 (58.3)</td>
<td>197 (69.1)</td>
</tr>
<tr>
<td>Exclusive breastfeeding</td>
<td>14 (2.8)</td>
<td>13 (4.6)</td>
</tr>
</tbody>
</table>

**Anthropometry at enrollment**

<table>
<thead>
<tr>
<th>Anthropometric Measure</th>
<th>Wealthy</th>
<th>Wealthiest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight-for-length/height z-score &lt; -2</td>
<td>59 (10.1)</td>
<td>41 (11.4)</td>
</tr>
<tr>
<td>Weight-for-age z-score &lt; -2</td>
<td>131 (22.3)</td>
<td>69 (19.2)</td>
</tr>
<tr>
<td>Length/height-for-age z-score &lt; -2</td>
<td>151 (25.7)</td>
<td>83 (23.1)</td>
</tr>
<tr>
<td>Child’s HIV-infected</td>
<td>11 (3.3)</td>
<td>6 (2.7)</td>
</tr>
</tbody>
</table>

**Food or drink offerings**

<table>
<thead>
<tr>
<th>Offered less than usual to drink</th>
<th>Wealthy</th>
<th>Wealthiest</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>248 (42.3)</td>
<td>167 (46.4)</td>
</tr>
<tr>
<td></td>
<td>40 (54.8)</td>
<td>455 (44.6)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Before Visiting Health Facility</td>
<td>At Health Facility</td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td></td>
<td>ORS</td>
<td>Zinc</td>
</tr>
<tr>
<td>Offered less than usual to eat</td>
<td>455 (77.5)</td>
<td>295 (81.9)</td>
</tr>
<tr>
<td>Treatments given before visiting health facility</td>
<td>73 (12.4)</td>
<td>55 (15.3)</td>
</tr>
<tr>
<td>ORS</td>
<td>19 (3.2)</td>
<td>9 (2.5)</td>
</tr>
<tr>
<td>Zinc</td>
<td>569 (96.9)</td>
<td>352 (97.8)</td>
</tr>
<tr>
<td>Zinc</td>
<td>58 (9.9)</td>
<td>39 (10.8)</td>
</tr>
<tr>
<td>IV treatment</td>
<td>63 (10.7)</td>
<td>49 (13.6)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>50 (8.5)</td>
<td>43 (11.9)</td>
</tr>
</tbody>
</table>

* N=1,000 as 20 children were missing the unique ID 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;

‡ 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 three years of GEMS (n=841) as questions related to breastfeeding practices were not compatible during the fourth year of GEMS.
Table 3. Results of Kaplan-Meier analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Log-rank test p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enteric Pathogen</strong>*</td>
<td></td>
</tr>
<tr>
<td><em>Cryptosporidium</em></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><em>Campylobacter jejuni</em></td>
<td>0.04</td>
</tr>
<tr>
<td>Enterotoxigenic <em>E. coli</em> any ST</td>
<td>0.07</td>
</tr>
<tr>
<td>Enteroaggregative <em>E. coli</em></td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Other Factors</strong></td>
<td></td>
</tr>
<tr>
<td>Child’s age</td>
<td>&lt;.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><strong>Anthropometry at enrollment</strong></td>
<td></td>
</tr>
<tr>
<td>Stunted at enrollment (HAZ &lt; -2)</td>
<td>0.04</td>
</tr>
<tr>
<td>Weight-for-length/height z-score &lt; -2</td>
<td>0.08</td>
</tr>
<tr>
<td>Weight-for-age z-score &lt; -2</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*Multiple enteric pathogens possible per child
Table 4. Results of Stratified Cox Proportional Hazards Model

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazards Ratio (CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stunted</td>
<td>0.03 (0.01, 0.10)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Children with &gt;14 days of diarrhea</td>
<td>1.14 (0.98, 1.32)</td>
<td>0.085</td>
</tr>
<tr>
<td>Children with &lt;14 days of diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main drinking water source considered unimproved</td>
<td>0.87 (0.76, 0.99)</td>
<td>0.035</td>
</tr>
<tr>
<td><strong>Enteric Pathogen</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptosporidium</td>
<td>0.75 (0.61, 0.93)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

*Multiple enteric pathogens possible per child
**Supplemental Table 1. Results of Stratified Cox Proportional Hazards Model among Case Children**

Enrolled only once as a case into GEMS (excluding children who were enrolled more than once as a case)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazards Ratio (CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stunted</td>
<td>0.03 (0.01, 0.12)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Children with &gt;14 days of diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children with ≤14 days of diarrhea</td>
<td>1.15 (0.98, 1.36)</td>
<td>0.087</td>
</tr>
<tr>
<td>Main drinking water source considered unimproved</td>
<td>0.90 (0.78, 1.03)</td>
<td>0.1332</td>
</tr>
<tr>
<td>*<em>Enteric Pathogen</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Cryptosporidium</em></td>
<td>0.77 (0.60, 0.98)</td>
<td>0.0310</td>
</tr>
</tbody>
</table>

*Multiple enteric pathogens possible per child
Figure 1: Memory Aid 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.

1. 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.
2. Go to the correct day. “o o” means today, “o o” means tomorrow, and so on. A day begins when you wake up in the morning and ends when you wake up the next morning.
3. If your child had diarrhea that day, mark “X” in the dark box for that day "X". If your child did not have diarrhea, mark “X” in the white box for that day "X". Each day, make only one “X”.
4. If you forget for a few days, try to start again on the correct day.
5. Keep this form in a safe place. We will come to your house to collect it in 60 days.

DIARRHEA

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

Proposed journal: American Society of Tropical Medicine and Hygiene
Title: Water, Sanitation, and Hygiene Characteristics among HIV-Positive Households Participating in the Global Enterics Multicenter Study in Rural Western Kenya, 2008-2012

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Author Institutions: ¹KEMRI/CDC, Kisumu, Kenya, ²Centre for Global Health Research, KEMRI, Kisumu, Kenya, ³Centers for Disease Control and Prevention, Atlanta, GA, USA, ⁴University of Maryland, School of Medicine, Center for Vaccine Development, Baltimore, MD, USA, ⁵CDC-Kenya, Nairobi, Kenya, ⁶Georgia State University, School of Public Health, Atlanta, GA, USA, ⁷Emory University, Emory Global Health Institute, Atlanta, GA, USA

Key words: HIV/AIDS, WASH, Kenya

Running title: WASH characteristics among HIV-positive households in Kenya

Word count (abstract): 200

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Number of figures: 3

Number of tables: 2

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ABSTRACT

Diarrheal illness is a common infection among people living with HIV (PLHIV) that is largely preventable through increased access to safe drinking water, and sanitation and hygiene facilities. We examine water, sanitation, and hygiene (WASH) characteristics among households with and without HIV-positive individuals enrolled in the Global Enterics Multicenter Study (GEMS) in rural western Kenya. Using bivariate logistic regression analysis we examined differences between HIV-positive and HIV-negative households in regards to WASH practices. Among HIV-positive households we explored the relationship between the length of time knowing their HIV status and GEMS enrollment. No statistically significant differences were apparent in WASH characteristics among HIV-positive and HIV-negative households. However, we found slight differences in WASH characteristics among HIV-positive households who were aware of their HIV status ≥ 30 days before enrollment compared with HIV-positive households who found out their status <30 days before enrollment or thereafter. Significantly more households tested before enrollment reported treating their drinking water (OR [CI]: 2.34 [1.12, 4.86]), use of effective water treatment methods (OR [CI]: 9.6 [3.09, 29.86]), and had better drinking water storage practices. This suggests that within this region of Kenya, HIV programs are successful in promoting the importance of practicing positive WASH-related behaviors among PLHIV.
INTRODUCTION

Worldwide, an estimated 36.9 million people are infected with HIV, with an estimated 25.8 million living in sub-Saharan Africa.\(^1\) Approximately 3.34 million children are infected with HIV, and every day about 700 more children are infected.\(^2\) Nationally in Kenya, approximately 5.6% of adults are infected with HIV.\(^3\) HIV prevalence is higher in women (6.9%) than in men (5.6%).\(^3\) It is estimated 190,000 children aged 0-14 years are living with HIV in Kenya.\(^3\)

HIV weakens the immune system of infected persons increasing their susceptibility to other infections. Diarrheal illness is a common infection among PLHIV, and often results from ingestion of contaminated food or water. In developing countries, contamination occurs as a result of inadequately protected water supplies and sanitation facilities, and poor hygiene practices.\(^2\) Certain enteric pathogens, especially intestinal parasites, have been more commonly identified among people living with HIV where they cause more severe, longer-lasting, illness than in immunocompetent persons.\(^4\text{-}6\)

Furthermore, PLHIV may have increased water needs to take medications (including anti-retroviral treatment), and to reduce the risk of dehydration, preventing opportunistic infections, and for taking medications such as ARV's.\(^7\text{-}9\)

Due to the increased risk of adverse consequences improving access to adequate water and sanitation facilities for PLHIV is especially important.\(^10\) Improving drinking water quality, sanitation, and hygiene (WASH) practices among PLHIV have demonstrated health benefits.\(^11\text{-}12\) In 2013, a systematic review examining studies of the health effects of WASH interventions among PLHIV\(^11\) found that water quality interventions reduced morbidity among PLHIV by 43% (RR=0.57, 95% CI: 0.38-0.86) when pooling the data from seven studies.\(^13\text{-}19\) The review included only one study of a handwashing intervention which found a morbidity reduction of 58% (RR=0.42, 95% CI: 0.33-0.54).\(^11,20\) In 2015, a more
A comprehensive review of reported health impact of WASH interventions concluded that both water quality and hand washing interventions reduced morbidity.\textsuperscript{12} It also found that households with improved water supplies had less diarrheal morbidity and lower prevalence of intestinal parasites, and that having a household sanitation facility (as compared to open defecation or sharing a facility) reduced the risk of diarrhea.\textsuperscript{12}

The evidence suggests improved WASH is important for PLHIV; however, numerous barriers limiting access to these services and facilities have been identified. Ignorance, attitudes, cost and debilitating illness have all been noted as factors that inhibit access to or usage of improved WASH services and facilities by PLHIV.\textsuperscript{21-22} Discrimination and social stigma have also limited access to WASH by PHIV, who have reportedly been shunned from using certain water sources and sanitation facilities and had to travel further to access alternative water sources and sanitation facilities.\textsuperscript{22, 23-25}

Many studies have reported the health impact of WASH interventions among PLHIV; however, limited knowledge exists on WASH access and practices among HIV-positive individuals in rural western Kenya where rates of HIV are high.\textsuperscript{26} Furthermore, we know little about the differences in WASH practices between HIV-positive and HIV-negative households. We explore WASH characteristics and practices among a subset of households with HIV-positive individuals and those without enrolled in the Global Enterics Multicenter Study (GEMS) in Kenya.

**MATERIALS AND METHODS**

**The Global Enterics Multicenter Study.**

GEMS was a case-control study of moderate-to-severe diarrhea (MSD) in young children in seven sites in Africa and Asia, designed to estimate the burden, etiology, risk factors, and complications
of MSD in children <5 years old. Detailed information about the clinical and epidemiological methods of GEMS are described elsewhere and summarized below.27

All case and control children resided within the Household Demographic Surveillance System (HDSS) boundaries. Census and surveillance data were collected by the Kenya Medical Research Institute (KEMRI)/Centers for Disease Control and Prevention (CDC) Kenya HDSS routinely.28 All case children met the case definition for MSD and were <5 years old. MSD was defined as three or more loose stools per day, for 7 days or less, with one or more of the following signs indicative of dehydration: sunken eyes, loss of skin turgor, intravenous rehydration administered or prescribed, dysentery, or hospitalization for diarrhea or dysentery. Control children were similar to cases in regards to age, sex, and geographic location.

At enrollment, demographic information, household level characteristics, and risk factors for diarrheal disease were obtained. Between 49 and 91 days a home visit was conducted during which time similar information was collected. In addition, HIV-related data was collected for a sub-set of cases, controls, and their biological parents, as will be described in greater detail below. Risk factors for diarrheal disease focused on household WASH characteristics including information about the household’s water source, water treatment and storage practices, sanitation facilities, and handwashing practices. Data collected on WASH characteristics at the follow-up visit were reported by the caregiver and confirmed through observation by a trained community interviewer. For the purposes of this analysis if the same data were collected at enrollment and at follow-up, the follow-up date were used as they were more often confirmed through observation. In those rare instances where data were not collected at follow-up, we report data collected at enrollment. At enrollment, the following WASH data were collected: whether the child was given untreated water, the amount of time it took to get water, whether water was available on a daily basis, how often water was fetched, whether the sanitation facility was shared, and when hands were typically washed. At follow-up stored drinking water was
tested for chlorine residuals, characteristics about the household’s storage containers for drinking water were observed, and the interviewer observed whether feces were visible in the defecation area or in the house or yard. At both enrollment and follow-up the following household data were obtained: the household’s main drinking water source, water treatment practices and whether or not these were effective, the means of disposing of the child’s feces and the type of sanitation facility used for household waste, and whether soap was observed in home.

**Study Area and Study Population.**

The GEMS-Kenya enrollment period was from January 31, 2008 to January 29, 2011 and from October 31, 2011 through September 30, 2012. The study site was located in rural western Kenya in Nyanza Province in the districts of Gem, Asembo, and Karemo, close to Lake Victoria. GEMS-Kenya was coordinated by the CDC and the KEMRI. Within GEMS-Kenya six sentinel health centers which enrolled case children. About 135,000 persons, of whom 21,000 were <5 years old, resided within the catchment area of these health centers.\(^{27,29}\) In comparison to other parts of Kenya, Nyanza Province has high rates of HIV/AIDS (13.9% among adults) and child mortality in both infants (27 per 1,000 live births) and children <5 years old (73 per 1,000 live births).\(^{26,30}\) Within the GEMS-Kenya catchment area rates of HIV/AIDS are even higher, the prevalence among adults 13-34 years old was 15.4% in 2004.\(^{31}\)

**Data Sources for HIV.**

Data on HIV were collected by two programs implemented by the CDC Kenya Division of Global HIV/AIDS (DGHA) and the International Emerging Infections Program: Home-Based Counseling and Testing (HBCT) and Provider Initiated HIV Testing and Counseling (PITC). Protocols established by Kenyan Ministry of Public Health and Sanitation for HIV testing and counseling were followed for both HBCT and PITC.\(^{31}\) Figure 1 is a timeline of HBCT and PITC within the regions of Gem, Karemo, and Asembo. HBCT was conducted on a rolling basis within the Health and Demographic Surveillance System (HDSS).

Voluntary HIV tests were conducted by trained counselors at the homes of people living within the
HDSS. Any child <5 years old living in the home was tested if the biological mother tested HIV-positive or was deceased. Adults and applicable children 18 months or older were tested via a parallel testing strategy whereby the Determine™ and Bioline® rapid antibody tests were completed at the same time. For ties, where one test was positive and the other negative, the Unigold® rapid antibody test was performed. For children < 18 months old, DNA-PCR was used to confirm any HIV-positive antibody test result. PITC was conducted in health facilities within the HDSS. Voluntary HIV tests were conducted on any patient and their caretakers attending the health facility regardless of the purpose of their visit to the facility. PITC HIV test results for anyone over 18 months old were conducted sequentially whereby the Determine™ rapid antibody test first. If positive, the result was confirmed through the Bioline® rapid antibody test. For ties, a Unigold® rapid antibody test was conducted. All children <18 months old with a positive HIV-antibody test were confirmed using DNA-PCR (Figure 2). Figure 2 is a diagram showing the testing strategy for PITC and HBCT. Participants in either PITC or HBCT who tested HIV-positive were referred to HIV care and treatment. The President's Emergency Plan for AIDS Relief (PEPFAR) as administered by DGHA Kenya operate and fund all HIV counseling, testing and treatment activities within the Kenya HDSS.

Data collected through HBCT and PITC were linked to GEMS-Kenya data using a unique identification number assigned to each person living in the KEMRI/CDC Kenya HDSS and available within each data source. Where available, HIV status and other data related to HIV such as treatment information and participation in child prevention interventions at birth and thereafter were linked to GEMS case and control children and to their biological mothers and fathers. For case children and their parents, HIV related data was collected in both HBCT and PITC, whereas for control children and their parents it was primarily collected via HBCT.

HBCT data were linked retrospectively and actively for case and control children and their parents. Retrospective data collection spanned the entire GEMS study period. PITC was abstracted in
real time by trained GEMS Kenya staff members at the health facility level using an approved, standardized chart abstraction form. PITC began within GEMS sentinel sites in January 2010 and continued through to the end of GEMS-1a enrollment.

Analysis Assumptions.

After consultation with GEMS and DGHA investigators, a series of assumptions related to the HIV data were made. First, for children tested in HBCT, we applied a HIV-negative result if their biological mother tested HIV-negative on or after the date the child was enrolled. Second, for parents of case children who were also enrolled as a control at some point during GEMS, results were applied to enrollment period(s) where HIV-related data was missing for the parents. We applied HIV-related data only in instances where the parent tested HIV-positive before the enrollment periods with missing data. It was assumed that an HIV-positive result would not change going forward; however, we could not assume a positive status during an earlier enrollment period nor could we assume negative results to remain constant over time. Last, if the HIV test results were available from both PITC and HBCT, the results obtained via PITC were used as these data are more reliable, and were captured in real time during enrollment of the child into GEMS.

Eligibility for Analysis.

For the purposes of this study, we included case-children enrolled only once into GEMS as a case and for who we had complete 60-day follow-up information. Only those observations where both the child and mother had HIV test results available were included. Control children were not included as the primary outcome of interest in this analysis was not MSD as it was for the overall GEMS study. In the original GEMS study design, control children were matched to case children, and therefore, it would not be appropriate to include them as they are not representative of an independent, random sample of the population. Furthermore, HIV test results were missing for a greater proportion of control children as
compared to case children. This is mostly due to the fact that PITC was conducted amongst case children only.

Definitions. HIV-positive households were defined as households where HIV test results were available for both the child and the biological mother, and where either or both had a positive HIV test. HIV-negative households were defined as households where HIV test results were available for both the child and the biological mother, and where both the child’s and the mother’s HIV test was negative. Households where the HIV status was unknown for the mother, the child, or both the mother and the child were not included within the analysis. Water and sanitation facilities were defined as unimproved or improved as outlined by the WHO/UNICEF Joint Monitoring Programme for Water Supply and Sanitation. Water treatment practices were defined as effective based on treatment methods proven to improve the quality of drinking water and to reduce diarrheal illness as outlined by the World Health Organization.

Statistical Analysis. This paper presents a descriptive analysis of the differences between HIV-positive and HIV-negative households with regards to their water, sanitation, and hygiene practices (either reported or observed). We also present results of bivariate logistic regression analysis exploring differences between the WASH characteristics of HIV-negative and HIV-positive households. To explore whether WASH practices and behaviors among persons who received their positive HIV test results earlier were different from those who had received their test results more recently, we examined the dichotomized time between the mother’s test date and the GEMS enrollment date (tested ≥ 30 days before GEMS enrollment date vs. tested <30 days before GEMS enrollment or after GEMS enrollment). To explore this relationship we conducted a bivariate logistic regression analysis. For both analyses odds ratios, confidence intervals, and p-values are presented. Data were analyzed using SAS 9.3.

Scientific Ethics.
All participants provided written informed consent before participating in this study. The GEMS protocol was approved by the following institutions: Kenya Medical Research Institute Scientific and Ethical Review Committee, the Institutional Review Board (IRB) at University of Maryland, School of Medicine, Baltimore, MD, USA; the Centers for Disease Control and Prevention, Atlanta, GA, USA, deferred to the IRB at the University of Maryland for review.

**Study enrollment and participants.**

Between January 31, 2008-January 29, 2011 and October 31, 2011 - September 30, 2012 4,226 children were enrolled into GEMS-Kenya; of these, 1,778 were enrolled as cases. Data from the 60-day follow-up visit were incomplete for 60 case children; another 7 children were followed-up outside of the required 49-91 day window, and were therefore excluded from the analysis. Two hundred and fifty-seven observations that were associated with children who were enrolled more than once as a GEMS case were excluded. Among the remaining 1,454 case-children, HIV test results were available for 842 case-children, 962 mothers of case-children, and 467 fathers of case-children (Figure 3).

**RESULTS**

In 798 households, HIV test results were available for both the child and mother. One hundred and seventy-two (21.6%) of the 798 households met criteria for HIV-positive households, and 626 (78.4%) met criteria for HIV-negative households.

**Descriptive data on study participants educational and wealth characteristics.**

Among the 798 case-households included within our analysis, caretakers living in HIV-negative households reported having lower levels of educational attainment (attended less than primary school) (n=304, 48.6%) as compared to HIV-positive households (n=78, 45.4%); this difference was not statistically significant. Slightly more HIV-negative households were categorized as being in the two richest wealth quintiles ( Richest: 16.5% vs. 15.7%, Rich: 18.9% vs. 14.0%), and in the poorest wealth
quintile (19.5% vs. 16.3%), whereas more HIV-positive households were categorized as being ‘Poor’ (23.3% vs. 20.3%) or ‘Middle’ (30.8% vs. 24.9); upon bivariate analysis these differences were not statistically different.

**Drinking Water: Source, treatment methods, storage, and availability.**

On bivariate analysis we found no statistically significant differences in the drinking water characteristics of HIV-positive and HIV-negative households. A higher proportion of HIV-negative households reported obtaining their water from an unimproved source (48.2% vs. 41.3%, OR [CI]: 0.75 [0.54, 1.06], not significant at α 0.05 [NS]). Approximately, 62% of both HIV-positive and HIV-negative households reported usually treating their drinking water (OR [CI]: 1.06 [0.75, 1.50], NS). At enrollment, 27.1% of HIV-positive households and 34.0% of HIV-negative households reported giving their child untreated drinking water (OR [CI]: 0.72 [0.45, 1.16], NS). Among those who reported usually treating their drinking water, effective treatment methods were reported by about 68% of HIV-positive households and 63% HIV-negative households (OR [CI]: 1.28 [0.87, 1.87], NS). Chlorine was the most commonly reported water treatment method in both HIV-positive and HIV-negative households.

Reported use of chlorine was higher in HIV-positive households (53.5% vs. 49.0%, OR [CI]: 1.19 [0.85, 1.68], NS), and positive chlorine residuals were found in more HIV-positive homes (19.5%) as compared to HIV-negative homes (11.7%)(OR [CI]: 1.73 [0.93, 3.24], NS) (see Table 1).

About 16% of HIV-positive households and 15% of HIV-negative households reported fetching water every day (OR [CI]: 1.15 [0.61, 1.97], NS). Water was reportedly not available on a daily basis for nearly 11% of HIV-positive households and about 8% of HIV-negative households (OR [CI]: 1.40 [0.80, 2.44], NS). The time it took to get water was reported as being at least 1 hour roundtrip if not longer by 8% of HIV-positive households and nearly 9% of HIV-negative households (OR [CI]: 0.80 [0.41, 1.97], NS). At enrollment a statistically significantly higher proportion of HIV-negative households reported giving their children stored water (91.4% vs. 86.1%, OR [CI]: 0.58 [0.35, 0.97], p: 0.04). At follow-up the
overwhelming majority of both HIV-positive (98.8%) and HIV-negative households (98.4%) had drinking water storage containers in use within the home (OR [CI]: 0.78 [0.25, 2.48], NS). Among those with storage containers observed, 77.2% of HIV-negative households and 79.3% of HIV-positive households (OR [CI]: 0.74 [0.74, 1.71], NS) had containers that were considered to be unsafe due to being uncovered or having large openings that allow for potential contamination.

**Household sanitation facilities and disposal of child’s feces.**

We examined the relationship between the household sanitation practices among HIV-positive and HIV-negative household and found no statistically significant differences on bivariate analysis. Slightly more HIV-negative households reported using unimproved sanitation facilities (27.0% vs. 22.2%, OR [CI]: 0.77 [0.52, 1.16], NS), while sharing a sanitation facility with one or more households was more commonly reported by HIV-positive households (80.1%) (78.7%) (OR [CI]: 1.09 [0.69, 1.74], NS).

Approximately 41% of HIV-positive households and 40% of HIV-negative households (OR [CI]: 1.04 [0.74, 1.48], NS) reported disposing of their child’s feces in a way that would be considered unimproved such as dumping in the bush, field, stream or on the ground. At the 60-day follow-up interview slightly more feces was observed in the specified defecation area of HIV-positive households (35.5% vs. 32.4%, OR [CI]: 0.561.15 [0.80, 1.63], NS), while slightly more HIV-negative households had feces observed in the home or in the yard as compared to HIV-positive households (9.0% vs. 8.1%, OR [CI]: 0.90 [0.49, 1.66], NS).

**Hand Hygiene.**

We found no statistically significant differences between hand hygiene practices of HIV-positive and HIV-negative households. The overwhelming majority of households reported washing their hands with soap and water at enrollment (HIV-positive households: 90.7%, HIV-negative households: 94.9% [data not shown]); however, at the 60-day follow-up interview soap was observed in only 51.7% of HIV-positive households and 45.0% of HIV-negative households (OR [CI]: 1.31 [0.94, 1.84], NS). When asked
about when hands were typically washed, responses reported by HIV-positive and HIV-negative households were quite similar. HIV-positive and HIV-negative households reported typically washing their hands before eating (82.0% vs. 82.3%, OR [CI]: 0.98 [0.63, 1.52], NS), after defecating (75.6% vs. 78.8%, OR [CI]: 0.84 [0.56, 1.24], NS), before cooking (34.9% vs. 36.7%, OR [CI]: 0.92 [0.65, 1.31], NS), before nursing (33.1% vs. 33.6%, OR [CI]: 0.98 [0.69, 1.40], NS), after cleaning children (30.8% vs. 30.7%, OR [CI]: 1.01 [0.70, 1.45], NS), after handling soil (7.6% vs. 8.3%, OR [CI]: 0.90 [0.48, 1.70], NS).

Influence of length of time knowing HIV status.

Among HIV-positive households, we explored whether being tested for HIV ≥ 30 days before enrollment into GEMS was associated with WASH practices. Of the 172 households that were HIV positive, 66 (38.4%) were aware of their HIV status ≥ 30 days before enrollment, 67 (39.0%) found out their status <30 days of enrollment or after enrollment, and the test date was missing for 39 (22.7%) households (Figure 2).

A significantly higher proportion of HIV-positive households tested within 30 days of GEMS enrollment reported using unimproved water sources as compared with households who were aware of their HIV status ≥ 30 days before enrollment (41.8% vs. 28.8%, OR [CI]: 0.56 [0.27, 1.16], NS) (see Table 2). In addition, a significantly higher proportion of households aware of their status ≥ 30 days before GEMS enrollment reported usually treating their drinking water (74.2% vs. 55.2%, OR [CI]: 2.34 [1.12, 4.86], p: 0.02) compared with households who found out their status more recently. Households aware of their status ≥ 30 days before enrollment were statistically significantly more likely to have reported treating their drinking water using an effective treatment method as compared to households who found out their status <30 days before enrollment or after enrollment (92.3% vs. 55.6%, OR [CI]: 9.6 [3.09, 29.86], p: <.0001). Detectable free chlorine residual were more often found in the drinking water in these homes, although this difference was not statistically significant (25.0% vs. 20.0%, OR [CI]: 1.33
Drinking water storage containers were classified as unsafe in statistically significantly fewer homes who were aware of their status ≥ 30 days before enrollment as compared with homes whom found out <30 days before enrollment or thereafter (69.7% vs. 84.9%, OR [CI]: 0.41 [0.17, 0.96], p: 0.04). There were no significant differences in sanitation practices or characteristics of HIV-positive households who found out their status <30 days before enrollment or after, and those tested earlier. Non-significant differences were found in the proportion that had household sanitation facilities that were considered unimproved (15.4% vs. 26.9%, OR [CI]: 0.49 [0.21, 1.17], NS), the proportion who reported sharing their sanitation facility with at least one other household (84.9% vs. 81.1%, OR [CI]: 1.31 [0.47, 3.63], NS), and the proportion that disposed of their child’s feces by methods considered unimproved (32.3% vs 43.9%, OR [CI]: 0.61 [0.30, 1.24], NS) who were aware of their status for ≥ 30 days before enrollment reported sharing their sanitation facility with at least one other household (84.9% vs. 81.1%, OR [CI]: 1.31 [0.47, 3.63], NS). A higher proportion of households tested ≥ 30 days before enrollment had visible feces in the homes or yards compared to those who were aware of their status <30 days before enrollment or after enrollment (7.6% vs. 3.0%, OR [CI]: 2.66 [0.50, 14.23], NS).

With one exception, no statistically significant differences were found in handwashing practices or characteristics of households who found out their status ≥ 30 days after enrollment and those tested <30 days before enrollment or after enrollment. Households who were aware of their status ≥ 30 days before enrollment more often reported handwashing after cleaning a child after defecation (40.9% vs. 22.4%, OR: 2.4 [1.13, 5.11], p: 0.02) (see Table 2).

DISCUSSION

In our study population of select GEMS case households in the regions of Gem, Asembo, and Karemo, we found that HIV-positive and HIV-negative households had very similar WASH characteristics.
In general, HIV-positive households seemed to have higher proportions of positive WASH-related behaviors as compared to HIV-negative households. However, few if any of these differences were statistically significant. For example, we found a higher proportion of HIV-positive households using an improved water source as their main source of drinking water and more reported treating their drinking water. Among those reporting treating their drinking water more reported using effective methods, and among those who reported treating their drinking water, a higher proportion had detectable free chlorine residual; however, none of these differences were statistically significant.

According to data collected in the Kenyan Demographic and Health Survey (DHS), \textsuperscript{26} rates of using unimproved water sources among households in our study sample were similar to those in other rural Kenyan households. Approximately 46\% of rural Kenyan households reported using unimproved water sources, and in our sample 41\% of HIV-positive households and 48\% of HIV-negative households reported using unimproved water sources. In our sample, more households reported treating their drinking water as compared with rural Kenyan households in the DHS. In our sample, approximately 62\% of both HIV-positive and HIV-negative households reported treating their drinking water whereas in rural Kenyan households only about 41\% reported treated their water. Sanitation facilities were quite similar in our sample as compared to the rural Kenyan households in the DHS. In our sample, unimproved sanitation facilities shared by more than one household were reported in 84\% and 83\% of HIV-positive and HIV-negative households, respectively; in rural households in the DHS unimproved sanitation facilities shared by more than one households were reported among nearly 80\% of respondents.

We had initially hypothesized that HIV-positive households would have poorer WASH access and practices than HIV-negative households due to the additional burden and barriers that PLHIV have to overcome, such as increased illness, stigma and discrimination.\textsuperscript{21-25} In previous publications, researchers in a number of countries including Tanzania, Papua New Guinea, Uganda, and Ethiopia reported that
PLHIV were discriminated against in terms of the WASH facilities they were allowed to use, and were obliged to travel further to fetch water and utilize sanitation facilities.\textsuperscript{21-25} In Ethiopia, Tanzania, and Nepal reports suggested that fetching water, using adequate sanitation facilities, and practicing proper hygiene were more difficult for PLHIV because of poorer health and increased periods of illness.\textsuperscript{21, 24, 26}

Furthermore, financial constraints have been noted as a major barrier to accessing and utilizing improved WASH among PLHIV.\textsuperscript{22-23, 25} Although we did not collect information on specific barriers to WASH access or usage in this study, we believe that barriers noted by others were minimized within our study population given the strikingly similar WASH characteristics identified between HIV-positive and HIV-negative households. This may result from more successful government, multilateral, and NGO programs for AIDS diagnosis and treatment in the region, and decreasing stigmatization of PHLIV within this population. HIV-positive households in this population that receive effective healthcare and education may have less illness and better WASH practices, such as treating and safely storing drinking water.

To explore this hypothesis, we examined the influence of the length of time knowing their HIV status on WASH characteristics and behaviors in the HIV-positive households in this subset. In particular we examined whether the amount of time from HIV testing to the time the household was enrolled in GEMS affected found out their status WASH characteristics and behaviors. We found that HIV-positive households that were aware of their HIV status $\geq 30$ days before GEMS enrollment had better WASH-related behaviors than households that had more recently received a diagnosis of HIV. Although our numbers were restricted to the subset of GEMS households with an HIV-positive child or mother (n=172), we detected statistically significant results upon bivariate analysis for some key characteristics including drinking water treatment (OR (CI): 2.34 (1.12, 4.86), $p$: 0.02), with an effective method (OR (CI): 9.6 (3.09, 29.86), $p$: <.0001). HIV-positive households that found out their status <30 days before enrollment or after enrollment were more likely to have drinking water storage containers that were
considered unsafe (OR (CI): 0.41 (.17, .96), p: 0.04), and more of these homes reported removing water from the container by scooping with a cup (OR (CI): 0.35 (.15, .82), p: .02), as opposed to those households aware of their status ≥ 30 days before enrollment, more reported removing the water from the container by a safer method such as pouring through a spigot/spout (OR (CI): 2.91 (1.28, 6.59), p: .01).

Although our study was not designed to look at why the length of time knowing one’s HIV status might influence WASH characteristics, it is reasonable to consider that the programs and services being provided to HIV-infected individuals in this area may be a significant factor. All HIV testing and counseling programs in Kenya offer pre-test and post-test counseling. During post-test counseling all persons who have tested HIV-positive are referred to comprehensive, evidence-based patient support and care services.\textsuperscript{8,34-35} One of these services involves improving WASH-related practices such as treating water, promoting safe drinking water storage, improving disposal of feces, and promoting handwashing with soap.\textsuperscript{35} The integration of WASH activities, including provision of household water treatment products and soap to PHLIV is supported through PEPFAR funded programs and these essential WASH goods have been incorporated into some basic care packages provided to PLHIV.\textsuperscript{8,36-37}

Other programs in this region that serve PLHIV, such as the Safe Water and AIDS Project, also focus on the promotion of low-cost, simple-to-use, household water treatment interventions and safe storage along with safe water handling, sanitation, and hygiene practices.\textsuperscript{38} Findings from a recent investigation among HBCT participants in this part of rural western Kenya support our assumption that HIV-positive households are seeking services to improve their health. In this investigation, researchers noted that after finding out their HIV status HIV-infected individuals sought care more frequently and suffered fewer episodes of acute febrile illness and diarrheal disease.\textsuperscript{39} Limited research has focused on healthcare seeking behaviors among recently tested individuals, and this warrants further investigation.
This study was subject to a number of limitations. For one, HIV related data were collected from two different programs and subsequently linked to the GEMS-Kenya data. Inconsistencies in data collection between the two programs limited the HIV-related data that we were able to link to GEMS Kenya data. However, each program followed the Kenya National Guidelines and we felt confident in the data collection methods for the linkable data.\textsuperscript{34} Second, due to the nature of this study we examined data at the household level rather than at an individual level and we only included households where both the mother and child both had a test result available. Father’s HIV test results were not considered when determining the status of a household because a high proportion had missing test results as compared to mothers and children. Furthermore, mothers are traditionally responsible for household tasks and more likely to influence WASH practices than fathers.\textsuperscript{40-41} Third, although we used observed practices and behaviors wherever possible, some of the WASH characteristics that we explored, especially those collected at enrollment, were reported and not observed by the interviewer, and are therefore subject to reporting bias. Last, this study’s findings are not generalizable to a broader setting; however, they provide insights into the WASH practices of HIV-negative and HIV-positive households in this region of western Kenya.

In summary, we found that HIV-positive and HIV-negative households within this region had very similar WASH practices. Interestingly, we noted somewhat better WASH behaviors and characteristics among HIV-positive households who were aware of their HIV status $\geq$ 30 days before GEMS enrollment as compared with HIV-positive households who were found out their status <30 days before enrollment or thereafter. This suggests that within this population HIV-positive households are effectively educated about the importance of drinking treated water, using improved sanitation facilities, and practicing good hand hygiene, and that the households within our study were making efforts to participate in these positive WASH behaviors. Future research should consider time as an important factor when examining WASH behaviors among PLHIV, taking into consideration the time it
takes for sustained behavior change to occur. It should also attempt to identify factors that promote positive WASH behaviors in order to optimize strategies to overcome the barriers to WASH faced by PLHIV.
ACKNOWLEDGMENTS

FINANCIAL SUPPORT

DISCLOSURES

AUTHOR INFORMATION
  NAME:
  ADDRESS:
  AFFILIATION:
  CITY:
  COUNTRY:
  EMAIL ADDRESS:
2. World Health Organization, 2013. 10 Facts on HIV/AIDS.


Figure 1. Six GEMS sentinel health centers in Asembo, Gem and Karemo

Provider Initiated HIV Testing and Counseling

Six sentinel health centers in Gem, Asembo, Karemo

Home-Based Counseling and Testing

Asembo

Gem

Karemo

January 31, 2008 
January 26, 2009 
January 24, 2010 
January 29, 2011 
October 31, 2011 
September 30, 2012
Figure 2. Testing Strategy for Home-Based HIV Counseling and Testing and Provider Initiated HIV Testing and Counseling within the Kenya HDSS

Provider Initiated HIV Testing and Counseling

- Conducted in health facilities within the HDSS
- Voluntary tests conducted on any person and their caregivers attending health facility, regardless of the purpose of their visit

Testing Strategy

Adults:
- DETERMINE™ Rapid Test
- All positive tests confirmed with BIOLINE® Rapid Test
- Tie breaker: UNIGOLD® Rapid Test

Children <18 Months Old:
- Confirmatory test: DNA-PCR test

Home-Based HIV Counseling and Testing

- Conducted at homes of people living within the HDSS
- Voluntary tests conducted on adults and any child <5 living in the home if the biological mother tested HIV-positive or was deceased

Testing Strategy

Adults:
- DETERMINE™ Rapid Test and BIOLINE® Rapid Test completed at same time
- Tie breaker: UNIGOLD® Rapid Test

Children <18 Months Old:
- Confirmatory test: DNA-PCR test if antibody test positive
**Figure 3.** Flow chart of GEMS Kenya Study Population, Case Children, 2008-2012

GEMS Kenya Study Population, 2008-2012

- **Case Children**
  - **N=4,226**

- **Case children n=1,778**
  - n=60, incomplete 60-day follow-up interview or not conducted;
  - n=7, 60-day follow-up interview conducted outside of 49-91 days

  - **n=1,711**

    - **n=257 enrollment periods associated with case children who were enrolled more than once**

    - **n=1,454**

    - **HIV test results available**

      - **Case children n=842**
      - **Mothers of case children n=967**
      - **Fathers of case children n=467**

      - **HIV test results available for both child and mother**

    - **Case Households n=798**

      - **HIV-positive households**
        - **n=172**
        - Tested at least 30 days before enrollment into GEMS
        - **n=66**
      - **HIV-negative households**
        - **n=626**
        - Tested within 30 days of enrollment into GEMS or thereafter
        - **n=67**
Table 1. Reported drinking water characteristics and sanitation facilities assessed at enrollment and at the 60-day follow-up interview among HIV-positive and HIV-negative case households—GEMS-Kenya, 2008-2012

<table>
<thead>
<tr>
<th>Drinking Water: Source, Treatment Methods, and Storage</th>
<th>HIV-positive HHs n=172</th>
<th>HIV-negative HHs n=626</th>
<th>Crude OR and CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main water source obtained from unimproved source*††</td>
<td>71 (41.3)</td>
<td>302 (48.2)</td>
<td>0.75 (0.54, 1.06)</td>
<td>0.11</td>
</tr>
<tr>
<td>Usually treats drinking water††</td>
<td>108 (62.8)</td>
<td>385 (61.5)</td>
<td>1.06 (0.75, 1.50)</td>
<td>0.76</td>
</tr>
<tr>
<td>Reported water treatment method effective‡††</td>
<td>104 (68.4)</td>
<td>355 (62.9)</td>
<td>1.28 (0.87, 1.87)</td>
<td>0.21</td>
</tr>
<tr>
<td>Chlorine test result**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>69 (75.0)</td>
<td>239 (77.9)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Positive</td>
<td>18 (19.6)</td>
<td>36 (11.7)</td>
<td>1.73 (0.93, 3.24)</td>
<td>0.09</td>
</tr>
<tr>
<td>Refused test</td>
<td>1 (1.1)</td>
<td>3 (1.0)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>No water in container</td>
<td>4 (4.4)</td>
<td>29 (9.5)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Child given untreated water¶</td>
<td>29 (27.1)</td>
<td>136 (34.0)</td>
<td>0.72 (0.45, 1.16)</td>
<td>0.18</td>
</tr>
<tr>
<td>Time to get water ≥ 60 min¶</td>
<td>11 (7.5)</td>
<td>51 (9.2)</td>
<td>0.80 (0.41, 1.58)</td>
<td>0.52</td>
</tr>
<tr>
<td>Water fetched daily¶</td>
<td>17 (15.9)</td>
<td>62 (14.7)</td>
<td>1.10 (0.61, 1.97)</td>
<td>0.76</td>
</tr>
</tbody>
</table>
Water not available daily¶ | 19 (11.1) | 51 (8.2) | 1.40 (0.80, 2.44) | 0.24
Child given stored water¶ | 148 (86.1) | 572 (91.4) | 0.58 (0.35, 0.97) | **0.04**
Observed containers in use in home** | 170 (98.8) | 616 (98.4) | 0.78 (0.25, 2.48) | 0.68
Main type of container observed is considered unsafe || ** | 134 (79.3) | 475 (77.2) | 1.13 (0.74, 1.71) | 0.57
Main container is covered** | Yes | 146 (85.9) | 493 (80.0) | 1.50 (0.84, 2.68) | 0.17
No | 15 (8.8) | 78 (12.7) | -- | --
Mixed | 9 (5.3) | 45 (7.3) | -- | --
How water is removed from container** | Scoop with cup | 133 (77.3) | 480 (76.7) | 1.04 (0.69, 1.55) | 0.86
Pour (spigot or spout) | 42 (24.4) | 164 (26.2) | 0.91 (0.62, 1.35) | 0.64
Sanitation
Disposal of child’s feces considered unimproved†† | 69 (40.8) | 242 (39.8) | 1.04 (0.74, 1.48) | 0.81
Household waste facility considered unimproved†† | 38 (22.2) | 167 (27.0) | 0.77 (0.52, 1.16) | 0.21
Household waste facility considered unimproved, and shared¶ | 144 (83.7) | 518 (82.8) | 1.07 (0.68, 1.69) | 0.76
Sanitation facility shared¶ | 113 (80.1) | 403 (78.7) | 1.09 (0.69, 1.74) | 0.71
Observed feces in defecation area** | 61 (35.5) | 203 (32.4) | 1.15 (0.80, 1.63) | 0.45
Observed feces elsewhere in house or yard** | 14 (8.1) | 56 (9.0) | 0.90 (0.49, 1.66) | 0.74
Hand Hygiene

30
**Wash hands with**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Water and soap††</td>
<td>89 (51.7)</td>
<td>281 (45.0)</td>
<td>1.31 (0.94, 1.84)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

**When do you typically wash your hands†|**

<table>
<thead>
<tr>
<th>When you wash your hands</th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Before eating</td>
<td>141 (82.0)</td>
<td>515 (82.3)</td>
<td>0.98 (0.63, 1.52)</td>
<td>0.93</td>
</tr>
<tr>
<td>Before cooking</td>
<td>60 (34.90)</td>
<td>230 (36.7)</td>
<td>0.92 (0.65, 1.31)</td>
<td>0.65</td>
</tr>
<tr>
<td>Before nursing</td>
<td>57 (33.1)</td>
<td>210 (33.6)</td>
<td>0.98 (0.69, 1.40)</td>
<td>0.92</td>
</tr>
<tr>
<td>After defecating</td>
<td>130 (75.6)</td>
<td>493 (78.8)</td>
<td>0.84 (0.56, 1.24)</td>
<td>0.37</td>
</tr>
<tr>
<td>After handling animals</td>
<td>21 (12.2)</td>
<td>61 (9.7)</td>
<td>1.29 (0.76, 2.18)</td>
<td>0.34</td>
</tr>
<tr>
<td>After cleaning child</td>
<td>53 (30.8)</td>
<td>192 (30.7)</td>
<td>1.01 (0.70, 1.45)</td>
<td>0.97</td>
</tr>
<tr>
<td>After cooking</td>
<td>2 (1.2)</td>
<td>2 (0.3)</td>
<td>3.67 (0.51, 26.25)</td>
<td>0.20</td>
</tr>
<tr>
<td>After handling soil</td>
<td>13 (7.6)</td>
<td>52 (8.3)</td>
<td>0.90 (0.48, 1.70)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

*Unimproved source included: open well in house/yard, open public well, pond or lake, shallow tube well, unprotected spring, river or stream, dam or earth pan, or bought

†At enrollment HH’s reporting usually treating their drinking water: HIV-positive HH’s, n=108, HIV-negative, n=385

‡Effective water treatment methods include: leaving water in the sun, using chlorine, boiling, filtering water through ceramic filter or other type of filter

§Reported main water source as being piped into house/yard, open or covered well in house/yard, or rainwater

||Unsafe storage container defined as a wide-mouth container or a mixture of wide-mouth and narrow-mouthed containers

¶Assessed at enrollment

**Assessed at follow-up

††Assessed both at enrollment and follow-up, follow-up measure used
Traditional pit latrines considered improved sanitation facility as we did not know whether the latrine had a slab or not.
Table 2. Reported water, sanitation, and hygiene characteristics among HIV-positive households that received HIV testing at least 30 days before enrollment into GEMS and HIV-positive households that received HIV testing within 30 days of enrollment or thereafter, western Kenya, 2008-2012

<table>
<thead>
<tr>
<th>Drinking Water: Source, Treatment Methods, and Storage</th>
<th>HIV-positive Households</th>
<th>Tested ≥ 30 days before enroll</th>
<th>Tested &lt; 30 days or after</th>
<th>Crude OR and CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n=66</td>
<td>n=67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main water source obtained from unimproved source*, ††</td>
<td>19 (28.8)</td>
<td>28 (41.8)</td>
<td>0.56 (0.27,1.16)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Usually treats drinking water††</td>
<td>49 (74.2)</td>
<td>37 (55.2)</td>
<td>2.34 (1.12, 4.86)</td>
<td><strong>0.02</strong></td>
<td></td>
</tr>
<tr>
<td>Reported water treatment method effective†, ††</td>
<td>48 (92.3)</td>
<td>35 (55.6)</td>
<td>9.60 (3.09, 29.86)</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>Chlorine test result positive**</td>
<td>10 (25.0)</td>
<td>6 (20.0)</td>
<td>1.33 (0.42,4.19)</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>Child given untreated water¶</td>
<td>13 (28.3)</td>
<td>10 (27.0)</td>
<td>1.06 (0.40, 2.80)</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Time to get water ≥ 60 min¶</td>
<td>3 (6.0)</td>
<td>4 (6.8)</td>
<td>0.88 (0.19, 4.12)</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Water fetched daily¶</td>
<td>3 (7.3)</td>
<td>9 (21.4)</td>
<td>0.29 (0.07, 1.16)</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Water not available daily¶</td>
<td>4 (6.1)</td>
<td>8 (11.9)</td>
<td>0.48 (0.14, 1.66)</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Child given stored water¶</td>
<td>58 (87.9)</td>
<td>58 (86.6)</td>
<td>1.12 (0.41, 3.12)</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Observed containers in use in home**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main type of container observed is considered unsafe</td>
<td></td>
<td>46 (69.7)</td>
<td>56 (84.9)</td>
<td>0.41 (0.17, 0.96)</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>Description</td>
<td>Count (Percentage)</td>
<td>Frequency (Mean, Standard Error)</td>
<td>p Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>----------------------------------</td>
<td>---------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main container is covered**</td>
<td>62 (93.9)</td>
<td>59 (89.4) 1.84 (0.51, 6.61)</td>
<td>0.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>How water is removed from container</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scoop with cup</td>
<td>44 (66.7)</td>
<td>57 (85.1) 0.35 (0.15, 0.82)</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pour (spigot or spout)</td>
<td>24 (36.4)</td>
<td>11 (16.4) 2.91 (1.28, 6.59)</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sanitation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disposal of child’s feces considered unimproved††</td>
<td>21 (32.3)</td>
<td>29 (43.9) 0.61 (0.30, 1.24)</td>
<td>0.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household waste facility considered unimproved††</td>
<td>10 (15.4)</td>
<td>18 (26.9) 0.49 (0.21, 1.17)</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household waste facility unimproved and shared¶</td>
<td>58 (87.9)</td>
<td>57 (85.1) 1.27 (0.47, 3.45)</td>
<td>0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanitation facility shared¶</td>
<td>45 (84.9)</td>
<td>43 (81.1) 1.31 (0.47, 3.63)</td>
<td>0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed feces in defecation area**</td>
<td>21 (31.8)</td>
<td>26 (38.8) 0.74 (0.36, 1.50)</td>
<td>0.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed feces elsewhere in house or yard**</td>
<td>5 (7.6)</td>
<td>2 (3.0) 2.66 (0.50, 14.23)</td>
<td>0.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hand Hygiene</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wash hands with</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water and soap††</td>
<td>35 (53.0)</td>
<td>41 (61.2) 0.72 (0.36, 1.43)</td>
<td>0.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>When do you typically wash your hands¶</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before eating</td>
<td>56 (84.9)</td>
<td>55 (82.1) 1.22 (0.49, 3.06)</td>
<td>0.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before cooking</td>
<td>28 (42.4)</td>
<td>20 (29.9) 1.86 (0.90, 3.83)</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before nursing</td>
<td>28 (42.4)</td>
<td>19 (28.4) 1.73 (0.85, 3.54)</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After defecating</td>
<td>49 (74.2)</td>
<td>53 (79.1) 0.76 (0.34, 1.71)</td>
<td>0.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After handling animals</td>
<td>5 (7.6)</td>
<td>9 (13.4) 0.53 (0.17, 1.67)</td>
<td>0.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After cleaning child</td>
<td>27 (40.9)</td>
<td>15 (22.4) 2.40 (1.13, 5.11)</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After handling soil</td>
<td>6 (9.1)</td>
<td>4 (6.0) 1.57 (0.42, 5.86)</td>
<td>0.50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Unimproved source included: open well in house/yard, open public well, pond or lake, shallow tube

well, unprotected spring, river or stream, dam or earth pan, or bought

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703  *Unimproved source included: open well in house/yard, open public well, pond or lake, shallow tube

704  well, unprotected spring, river or stream, dam or earth pan, or bought

---
†At enrollment HH’s reporting usually treating their drinking water: HIV-positive HH’s, n=212, HIV-negative, n=742; At 60-day follow-up interview: HIV-positive HH’s, n=192, HIV-negative HH’s, n=673.

‡ Effective water treatment methods include: leaving water in the sun, using chlorine, boiling, filtering water through ceramic filter or other type of filter

§Reported main water source as being piped into house/yard, open or covered well in house/yard, or rainwater

||Unsafe storage container defined as a wide-mouth container or a mixture of wide-mouth and narrow-mouthed containers

¶ Assessed at enrollment

**Assessed at follow-up

††Assessed both at enrollment and follow-up, follow-up measure used
Chapter 4: Handling Extreme Values within Anthropometric Data: A Comparison of Outlier Detection Methods

Proposed journal: The Journal of Nutrition
Title: Handling Extreme Values within Anthropometric Data: A comparison of outlier detection

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\end{flushleft}
ABSTRACT

Background: To assess malnutrition, a leading cause of morbidity and mortality in young children globally, anthropometric data or body measurements are collected. Guidance on how best to deal with extreme values within anthropometric data is limited.

Objectives: The purpose of this paper is to explore the application of various robust univariate outlier detection methods as well as one objective method to flag seemingly biologically implausible values on height measurements and their associated HAZ scores collected during Global Enterics Multicenter Study Kenya site.

Methods: Five univariate outlier detection methods along with one objective method using criteria based on biological plausibility were applied to height measurements obtained at enrollment, follow-up and the difference between the two time points as well as for height-for-age z-score (HAZ). After applying each method extreme values detected by each were removed. To demonstrate how each method influenced the data, measures of location and dispersion are presented for each method and for the full dataset and the proportion of children stunted.

Results: We found using the trimmed mean technique flagged the highest proportion of observations, followed by the standard deviation method, next highest were the objective cut-offs, then the Inner Tukey technique, and finally the Median Absolute Deviation (MAD) and the Outer Tukey techniques. Among all height and HAZ measures, we found very little difference between the measures of location and dispersion.

Conclusions: Due to the limited recommendations on how best to deal with extreme values within anthropometric data, we recommend that relevant, robust, simple outlier detection techniques be applied. These methods will likely reduce bias introduced as a result of human error or faulty equipment. We suggest applying the Inner Tukey and Outer Tukey techniques to height and HAZ.

Key Words: Anthropometry, data cleaning, outlier detection, height-for-age z-score, height, children, Kenya.
INTRODUCTION

Malnutrition is a leading cause of morbidity and mortality in young children globally (1). Worldwide, approximately 2.2 million children under five years old die as a result of being malnourished (1). Malnutrition can lead to delays in physical and cognitive development among other health complications (1). A common way of assessing malnutrition in young children is to collect anthropometric data or body measurements such as height, weight, mid-upper arm circumference, or head circumference. These values along with the gender and age of the child are used to compute indicators, typically expressed as z-scores, such as weight-for-age z-scores (WAZ), height-for-age z-scores (HAZ), or weight-for-height z-scores (WHZ) (2). These indicators can then be compared to a standardized reference population from a healthy, ethnically-diverse population of children (3). Z-scores below certain thresholds are indicative of the level and severity of nutritional deficiencies. Three commonly well-known and well-accepted indicators include a HAZ < -2 which is indicative of stunting, a WAZ < -2 indicates being underweight, and a WHZ < -2 is considered wasting (4). Being stunted is a long-term indicator of malnutrition whereas wasting is an indicator of short-term malnutrition (4).

Anthropometric measures are good predictors of the nutritional status at both the individual and population level (5). Furthermore, they can be obtained economically and can be collected in a reasonable amount of time (6). In order to obtain accurate measures, however, data must be collected methodically as there are numerous ways error can be introduced. When differences occur between the replication of two or more measurements the measures are often classified as being unreliable. These typically occur because of error introduced by the person or persons obtaining the measurement or for some physiological reason (7). Another form of error occurs when measurements deviate from the real value, also known as inaccurate measures (7). These result from defective equipment or in the methods of how one is measured (7).
A number of strategies are recommended to minimize sources of error within anthropometric data. Staff must be adequately trained on the techniques to properly measure children (6). Continued supervision and on-going training is recommended to ensure the quality of work overtime (6). Quality assurance and quality control measures are important; it’s recommended that measures are reviewed for accuracy after being collected and where necessary children are re-measured within a reasonable time frame (6). Furthermore, staff must have functioning equipment; the equipment must be in good, working condition, and must be calibrated correctly (6). Last, it’s highly recommended that software designed specifically to calculate z-scores and analyze anthropometric data is used for the analysis and interpretation of nutritional data (6). Even after all these efforts are implemented it’s still likely that data will contain some extreme values. Software developed to analyze anthropometric data have built in flagging systems to detect data points that are likely erroneous due to error in recording or measurement (6, 8). Once flagged, these observations can be removed from further analysis. The guidelines for flagging extreme values provided by WHO are quite liberal, for example the HAZ must be > 6 or < -6 to be flagged as extreme (3, 8).

As part the Global Enterics Multicenter Study (GEMS), a study of moderate-to-severe diarrhea (MSD) in young children, anthropometric measurements were obtained from both case and control children at enrollment as well as at the 60-day follow-up interview. When exploring the anthropometric data within GEMS-Kenya and for the broader pan-site data we noted observations that seemed biologically implausible. When looking at the data from all seven countries we noticed that the mean measures obtained at enrollment were quite different for each country. The broad application of applying liberal cut-offs did not seem appropriate. These issues, along with the need for a consistent method of dealing with extreme values across multiple analyses, and limited guidance within the literature led us to explore outlier detection techniques to deal with these observations.
An outlier is a data point that falls outside most other observations within a dataset. Outliers can be a result of error, either in measurement or data entry, or they might very well be real, rare occurrences. It is important to assess outliers because they can greatly influence the results of statistical analysis (9, 10). Methods to identify and detect outliers include univariate and multivariate methods.

This paper will focus on univariate methods. Univariate methods are used on a single variable to help identify extreme values within that variable in a process known as labeling. Values are labeled based on specific criteria or intervals (10-12). Labeling outliers can be used to identify values outside of their expected distribution in advance of multivariate methods or it can simply be used identify ‘extreme’ values within the data(12). Techniques that are robust, meaning they are insensitive to extreme values within the data, are recommended (13). Often robust statistics make use of measures such as the median or interquartile range as compared to the mean. A variety of established robust labeling techniques exist.

Guidance on how best to deal with extreme values within anthropometric data is limited (4, 6, 14). The criteria that do exist are very liberal, and do not focus on the change in growth over time. Because of this and the wealth of guidance on outlier detection analysis, we describe here within a comparative analysis using five outlier detection methods and one set of objective cut-offs. The purpose of this paper is to explore the application of various robust univariate outlier detection methods as well as one objective method to flag seemingly biologically implausible values on height measurements and their associated HAZ scores collected during GEMS-Kenya. In this paper we will describe each outlier detection method and the objective set of cut-offs we used in greater detail and will demonstrate how each technique influences the data in terms of the measures of location and dispersion.

METHODS

*The Global Enterics Multicenter Study*
To explore the risk factors, etiologies, and consequences of MSD the Global Enterics Multicenter Study (GEMS), a case-control study among African and Asian children less than 5 years old was conducted (15). Methods used to conduct GEMS have been described elsewhere (15). Children with MSD must have met the following case definition: three or more loose stools per day, for 7 days or less, as well as one or more of the following signs indicative of dehydration: sunken eyes, loss of skin turgor, intravenous rehydration administered or prescribed, dysentery, or hospitalized with diarrhea or dysentery. Control children were enrolled at home within 14 days of their matched case; control children were matched on age, sex, and location.

For all case and control children, anthropometric data was obtained at enrollment and at a follow-up home visit conducted between 49 to 91 days. A wealth of other information was collected as well, but will not be discussed further as it is beyond the scope of this paper. In GEMS, children were measured according to established guidelines on how to properly measure children (16). Height, weight, and mid-upper arm circumference were collected at enrollment and at the follow-up interview for both cases and controls.

Height measures and their associated z-scores were chosen as the focus of this paper as they are thought to be more stable in terms of their inability to fluctuate overtime as compared to weight measures (17). This is especially important in the context of GEMS where the outcome of interest was MSD. In order to be eligible for enrollment into GEMS as a case, a child must have had least one sign indicative of dehydration, a factor that greatly influences fluctuations in a child’s weight (18). Therefore, the methods used for measuring the length/height of children will be described here within as the focus of this paper is on height and HAZ. Children younger than 24 months or those who were unable to stand were measured lying down. To measure the child, a board with a stationary piece for the head and an adjustable piece for the feet was used. Children 24 months or older were measured standing. A board
with a stationary piece for the feet and an adjustable piece for the head was used. The length/height of each child was measured three times. The mean and median of the three measurements was calculated. For the purposes of this paper the median value will be used.

Study Area and Study Population

GEMS-Kenya began enrolling children on January 31, 2008 through January 29, 2011 and again starting on October 31, 2011 through September 30, 2012. The Centers for Disease Control and Prevention (CDC) and the Kenya Medical Research Institute (KEMRI) Research Station coordinated the GEM-Kenya site located in rural western Kenya, near Lake Victoria, in Nyanza Province within the districts of Gem, Karemo, and Asembo. Children were enrolled at 6 sentinel health centers. The health centers catchment area served about 135,000 people, 21,000 of whom were young children (<5 years) (15, 19). Child mortality and HIV/AIDS rates are high in this region of Kenya (20, 21).

Procedures for Anthropometric Data

A program developed by the WHO was utilized to calculate z-scores from the anthropometric data collected in GEMS; the program was developed to assist researchers in properly calculating z-scores. The program was called the WHO Child Growth Standards, SAS igrowup, standard analysis package (3, 22). Z-scores were calculated for height-for-age as well as a number of other indicators that are outside of the scope of this paper. A z-score was calculated for the measurement obtained at enrollment and the measurements obtained at follow-up. As height was measured three times, z-scores were calculated for both the mean and the median of the three values as well; however, this paper will focus on the median scores only. In addition to calculating the z-score, a variable flagging z-scores that were < -5 or < -6 and > 5 or > 6 was constructed to identify biologically implausible values as per WHO standards (3).
To calculate the change in the height measures and HAZ from enrollment to follow-up the difference between the heights and/or HAZ at follow-up was subtracted from the height and/or HAZ reported at enrollment.

Methods to detect outliers

Five outlier labeling techniques along with one objective set of cut-offs were applied to the following measures: HAZ as measured at enrollment, HAZ as measured at the 60-day follow-up interview, and the difference between the HAZ at enrollment as compared to the HAZ as measured at follow-up. Similarly, these methods were applied to the median height measures. Each method and its application are described below.

Standard Deviation

One common way of detecting outliers is to use the standard deviation (SD), a measure displaying the dispersion within the data. In normally distributed data, observations within 2 SD from the mean represent about 95% of the data and observations within 3 SD represent approximately 99% of the data (23). To detect outliers using this method any data point outside of 2 SD are considered outliers. The formula used to calculate the SD is below:

$$\pm 2 \text{ SD} = \sqrt{\frac{\sum (x - \bar{x})^2}{N - 1}}$$

Median Absolute Deviation

The Median Absolute Deviation (MAD) is another commonly used, robust method to detect outliers. To use this technique one must first identify the median of the data. Next each value within the data is subtracted from the median and expressed in terms of its absolute value (24). The median of the absolute values represents the MAD (24). Any observation outside of a certain distance, in our case 3.5 as suggested by Iglewicz and Hoaglin (25), from the MAD are considered outliers. To calculate the MAD and to identify observations we used the following formula:
To identify outliers using the trimmed mean technique the data are first ranked from smallest to largest, then the top 5% of the data and the bottom 5% of the data are excluded. Upon excluding these data the mean of the ‘trimmed’ data is then computed.

Two of the outlier detection methods used in this paper are derived from the boxplot. A boxplot graphically displays the distribution of the data using a box and whiskers also known as fences (26). The box itself represents approximately 50% of the data; the bottom of the box represents the 25th percentile (Quartile 1 [Q1]), the middle indicates the median (50%), and the top of the box represents the 75th percentile (Quartile 3 [Q3]) (26). Data points falling either above or below a certain distance from the first or third quartiles are known as “outside” and “far out” outliers, also known as Tukey’s inner fences and Tukey’s outer fences, respectively (26). The formulas for identifying these observations are:

\[
\text{Tukey’s Inner Fences} = Q1 - 1.5 \times IQR, \quad Q3 + 1.5 \times IQR \\
\text{Tukey’s Outer Fences} = Q1 - 3.0 \times IQR, \quad Q3 + 3.0 \times IQR
\]

In addition to the outlier detection methods, we choose to remove observations based on a series of criteria indicative of biologically implausible growth measures. First, we removed any observation where the height decreased by 1.5cm from enrollment to follow-up. Second, we removed children who grew more than likely possible over the specified period of time. For children whose 60 day follow-up interview was conducted between 49-60 days we removed any infant between 0-6 months whom grew more than 8cm; for children 6 months and older we removed any child whom grew

\[
MAD = \text{median}(|X_i - \text{median}(X_i)|)
\]
4cm or more. For children whose 60-day follow-up interview was conducted between 61-91 days, we removed any infant aged 0-6 months who grew 10cm or more; for children older than 6 months we removed any child who grew 6cm or more (27). Furthermore, if the HAZ measured at enrollment or follow-up was greater than 6 SD or less than -6 SD or the ΔHAZ was greater than 3 SD the observation was removed (4).

Eligibility for Analysis

A number of children were not included within the analysis. Any child that died during the study period was not included. We did not include children with incomplete 60-day follow-up interviews nor children who were followed-up outside of the 49 to 91 day period as stated per the GEMS protocol. Furthermore, if a child was missing height measurements at enrollment or follow-up the child was excluded from analysis.

Statistical Analysis

This analysis will focus on both the raw height measurements obtained at enrollment, follow-up and the difference between the two time points as well as the HAZ. To identify extreme values six methods were applied to raw height and HAZ measures. The five univariate outlier detection methods described along with one objective method using criteria based on biological plausibility were applied to the following raw height measures: the median height as measured at enrollment, the median height as measured at the 60-day follow-up interview, and the difference between the median height measured at enrollment as compared to the median height measured at follow-up. Similarly, these methods were applied to the HAZ, calculated using the median of the three height measures obtained at enrollment and follow-up.

To identify potential data entry errors, prior to the application of the outlier detection methods, we examined the raw height measurements from data collected during the first 3 years of GEMS-Kenya. Specifically, we identified any child that grew 8 cm or more or any child that shrank 1 cm or more from...
enrollment to follow-up. For any child identified as meeting these criteria, the original paper-based form was requested and electronically sent to CDC-Atlanta for further review. The height variables on the paper-based forms were reviewed for data entry errors. Any form found to have an error was rectified within the dataset.

Outlier detection relies on the distributional properties of the data. We expected variations within the data for certain variables such as the child’s age and the child’s case/control status. Each of these groups contain important distributional differences making an across the board application of outlier detection techniques not appropriate, and therefore we controlled for each of these factors. For example, as shown in Figure 1, the distribution of HAZ at enrollment for each of the age categories that we used is displayed graphically using boxplots. The boxplots show how the distribution changes within each age category. We controlled for these various factors for a number of important reasons. For one, children, depending on their age grow at various rates; younger children growing at much higher rates than older children (36). The child’s age was broken down into five groups: 0-6 months, 7-11 months, 12-17 months, 18-23 months, and/or 24-59 months. Second, whether a child was enrolled as a case or a control was conditioned upon as case children were ill at the time of enrollment and hence likely have poorer health outcomes. To control for these variables, we created a separate subset of data for every combination between the five age categories and case/control status. Each outlier detection method was then applied to the 10 subsets of data. Once extreme values within each subset were identified the data was then combined back into one dataset.

Once each method was applied to the raw height measures and to the HAZ, the outlying observations detected by each method were removed from the data and new measures of location and dispersion were calculated. In this paper we present the number of observations removed using each method. To demonstrate how each method influenced the data, measures of location and dispersion such as the mean, median, mode, range, interquartile range, standard deviation, and variance are
presented for each method and for the full dataset. We also present the proportion of children stunted, defined as HAZ < -2, at enrollment and at follow-up for the full dataset, and for the datasets excluding observations using the outlier detection methods and the objective set of cut-offs. Data were analyzed using SAS 9.3.

Scientific Ethics

Before enrollment into GEMS every participant provided written informed consent. The Kenya Medical Research Institute Scientific and Ethical Review Committee and the Institutional Review Board (IRB) at University of Maryland, School of Medicine, Baltimore, MD, USA approved the GEMS protocol. The GEMS protocol was deferred by the Centers for Disease Control and Prevention, Atlanta, GA, USA, IRB to the IRB at the University of Maryland for review.

Study enrollment and participants

During GEMS-Kenya (January 31, 2008-January 29, 2011 and October 31, 2011- September 30, 2012), 4,226 children were enrolled; of these 1,778 were enrolled as cases and 2,448 as controls (Figure 2). A total of 76 (1.8%) children enrolled into GEMS died during the study period (62 [3.5%] case children, 14 [0.6%] control children), these children were not included within our analysis. We did not include 120 (2.8%) children whom were lost to follow-up (60 [3.4%] case children and 60 [2.5%] control children) within our analysis. Per protocol it was required that the 60-day follow-up visit be conducted between 49 and 91 days, 18 (0.4%) children (7 [0.4%] cases, 11 [0.5%] controls) did not meet these criteria and were therefore not included within the analysis. Among the remaining children, 6 (3.0%) had a missing height measurement at enrollment or follow-up (2 [0.3%] case children, 4 [0.2%] control children) and so are not included within our analysis. Our analysis included the 4,006 children (1,647 case children, 2,359 control children) with complete data. Among the 4,006 children included within our analysis, 619 (15.5%) were between 0-6 months of age, 991 (24.7%) were 7-11 months, 785 (19.6%)
were 12-17 months, 453 (11.3%) were between 18 and 23 months, and 1,158 (28.9%) were 24 to 59 months of age; 1,733 (43.3%) were females.

RESULTS

Review of hard copy forms

We reviewed hard copy forms to identify data entry errors among the 3,359 children enrolled in the first three years of GEMS. We identified 281 (8.4%) observations where the child either grew more than 8cm from enrollment to follow-up or shrank 1cm or more from enrollment to follow-up. Among the 281 forms reviewed we found errors in the height measurements on 21 (7.5%) forms; however, one form was missing a page of the survey itself and therefore we were unable to determine what the information on this form contained to see if it was erroneous. Assuming this form to be excluded we found errors on 20 (7.1%) of the 281 forms reviewed. All errors identified were corrected within the complete dataset prior to analysis.

Distribution of complete dataset

Prior to application of the outlier detection techniques we explored the distribution of the data for all height and HAZ measures using the complete dataset regardless of the child’s age or case status. At enrollment the median value for height was 75.5cm, the mean was 74.2cm (Table 1). The values ranged from 45.0cm to 111.0cm with 25% of the data at 67.3cm and 75% at 82.7cm. The SD was 11cm and the variance 120.7cm. At follow-up the median was 77.1cm, the mean 75.4cm. The minimum value was 49.5cm, the lower quartile was 69.1cm, the upper quartile was 83.6cm and the maximum value was 114.9cm. The SD was 10.4cm and the variance 108.9cm. For the difference in height, the median was 1.4cm and the mean 1.5cm. The data ranged from -17.5cm to 41.8cm; the lower quartile was 0.7cm and the upper quartile was 2.3cm. The SD was 1.7cm and the variance 2.8cm.
For all children, the mean and median HAZ at enrollment was -1.4 (Table 1). At enrollment, HAZ ranged from -7.7 to 4.5; the lower quartile was -2.2 and the upper -0.5. The SD for the HAZ at enrollment was 1.3 and at follow-up was 1.2 with a variance of 1.6 and 1.5, respectively. At follow-up, the mean was -1.6 and the median -1.5. At follow-up the lowest value in the data was -6.5, the lower quartile was -2.3, the upper quartile was -0.7, and the maximum value in the data was 4.2. The mean and median values for the change in HAZ were -0.2. The data ranged from -6.8 to 9.1; the lower quartile was -0.4 and the upper quartile was 0.1. The SD was 0.5 and the variance was 0.3.

**Outlier identification**

After applying each outlier detection method and the one set of objective cut-offs we present the number of observations flagged by each technique for both height and HAZ measures obtained at enrollment, follow-up, and the difference between the two time points as shown in Table 2. Across the board, the trimmed mean method flagged the most observations for cases, controls, and all children regardless of height or HAZ. Using this method approximately, 5-8% of the data was flagged; the higher proportions, 8%, were for the difference in height and HAZ. The standard deviation method flagged roughly similar proportions to the trimmed mean; approximately 4-5% of the data was flagged using this method. Across all measures, the Inner Tukey method identified between 1-4% of the data as being outliers. The Outer Tukey and MAD methods flagged 1% or less of the data. Finally, the objective cut-offs identified between 2-3% of the observations as being outliers.

To demonstrate the amount of overlap amongst the various methods used to detect extreme values within our data we present a Venn Diagram (Figure 3) (28). To simplify the Venn Diagram we created one grouping for the extreme values detected using the Inner Tukey method, the Outer Tukey method, and the MAD method. We did this because the two extreme values detected using the Outer Tukey method and the 11 extreme values detected using the MAD method were also detected by the Inner Tukey method; and therefore, we assumed that it was reasonable to combine. As shown in the Figure
3, there is much overlap between many of the techniques applied for HAZ at enrollment. For example, the trimmed mean and SD methods flagged 113 of the same observations (shown in purple). All observations flagged by Inner Tukey, Outer Tukey, or MAD were also captured by SD and trimmed Mean (n=48) or by the trimmed Mean and the objective cut-offs (n=10). Three observations were captured within the objective cut-offs, SD, and trimmed mean, and two observations overlapped between the objective cut-offs and the trimmed mean. Seventy-six observations were flagged uniquely by the objective cut-offs, 50 by the trimmed mean method, and 4 by SD.

Another way to look at the overlap is depicted in Figure 4. Figure 4 is an overlaid histogram showing the distribution of HAZ at enrollment for the complete dataset as compared to the dataset when excluding outliers detected by the Inner Tukey method and when excluding outliers by the trimmed mean method. It’s clear to see the distributional changes once outliers have been excluded as compared to the complete data. To note, the trimmed mean has the fewest observations, followed by the Inner Tukey, and then the complete dataset. Furthermore, the complete dataset has longer tails or a wider distribution as compared to the trimmed mean and Inner Tukey datasets.

Measures of location and dispersion

After removing the extreme values identified by each of the outlier detection methods and the objective set of cut-offs we examined the measures of location and dispersion for height and HAZ within each dataset (Tables 3 and 4). For HAZ and height, the values between all measures of location and dispersion were all very similar.

After the removal of extreme values detected by each outlier detection technique, the mean and median values were similar for height values measured at enrollment and at follow-up among all outlier detection techniques. At enrollment, the mean in all datasets ranged from 75.5 cm to 75.6 cm. The median was 74.2 cm for all datasets except one, the method using the objective cut-offs, the median for this dataset was 74.1 cm. The objective cut-offs and the Outer Tukey datasets had the largest
range where data spanned from 45.0cm to 111.0cm. The dataset with the smallest range was the
trimmed mean, data spanned from 54.3cm to 102.9cm. The lower and upper quartile fell at roughly the
same point for all datasets, about 67cm and about 83cm, respectively. The SD ranged from 10.5cm to
11.0cm, and the variance from 110.8cm to 121.2cm. At follow-up the mean value for all datasets was
about 77cm and the median about 75 cm. The objective cut-offs had the largest range 49.5cm to
111.8cm and the trimmed mean had the smallest, 58.3cm to 104.9cm. The SD was between 10.0cm and
10.5cm, the variance between 100.9cm to 109.4cm. When looking at the change between enrollment
to follow-up the mean value for all datasets was 1.5cm and the median was 1.4cm. The range was
largest in the dataset excluding observations using the Outer Tukey technique, -4.2cm to 8.1cm, and
largest in the dataset excluding observations using the Trimmed Mean technique, -1.3cm to 6.2cm. In
all datasets the lower quartile was 0.7cm and the upper quartile was 2.2cm. The SD ranged from 1.2cm to
1.3cm and the variance from 1.4cm to 1.8cm.

Similar to height, the measures of location and dispersion were quite similar for HAZ. At
enrollment, the mean and median were -1.3 for the datasets that excluded the highest number of
observations (SD, trimmed mean, and Inner Tukey); the mean and median were -1.4 for the remainder
of the datasets. The range of the data was largest in the dataset that excluded the least number of
observations, Outer Tukey. In this dataset the data ranges from -6.7 to 4.5. The dataset excluding the
most observations through the trimmed mean method had the smallest range, where the minimum
value was -4.4 and the maximum value was 1.3. The lower and upper quartiles for all data were quite
similar. The lower quartile ranged between -2.1 and -2.2, and the upper quartile between -0.5 and -0.6.
The SD ranged from 1.1 to 1.3, and the variance from 1.2 to 1.6. At follow-up, the mean was slightly
lower in the three datasets excluding the most observations (SD, trimmed mean and Inner Tukey); it was
-1.5 in these datasets as compared to -1.6 in the other datasets. The median value for all datasets was
-1.5. The minimum value in each dataset ranged from -6.5 (Objective cut-offs) to -4.4 (trimmed mean),
the maximum values ranged from 1.2 (trimmed mean) to 4.2 (objective cut-offs and Outer Tukey). The lower quartile was between -2.2 and -2.3 and the upper quartile between -0.7 and -0.8. The SD ranges from 1.0 to 1.2 and the variance from 1.1 to 1.5. For the change in HAZ the mean and median values were the same, -0.2, for all datasets. The objective cut-offs had the smallest minimum value of -2.3, whereas the largest minimum value was -1.5 in the trimmed mean dataset. The smallest maximum value was 0.8 in the trimmed mean dataset and the largest maximum value was 1.7 was found in three datasets: the Outer Tukey, MAD, and the objective cut-offs. The lower and upper quartiles were the same for all datasets -0.4 to 0.1 with the exception of the trimmed mean dataset having a slightly lower upper quartile value of 0.04. The SD ranged from 0.4 to 0.5, and the variance from 0.1 to 0.3.

**Proportion of Children Stunted**

To explore how each outlier detection method influenced a common health outcome of interest we looked at the proportion of children stunted, defined as HAZ < -2, at enrollment and follow-up (Table 5). In the full dataset, more children were stunted at follow-up (34.0%) as compared to enrollment (28.9%). A larger proportion of control children (30.3%) were stunted at enrollment as compared to case children (26.8%); however, at follow-up a higher proportion of case children were stunted as compared to control children, 34.5% and 33.7% respectively. In general, the methods excluding the most observations have the lowest proportion of children stunted. For example, the lowest proportions of children stunted were found when excluding observations using the trimmed mean method. In this dataset, 26.9% of all children were stunted at enrollment. At enrollment, 28.3% of control children were stunted and 24.9% of case children were stunted. At follow-up, 33.6% of all children were stunted.

More case children were stunted as compared to control children at follow-up, 33.3% vs. 32.1%. Similar proportions of children stunted in the complete dataset were also found when excluding values using the objective cut-offs. Using this method 28.8% of all children, 26.7% of case children, and 30.3% of case children were stunted at enrollment. At follow-up, 33.6% of all children, 34.1% of case children,
and 33.6% of control children were stunted. The method excluding the least number of extreme values, Outer Tukey, had nearly the same proportion of children stunted for the complete dataset. At enrollment, 28.8% of all children were stunted, 30.3% of control children and 26.7% of case children were stunted. At follow-up, 34.0% of all children, 34.5% of case children, and 33.7% of control children were stunted.

**DISCUSSION**

In this investigation we applied five outlier labeling techniques and one objective set of cut-offs to height measures and their associated HAZ collected at enrollment, follow-up, and for the difference between enrollment to follow-up. Our goal was to get a better understanding of how the various methods affected the data in terms of the number of observations excluded and the influence on the measures of location and dispersion. We found using the trimmed mean technique flagged the highest proportion of observations, followed by the standard deviation method, next highest were the objective cut-offs, then the Inner Tukey technique, and finally the MAD and the Outer Tukey techniques. After removing extreme values using each of the different techniques, we examined the measures of location and dispersion in each dataset. Among all height and HAZ measures, we found very little difference between the measures of location and dispersion. When exploring the proportion of children stunted for the full dataset as compared to the datasets excluding observations via the outlier detection methods or the objective cut-offs we see that the datasets excluding the most extreme values have the lowest proportion of children stunted. The proportion stunted using the Inner Tukey method, Outer Tukey method, and the objective cut-offs were quite similar at enrollment and at follow-up. Although it is beyond the scope of this study, it would be interesting to further compare the children who were stunted using each of the various methods via a sensitivity analysis.
It’s likely that we found little differences in these measures as we had a large database, and relatively speaking a small proportion of the data was flagged and then excluded. Hence the measures of location and proportion of children stunted were minimally influenced. To note, we found data entry errors on approximately 7% of the forms. On the remaining forms we found no error between the data recorded within the dataset as compared to the recorded values on the form itself. We are unable to identify the cause of these extreme values, but speculate it could be due to measurement error or true extreme measures.

Some outlier detection methods are more suitable than others based on the measures in which they derived from. Certain measures of location and dispersion, specifically the mean, standard deviation, and range are highly influenced by outliers (25). This is due to the fact that one extreme value within the data can potentially change these measures quite significantly (25). Furthermore, using methods based on these measures assumes the data to be normally distributed (25). Other methods using the median and interquartile range are more robust meaning they are less affected by extreme values because they have what’s known as a high breakdown point (25). The breakdown point is the proportion of extreme data points needed to excessively influence the estimator (29). The largest breakdown point is 50%. Among the outlier detection techniques we examined, MAD has the highest breakdown point, 50%, the interquartile range has a breakdown point of 25%, and the trimmed mean in our study has a breakdown point of 10% as we ‘trimmed’ each end of the data by 5% (24, 29).

Among the various outlier detection techniques we explored within this investigation the technique excluding the least number of observations was the Outer Tukey method. This method excluded about 1% or less of the data, as would be expected due to the nature of the calculation. The method with the highest breakdown point, MAD, excluded a similar proportion of extreme values. We found the standard deviation method and the trimmed mean technique to identify the most extreme values. The standard deviation method is more sensitive to outliers as compared to some of the other...
techniques we examined. The trimmed mean technique is considered robust; however, we used a 5% ‘trimming’ technique which is lower than the 15% that others have recommended (25).

We choose to examine an objective set of cut-offs based on criteria indicative of biologically implausible growth measures. We included this within our analysis as some researchers apply justifiable criteria to perform additional data cleaning on nutritional data. An advantage of using objective cut-offs is they make biological sense; however, they do not account for the measurement error that is almost certainly prominent within anthropometric data. For example, in our study we used criteria applied in a linear growth study conducted using the GEMS pansite data (30). There is no standardized approach to applying criteria of this nature. Furthermore, there are no established, consistently used criteria with the exception of the WHO standards (4). Often studies do not describe the criteria they use in detail in terms of what they did or how it was applied (31-35). Because these criteria often go unreported data cleaning techniques are not consistent across studies.

There are limited recommendations on how best to deal with extreme values within anthropometric data. The guidelines that do exist are quite liberal. Current recommendations suggest that z-score values between $<-5$ or $<-6$ and $>5$ or $>6$ depending on the indicator of interest are to be removed from the data prior to analysis (3). Because we do not know whether the extreme values are a result of measurement error or ‘true’ variations within the data, applying outlier detection techniques such as we did here, may be useful as it helps to eliminate bias. We recommend that relevant, robust, simple outlier detection techniques be applied to anthropometric data. These methods will likely reduce bias introduced as a result of human error or faulty equipment. In this investigation the MAD and Outer Tukey techniques identified a very similar proportion of extreme values within our data from both height measures and their associated HAZ. Furthermore, we found that the objective cut-offs excluded slightly more, but very close to the proportion of extreme values detected by the Inner Tukey method. Because the Inner and Outer Tukey techniques are well-known, widely-accepted, and simple
to apply we recommend applying one method or ideally both methods to nutritional data. Once these methods have been applied a simple sensitivity analysis can be conducted to determine what method is most appropriate for the data being analyzed. The Inner Tukey method is more conservative and will exclude more observations, whereas the outer Tukey method is more liberal allowing for more extreme values within the data.

This study was subject to a number of limitations. For one, our data has a very large sample size, and so our findings might not be applicable for smaller samples. Furthermore, many outlier detection techniques exist and we did not explore all of these; however, we explored a reasonable amount of robust, well-known techniques that could be simply and easily applied in a real world setting. Finally, our findings may not be applicable to other children from other areas of Kenya or other countries.

Future research should explore the application of outlier detection methods to broader datasets, potentially the pansite GEMS data. Furthermore, due to the variations in the mean height and HAZ measures noted at enrollment in the pansite GEMS data, it would be useful to examine further differences between raw height measures as compared to their associated HAZ. In conclusion, we found that robust, simple outlier detection methods were a useful tool in determining extreme values within nutritional data. We recommend future research to apply similar methods to eliminate bias and to allow for greater consistency in the analysis of nutritional data across the studies.
ACKNOWLEDGEMENTS

Statement of authors’ contributions to manuscript
Figure 1. Box plots for HAZ at enrollment by age group
Figure 2. Flow chart of GEMS Kenya Study Population, 2008-2012

N=4,226

n=1,778 Cases
n=62 died
n=1,716 Cases
n=60, information from 60-day follow-up interview incomplete
n=1,649 Cases
n=2 missing height measurement
-1 at enrollment
-1 at follow-up
n=1,647 Cases

n=2,448 Controls
n=14 died
n=2,434 Controls
n=60, information from 60-day follow-up interview incomplete
n=2,363 Controls
n=4 missing height measurement
-0 at enrollment
-4 at follow-up
Figure 3. Venn Diagram of overlap between the six methods to detect extreme values for HAZ as measured at enrollment.

*Observations detected by the Outer Tukey (n=2) and MAD (n=11) methods were also captured by the Inner Tukey and therefore for the sake of simplicity are included within one group.
Figure 4. Distribution of HAZ as measured at enrollment for the complete dataset (yellow), dataset with outliers detected using Inner Tukey removed (blue), and dataset with outliers detected using Trimmed Mean removed (red).
Table 1. Measures of location and dispersion for the complete GEM-Kenya dataset for both HAZ and median height (cm) as measured at enrollment, follow-up, and its change over time, 2008-2012

<table>
<thead>
<tr>
<th></th>
<th>HAZ at enrollment</th>
<th>HAZ at follow-up</th>
<th>Difference in HAZ</th>
<th>Median height at enrollment</th>
<th>Median height at follow-up</th>
<th>Difference in median height</th>
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<tbody>
<tr>
<td>Mean</td>
<td>-1.4</td>
<td>-1.6</td>
<td>-0.2</td>
<td>75.5</td>
<td>77.1</td>
<td>1.5</td>
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<td>Median</td>
<td>-1.4</td>
<td>-1.5</td>
<td>-0.2</td>
<td>74.2</td>
<td>75.4</td>
<td>1.4</td>
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<tr>
<td>Range (Min, Max)</td>
<td>12.2 (-7.7, 4.5)</td>
<td>10.6 (-6.5, 4.2)</td>
<td>15.9 (-6.8, 9.1)</td>
<td>66.0 (45.0, 111.0)</td>
<td>65.4 (49.5, 114.9)</td>
<td>59.3 (-17.5, 41.8)</td>
</tr>
<tr>
<td>IQR (1st Q, 3rd Q)</td>
<td>1.6 (-2.2, -0.5)</td>
<td>1.6 (-2.3, -0.7)</td>
<td>0.5 (-0.4, 0.1)</td>
<td>15.4 (67.3, 82.7)</td>
<td>14.5 (69.1, 83.6)</td>
<td>1.6 (0.7, 2.3)</td>
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<tr>
<td>Standard Deviation</td>
<td>1.3</td>
<td>1.2</td>
<td>0.5</td>
<td>11.0</td>
<td>10.4</td>
<td>1.7</td>
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<tr>
<td>Variance</td>
<td>1.6</td>
<td>1.5</td>
<td>0.3</td>
<td>120.7</td>
<td>108.9</td>
<td>2.8</td>
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<td>Skewness</td>
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<td>-0.2</td>
<td>1.2</td>
<td>0.5</td>
<td>0.6</td>
<td>3.7</td>
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Table 2. Number of observations flagged by each outlier detection method for raw height measures and height-for-age z-scores, GEMS-Kenya 2008-2012

<table>
<thead>
<tr>
<th></th>
<th>Median height at enrollment</th>
<th>Median height at follow-up</th>
<th>Difference in median height from enrollment to follow-up</th>
<th>HAZ at enrollment</th>
<th>HAZ at follow-up</th>
<th>Difference in HAZ from enrollment to follow-up</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Case n (%)</td>
<td>Control n (%)</td>
<td>Total n (%)</td>
<td>Case n (%)</td>
<td>Control n (%)</td>
<td>Total n (%)</td>
</tr>
<tr>
<td>Trimmed Mean*</td>
<td>n=1647</td>
<td>n=2359</td>
<td>n=4006</td>
<td>n=1647</td>
<td>n=2359</td>
<td>n=4006</td>
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<tr>
<td></td>
<td>85 (5)</td>
<td>107 (5)</td>
<td>192 (5)</td>
<td>102 (6)</td>
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<td>209 (5)</td>
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<td>132 (8)</td>
<td>170 (7)</td>
<td>302 (8)</td>
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<td>101 (6)</td>
<td>155 (7)</td>
<td>256 (6)</td>
<td>131 (8)</td>
<td>199 (8)</td>
<td>330 (8)</td>
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<tr>
<td>SD†</td>
<td>66 (4)</td>
<td>104 (4)</td>
<td>170 (4)</td>
<td>79 (5)</td>
<td>99 (4)</td>
<td>178 (4)</td>
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<tr>
<td></td>
<td>52 (3)</td>
<td>88 (4)</td>
<td>140 (3)</td>
<td>69 (4)</td>
<td>109 (5)</td>
<td>178 (4)</td>
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<td></td>
<td>79 (5)</td>
<td>123 (5)</td>
<td>202 (5)</td>
<td>59 (4)</td>
<td>89 (4)</td>
<td>148 (4)</td>
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<td>Inner Tukey‡</td>
<td>14 (1)</td>
<td>22 (0.9)</td>
<td>36 (1)</td>
<td>12 (1)</td>
<td>21 (0.9)</td>
<td>33 (1)</td>
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<td></td>
<td>47 (3)</td>
<td>74 (3)</td>
<td>121 (3)</td>
<td>18 (1)</td>
<td>40 (2)</td>
<td>58 (1)</td>
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<td></td>
<td>18 (1)</td>
<td>37 (2)</td>
<td>55 (1)</td>
<td>58 (4)</td>
<td>84 (4)</td>
<td>142 (4)</td>
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<tr>
<td>MAD§</td>
<td>3 (0.2)</td>
<td>3 (0.1)</td>
<td>6 (.1)</td>
<td>2 (0.1)</td>
<td>5 (0.2)</td>
<td>7 (.2)</td>
</tr>
<tr>
<td></td>
<td>20 (1)</td>
<td>34 (1)</td>
<td>54 (1)</td>
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*Excludes the top 5% and bottom 5% of ranked observations

†Excludes observations outside of +/- 2 Standard Deviation

‡Excludes observations +/- 1.5*IQR

§Excludes observations +/- 3.5 MAD

¶Excludes observations +/- 3*IQR

\Excludes observations that met the following criteria: height decreased by 1.5cm from enrollment to follow-up, height increased more than ≥4cm (children 6 months or older) or ≥8cm (infants between 0-6 months) between 49-60 days, height increased ≥6cm (children 6 months or older) ≥10cm (infants between 0-6 months), HAZ was +/− 6, or if the change in HAZ was >3 SD
Table 3. Measures of location and dispersion for the median height (cm) as measured at enrollment, at follow-up, and its change over time by each outlier detection method, using objective cut-offs, and for the complete dataset, GEMS-Kenya 2008-2012

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<td>10.4</td>
<td>108.6</td>
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<tr>
<td><strong>Objective cut-offs</strong>†</td>
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<td>75.3</td>
<td>62.3 (49.5, 111.8)</td>
<td>14.7 (69.0, 83.7)</td>
<td>10.5</td>
<td>109.4</td>
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**Difference in median height from enrollment to follow-up**

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*Excludes the top 5% and bottom 5% of ranked observations

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§Excludes observations +/- 3*IQR

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Table 4. Measures of location and dispersion for the HAZ as measured at enrollment, follow-up, and its change over time by each outlier detection method, using objective cut-offs, and for the complete dataset, GEMS-Kenya 2008-2012

<table>
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<th>N</th>
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<th>IQR (1st Q, 3rd Q)</th>
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*Excludes the top 5% and bottom 5% of ranked observations
†Excludes observations outside of +/- 2 Standard Deviation
‡Excludes observations +/- 1.5*IQR
§Excludes observations +/- 3.5 MAD
¶Excludes observations +/- 3*IQR
Excludes observations that met the following criteria: height decreased by 1.5cm from enrollment to follow-up, height increased more than >4cm (children 6 months or older) or >8cm (infants between 0-6 months) between 49-60 days, height increased >6cm (children 6 months or older) >10cm (infants between 0-6 months), HAZ was +/- 6, or if the change in HAZ was >3 SD
Table 5. Proportion of case and control children stunted at enrollment and at follow-up when excluding extreme observations using the by each outlier detection method, using objective cut-offs, and for the complete dataset, GEMS-Kenya 2008-2012

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<th>HAZ at follow-up</th>
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<td>Controls</td>
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<td>403/1578 (25.5)</td>
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<td>425/1595 (26.7)</td>
<td>703/2320 (30.3)</td>
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*Excludes the top 5% and bottom 5% of ranked observations
†Excludes observations outside of +/- 2 Standard Deviation
‡Excludes observations +/- 1.5*IQR
§Excludes observations +/- 3.5 MAD
¶Excludes observations +/- 3*IQR
Excludes observations that met the following criteria: height decreased by 1.5cm from enrollment to follow-up, height increased more than $\geq 4\text{cm}$ (children 6 months or older) or $\geq 8\text{cm}$ (infants between 0-6 months) between 49-60 days, height increased $\geq 6\text{cm}$ (children 6 months or older) $\geq 10\text{cm}$ (infants between 0-6 months), HAZ was $\pm 6$, or if the change in HAZ was $>3$ SD.
REFERENCES


Chapter 5: Global Perspective
Discussion

Data from GEMS allowed us to explore these three health problems more closely in children living in rural western Kenya. GEMS was the largest ever, international, epidemiological study on diarrheal diseases specifically exploring the risk factors and health effects of MSD. A significant breadth of information was collected in GEMS; this data has allowed us to have a better understanding of the risk factors, burden of, etiologies, and consequences of MSD in children less than 5 years of age in sub-Saharan Africa and south Asia. Within this dissertation we were able to explore further diarrheal duration, WASH characteristics among PLHIV, and height and HAZ data among children living in one low-income country in sub-Saharan Africa using data from GEMS.

In our analysis, we found that this population of children participating in GEMS in rural western Kenya are facing significant health challenges. At enrollment, a large proportion, nearly 29%, of all children, were stunted. At follow-up, an even greater proportion, 34% of all children, were stunted. This is indicative of long-term nutritional deficiencies and malnutrition within this population. Within the subset of data explored within this dissertation, approximately, 22% of households had a mother or child living with HIV/AIDS. Among GEMS case children, 58% had diarrhea lasting 1-6 days, 35% had diarrhea lasting 7-13 days and 7% had diarrhea lasting 14 or more days. Furthermore, a large proportion of these children had multiple episodes of diarrhea. Of the 1,578 case children with complete diarrhea duration data, 448(28%) had two episodes of diarrhea, and 110 (7%) had three episodes of diarrhea. Key findings throughout these three papers were the etiologic agent in which one was infected, the nutritional status of the child, and the importance of the main drinking water source.

Etiologic Agent

We found that the etiologic agent in which the child was infected played an important role in diarrheal duration. In our analysis of crude and adjusted risk factors for diarrheal duration we identified
a number of etiologic agents associated with diarrheal duration including Cryptosporidium, EAEC, ETEC (any ST), and C. jejuni; however, Cryptosporidium was the only independent risk factor for longer duration diarrhea. Numerous studies have identified Cryptosporidium as being associated with ProAD and PD (Lima & Guerrant, 1992; Moore et al., 2010; Nataro & Sears, 2001). Cryptosporidium is commonly spread through drinking contaminated water (Baldursson & Karanis, 2011). It is resistant to some easy to use, low-cost, point-of-use water treatment methods such as chlorine (Keegan, Daminato, Saint & Monis, 2008). Of additional importance, Cryptosporidium was one of the most commonly identified etiologic agents in all seven GEMS sites (Kotloff et al., 2013). In children with MSD aged 12 to 23 months Cryptosporidium was associated with an increased risk of death (Kotloff et al., 2013). Cryptosporidiosis can cause significant illness in healthy individuals; however, in individuals with weakened immune systems, such as PLHIV the severity of illness can be much greater (CDC, 2015). In Kenya, a GEMS site with high rates of HIV, it was identified in significantly more case children with MSD as compared to control children (Kotloff et al., 2013).

Nutritional Deficiencies

Nutritional status was an important theme within these papers. We identified a large proportion of children within this population whom were stunted, indicating long-term nutritional deficiencies and malnutrition. Furthermore, children who were stunted at enrollment tended to have longer duration diarrhea. The two-way relationship between malnutrition and diarrheal duration is well established; it’s been noted as one of the most significant risk factors for PD (Bhutta et al., 2004). When a child is malnourished he is less able to fight off infection and therefore diarrhea can cause more severe illness that tends to last longer (Nel, 2010). On the other hand if the child has diarrhea, particularly PD the child may be eating less than usual and the body may be unable to absorb nutrients as it would if the child were healthy, in turn leading to poorer nutritional status (Nel, 2010). Moreover, malnutrition is often a common complication in PLHIV due to their weakened immune state.
The interpretation of anthropometric data can have major impact on nutritional outcomes at the individual and population level. Anthropometric data, specifically height and HAZ, are complex and can be difficult to analyze. There are limited recommendations on how best to deal with extreme values within anthropometric data. Oftentimes, to deal with extreme values within anthropometric data cleaning criteria are applied based on biological plausibility; however, there are no established, consistently used criteria with the exception of the WHO standards (WHO, 1995). These methods are often not reported in detail and therefore are applied on a study-by-study basis. Furthermore, these methods typically do not account for measurement error. A more standardized approach to dealing with extreme values within anthropometric data is important to the understanding and interpretation of these measurements.

*Drinking water source*

Water quality was another important key finding identified within this dissertation. We found using an unimproved water source was an independent risk factor for longer duration diarrhea upon both crude and adjusted analysis. Unimproved water sources included using any of the following sources: an open well in house/yard, open public well, pond or lake, shallow tube well, unprotected spring, river or stream, dam or earth pan, or using water that was bought. It’s likely that these water sources as compared to improved water sources contain more harmful contaminants, such as *Cryptosporidium*. As a result it appears they are contributing to more severe, longer-lasting illness. To our knowledge no other studies have identified using an unimproved water source as an independent risk factor for diarrheal duration. In Bangladesh, using an unimproved water source was associated with PD upon crude analysis; however, when adjusting for other factors this association was no longer significant (Karim et al., 2001).

We found that HIV-positive and HIV-negative households in this region of rural western Kenya had very similar WASH characteristics. We found no statistically significant differences in whether the
main drinking water source was improved or unimproved among HIV-positive and HIV-negative households. Furthermore, there were no differences between the main drinking water source, either improved or unimproved among HIV-positive households who found out their status ≥ 30 days before enrollment into GEMS as compared to those tested <30 days before enrollment or after enrollment.

We initially hypothesized HIV-positive households to have poorer WASH practices as compared to HIV-negative households due to the additional burden and barriers that PLHIV have to overcome, such as increased illness, stigma and discrimination (WaterAid, 2014; Magambe et al., 2013; Yallew et al., 2012; WaterAid, 2010; Nkongo, 2009). It’s been found that PLHIV were discriminated against in terms of the WASH facilities they were allowed to use. Therefore, often times PLHIV were forced to travel further distances to fetch water and utilize sanitation facilities (WaterAid, 2014; Magambe et al., 2013; Yallew et al., 2012; WaterAid, 2010; Nkongo, 2009). It’s also been noted that fetching water, using adequate sanitation facilities, and practicing proper hygiene were more difficult among PLHIV due to the individuals’ poorer health and increased periods of illness (WaterAid, 2014; Yallew et al., 2012; Nkongo, 2009). Even though we did not collect information about potential barriers to WASH in this study, we speculate that based on the strikingly similar WASH characteristics identified between HIV-positive and HIV-negative households, that the barriers noted by others are minimized within our study population. We hypothesis this could be due to less stigma and discrimination surrounding HIV/AIDS within this population. Second, its possible HIV-positive households in this population are receiving health services and that these health services are having positive impacts on healthy behaviors, such as treating drinking water and drinking water storage practices.

**Future Research**

Future research should focus on reducing the burden of diarrheal disease, malnutrition and HIV/AIDS in young children living in sub-Saharan Africa. It should focus on interventions to reduce diarrheal duration and to identify diarrheal management strategies that can be implemented on a large
scale. Furthermore, it should focus on strategies to improve overall nutrition. Last, it should focus on promoting healthy behaviors and improved well-being in PLHIV, such as improving access to WASH.

In addition, some relationships were difficult to explore within these papers and warrant further investigation. For example, there are groups of children who would seem to be inherently different, and yet very important populations to explore further. For example, we limited the duration of diarrhea data analysis to cases with a single episode of diarrhea. It would be of interest to explore children who had multiple episodes of diarrhea further as these children were reportedly more ill and may have different risk factors for diarrheal duration. However, one difficulty in examining the data from these children is that the risk factor assessment and stool specimens were collected at the beginning of the first episode of diarrhea. Although diarrheal duration data were collected by the caregiver we do not have information about what other factors might be contributing to the child’s diarrhea.

Another group that would be of interest to explore further is case children who were enrolled into GEMS more than once as a case. These children are an important group because again they are more ill as compared to case children enrolled only once during the four year period of GEMS. These children will likely paint a different picture; even though when looking at their diarrheal duration the risk factors do not appear to be different.

**Recommendations**

As shown here, within this population in rural western Kenya, these health problems are significant. Strategies to combat these serious child health problems are important. Improving overall nutrition and early nutritional interventions are warranted. Increasing access to improved water sources and access to high-quality drinking water is important. Identifying treatments for certain enteric pathogens, such as *Cryptosporidium* is also imperative.

A number of strategies to improve overall nutrition and combatting diarrheal disease may include the promotion of exclusive breastfeeding up to 6 months of age, feeding the child while they are
ill, and administering ORS and zinc supplementation (Das & Bhutta, 2015; UNICEF/WHO, 2009). To do this, parental education is imperative as caregivers are typically responsible for feeding the child. Educating parents on feeding practices, including what to feed and when to feed may help to combat this cyclic process. On a broader scale, the UN has recommended increases in farming production to ensure adequate supplies of food, and to improve mother and child education programs.

We noted a number of enteric pathogens that seemed important, one of which was Cryptosporidium. Cryptosporidium was identified as an independent risk factor for diarrheal duration. It has also been shown to be more severe in persons with weakened immune systems, such as PLHIV. It is resistant to some easy to use, low-cost, point-of-use water treatment methods such as chlorine (Keegan et al., 2008). Treatments and vaccines for Cryptosporidium are not highly effective nor readily available (Ryan & Hijjawi, 2015). Efforts to find alternative water quality interventions as well as effective treatments and vaccines are imperative.

Last, inadequate water and sanitation facilities along with poor hygiene have long been associated with diarrheal disease. Our study suggests that these factors, in particular using an unimproved water source, could also be associated with longer diarrheal events. To mitigate illness related to poor WASH increased access to improved water sources are needed. In places like this region of rural western Kenya, where water and sanitation infrastructure may not be a reality in the near future interim solutions are needed. Although we found no relationship between water treatment and diarrheal duration an interim solution to improving water quality could be through simple-to-use, low-cost, proven household water treatment interventions. Preferably, these should include methods, such as ceramic filtration or flocculent-disinfectants that are able to adequately combat etiologic agents such as Cryptosporidium which appear to be of great concern in this population. Furthermore, awareness about adequate sanitation and promotion of handwashing with soap should be encouraged. Improving water quality and ensuring adequate access to sanitation and hygiene facilities is an important
component to preventing diarrheal disease in general, but our findings suggest it may also help reduce the length of the diarrheal event.

Even though we anticipated HIV-positive households to have poorer WASH practices as compared to HIV-negative households due to the additional burden and barriers that PLHIV have to overcome, such as increased illness, stigma and discrimination (WaterAid, 2014; Magambe et al., 2013; Yallew et al., 2012; WaterAid, 2010; Nkongo, 2009). We found they had very similar WASH characteristics. Interestingly, we found that HIV positive households who were aware of their status ≥ 30 days before enrollment into GEMS had better WASH practices as compared to those tested <30 days before enrollment or after enrollment into GEMS. We speculate this might be due to an increase in HIV testing and counseling within these regions of western Kenya which is in turn leading to increases in access to health services. We suspect that HIV-positive households within our population were accessing available HIV support and care services, and translating these services into action at the household level. This could potentially be an important finding that warrants further exploration.

Limitations

These studies were subject to a number of over-arching limitations. For one, the data at enrollment are subject to reporting bias. The risk factors, in particular those related to WASH were assessed at enrollment through reports from the caregiver, whereas at follow-up the characteristics were observed by a trained community interviewer. These measures are likely more accurate because they are observed rather than reported. Second, the HIV related data were obtained and collected through two different programs and subsequently linked to the GEMS-Kenya data. Data collected between the two programs were not consistent and therefore we were limited in the HIV-related data that we were able to link to our data. Last, these study’s findings are not generalizable to a broader setting; however, they provide insights into what’s happening in this region of western Kenya.

Conclusion
As evidenced here the burden of diarrhea, malnutrition, and HIV/AIDS is significant within this population in rural western Kenya. It’s likely that in many countries in sub-Saharan Africa similar health problems and challenges are being experienced in young children. These studies contribute to the epidemiology of diarrheal duration. They add to the knowledge about the WASH practices and behaviors among HIV infected individuals. And, they contribute to the methodological processes for cleaning anthropometric data.

Based on findings from our studies, stunting, a signal of long-term nutritional deficiencies and malnutrition is a serious health problem within this population. We found that a high proportion of both case and control children were stunted. In addition, children who were stunted at enrollment tended to have longer duration diarrhea. Improving overall nutritional status among young children in rural western Kenya is imperative. Furthermore, a more standardized approach to dealing with extreme values within anthropometric data is important so that these measures can be better understood and interpreted. Another key finding was the importance of the main drinking water source. We found using an unimproved water source to be a risk factor for diarrheal duration. We found no differences in drinking water sources among HIV-positive households as compared to HIV-negative households. However, a large proportion of HIV-positive and HIV-negative households were using unimproved water sources. Due to the increased adverse consequences among PLHIV and the increased risk for longer duration diarrhea improving access to adequate water sources is especially important among children living in this region of rural western Kenya. Our studies also highlighted differences in WASH practices among HIV-positive households who were aware of their status for at least one month prior to enrollment into GEMS as compared to households who found out their status more recently. Further investigation should identify what is contributing to these results so they can be applied at a larger scale in similar populations. Last, the etiologic agent in which the child is infected seemed to be an important
factor in diarrheal duration. Prevention and treatment methods for pathogens causing severe illness, such as Cryptosporidium are warranted.
References


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