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Baseline Data and Implications for Vaccine Safety Monitoring and Impact Evaluation

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Responsible supervisor and Custos	Professor Pekka Nuorti Tampere University Finland	
Supervisor	Professor Robert F. Breiman Emory University U.S.A	
Pre-examiners	Dr. Michael Gottlieb Foundation for the National Institutes of Health U.S.A	Docent Bright Nwaru University of Gothenburg Sweden
Opponent	Dr. Roger I. Glass Fogarty International Center National Institutes of Health U.S.A	

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PunaMusta Oy – Yliopistopaino
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DEDICATION

This work is dedicated to my wife Eudiah Wasonga Omedi, our daughter Cheryl Effie Amondi, Jr., our two sons Brian Otieno Onyando, Jr. and Lameck Onyango, my late father Gabriel Onyando, and my late mother Aphlina (Effie) Ayaga.

ABSTRACT

Diarrheal diseases are the second leading cause of childhood deaths globally. Rotavirus is a leading cause of severe dehydrating diarrhea which is particularly associated with morbidity and mortality among children under five years of age in low- and middle-income countries. The rotavirus vaccine was introduced into Kenya's public immunization program in July 2014, with a two-dose schedule at six and ten weeks of age. Estimating the burden of rotavirus-associated disease before vaccine introduction is essential for assessing the population-level impact of vaccination programs. The aim of this dissertation is to estimate the burden of diarrheal illness among children under five years of age before the introduction of rotavirus vaccine in Kenya and to provide baseline information on health care seeking, prevalence, hospitalizations, and potential complications of childhood diarrhea to help evaluate the impact of rotavirus vaccine program implementation in Kenya.

This dissertation consists of four original studies. In Study I, we conducted household interviews with caretakers of 1,043 children under five in a baseline cross-sectional survey (April–May 2007) and of more than 20,000 children on five subsequent surveys between May 2009 and December 2010 to assess healthcare-seeking patterns for childhood diarrhea (defined as ≥ 3 loose stools in 24 hours).

In Study II, we conducted inpatient surveillance of children with acute gastroenteritis (AGE) (diarrhea and/or one or more episodes of unexplained vomiting occurring within seven days of admission) to estimate hospitalization and mortality rates due to all-cause and rotavirus acute gastroenteritis (RVAGE). Person-years of observation from an active Health and Demographic Surveillance System (HDSS) in western Kenya were used as denominators. In Study III, we conducted hospital-based surveillance of children under five years with acute, non-dysenteric moderate-to-severe diarrhea (MSD) to assess factors associated with rotavirus gastroenteritis and to describe illness severity. We defined non-dysenteric MSD as diarrhea with one or more of the following: sunken eyes, skin tenting, intravenous rehydration, or hospitalization, and acute to mean seeking care for the diarrhea episode within seven days of illness onset at a study sentinel health center

located within the HDSS. Stool specimens from participants enrolled in Studies II and III were tested for rotavirus using an enzyme immunoassay. To describe the epidemiology and risk factors for intussusception-related mortality, we retrospectively reviewed medical chart data of patients under five years old diagnosed with intussusception in 12 Kenyan leading referral hospitals (Study IV).

Our results showed that the two-week population-based incidence proportion of any diarrhea during the study period ranged from 26% at baseline (2007) to 4–11% during 2009–2010. A key finding of the surveys was that less than half of the children with diarrheal illness received care at a healthcare facility. Caretakers were actually less likely to seek health care outside the home for infants with diarrhea than for older children. Seeking care outside the home for childhood diarrhea was significantly more common for children who had sunken eyes during their diarrheal episode. Substantial proportion of children with diarrhea were given less food and drink than normally, even when vomiting accompanied their diarrheal episode. They were also not offered oral rehydration solution (ORS) at home. Mothers with formal education, however, were more likely than those without formal education to provide their children with ORS at home and to take them to a health care facility. Furthermore, caretakers sought care from a healthcare facility when their child`s diarrheal illness became more severe— possibly as a consequence of giving no remedy at home. Infants 6–11 months had the highest population-based incidence rates for hospitalization and mortality due to AGE and RVAGE. Rotavirus-positive cases were younger (median age, 8 vs. 13 months), had more severe illness, and had to be hospitalized more frequently than those who were negative for rotavirus. Independent factors that were associated with rotavirus disease included being an infant and presenting with vomiting 3 or more times within 24 hours during the diarrhea episode. Two-thirds of intussusception cases treated from 2002 through 2013 were infants who presented with at least one of the following symptoms: vomiting, diarrhea, or blood in stool. The case-fatality proportion was 6.4%. Compared with patients who survived, patients who died were younger, more likely to seek care late after illness symptom onset, to report history of fever on admission or, to have undergone surgery.

In summary, the studies in this thesis demonstrate that diarrhea among young children presenting to health care facilities is a significant public health problem in Kenya. However, the cases attending health care facility are only the tip of an iceberg. Our findings that suggest delay in seeking care for the child`s severe diarrheal illness are disconcerting. In addition, among children with severe disease symptoms and intussusception patients who died had sought care later after

symptom onset than those who survived. Our data also confirmed that morbidity and mortality associated with AGE, RVAGE, and intussusception was most common among infants. These findings supported the Kenyan Ministry of Health's decision to introduce a rotavirus vaccination program in July 2014. They are also consistent with the WHO recommendation to administer rotavirus vaccines to children at six and ten weeks of age, before the peak of disease incidence in Kenya. As a whole, the results of this thesis provide a comprehensive baseline data on occurrence, risk factors and complications of rotavirus diarrhea among young children in Kenya against which the population-level vaccine program impact can be evaluated in the future. Continuing surveillance efforts aimed at demonstrating the real-world impact and value of rotavirus vaccines need to take into consideration the observed trends in health care utilization.

TIIVISTELMÄ

Ripulitaudit ovat toiseksi yleisin alle viisivuotiaiden lasten kuolinsyy maailmanlaajuisesti. Rotavirus on tärkein lasten vakavien, kuivumista aiheuttavien ripulitautien aiheuttajista ja merkittävä kansanterveysongelma etenkin matalan ja keskitulotason maissa. Rotavirusrokotukset aloitettiin Kenian kansallisessa rokotusohjelmassa heinäkuussa 2014 (kaksi annosta, kuuden ja kymmenen viikon ikäisenä). Rotaviruksen aiheuttaman tautitaakan perustason määrittäminen paikallisesti ennen rokotusten aloittamista on välttämätöntä, jotta rokotusohjelman vaikuttavuutta väestötasolla voidaan jatkotutkimuksissa arvioida. Tämän väitöskirjatyön tavoitteena oli arvioida kattavasti alle viisivuotiaiden lasten ripulitaudin ja rotaviruksen aiheuttamaa tautitaakkaa, hoitoon hakeutumista ja komplikaatioita ennen rotavirusrokotusten aloitusta Keniassa. Väitöskirjan tutkimuksissa käytettiin Kenian lääketieteellisen tutkimuslaitoksen (Kenya Medical Research Institute, KEMRI) ja USA:n tautikeskuksen (Centers for Disease Control and Prevention, CDC) länsi-Keniassa sijaitsevan väestöpohjaisen, aktiivisen seurantajärjestelmän tietoja. Näiden tietojen perusteella määritettiin hoitoon hakeutumisen syyt ja yleisyys, taudin ilmaantuvuus ja riskitekijät, sekä sairaalahoidot ja kuolleisuus. Lisäksi vakavan ripulitaudin aiheuttamien komplikaatioiden (suolentukkeuma - intussusception) esiintyvyyttä ja ennusteeseen vaikuttavia tekijöitä arvioitiin takautuvasti sairaalojen potilaskertomustietojen avulla. Tutkimusten tavoitteena oli muodostaa kattava kuva rotavirustaudin epidemiologiasta, jota voidaan jatkotutkimuksissa käyttää vertailukohtana arvioitaessa rotavirusrokotusohjelman kansanterveydellistä vaikuttavuutta Keniassa.

Väitöskirja koostuu neljästä alkuperäistutkimuksesta (I-IV). Väestöpohjaisessa kenttätutkimuksessa (I) haastateltiin ensin 1 043 alle viiden vuoden ikäisen lapsen huoltajaa (yleensä äitiä) poikkileikkaustutkimuksessa (huhti–toukokuu 2007) lasten ripulitauteihin liittyvän hoitoon hakeutumisen käytäntöjen määrittämiseksi (ripulin määritelmä ≥ 3 löysää ulostetta 24 tunnin aikana). Tämän jälkeen yli 20 000:n lapsen huoltajia haastateltiin viidessä peräkkäisessä poikkileikkaustutkimuksessa toukokuun 2009 ja joulukuun 2010 välisenä aikana.

Tutkimuksessa (II) tunnistettiin sairaalahoitoon tulleet potilaat, joilla oli äkillinen ripulitauti (akuutti gastroenteriitti, AGE) - potilaalla ripuli ja/tai yksi/useampi selittämätön oksenteluepisodi seitsemän päivän sisällä sairaalaan tulosta. Tutkimuksessa määritettiin sairaalahoitoa vaativan akuutin gastroenteriitin sekä rotaviruksen aiheuttaman gastroenteriitin (RVAGE) ilmaantuvuudet ja niihin liittyvä kuolleisuus. Nimittäjätiedot saatiin länsi-Kenian terveys- ja demografiatietojen seurantajärjestelmästä (HDSS).

Sairaalapohjaisessa tutkimuksessa (III) selvitettiin rotaviruksen aiheuttaman ripulitaudin riskitekijöitä ja taudinkuvan vakavuutta. Seurannassa tunnistettiin sairaalahoitoon tulleet lapset, joilla oli akuutti, ei-verinen kohtalaisen vakava tai vakava ripulitauti (MSD). Rotavirus taudinaiheuttajana tunnistettiin tutkimuksiin II ja III osallistuneiden lasten ulosteenäytteistä EIA-määrityksellä. Takautuvassa tutkimuksessa (IV) selvitettiin potilaskertomustietojen avulla suolentukkeumaan liittyviä tekijöitä ja tapauskuolleisuutta alle viiden vuoden ikäisillä potilailla, joilla oli diagnosoitu suolentukkeuma 12 Kenialaisessa keskussairaalassa vuosina 2002-2013.

Väestöpohjainen ripulin ilmaantuvuusosuus kahden viikon aikana vaihteli ensimmäisen seurantavuoden (2007) 26%:sta 4–11%:iin vuosina 2009–2010. Alle puolet ripulitautia sairastavista lapsista hoidettiin terveydenhuollon yksiköissä. Huoltajat veivät imeväisikäisiä lapsiaan hoitoon kodin ulkopuolelle merkitsevästi harvemmin kuin vanhempia lapsia. Hoitoon vieminen kodin ulkopuolelle oli

kuitenkin yleisempää niillä lapsilla, joiden silmät olivat painuneet sisään kuivumisen takia ripulijakson aikana. Merkittävälle osalle sairaista lapsista annettiin myös vähemmän nestettä ja ruokaa kuin normaalisti, eikä heille tarjottu nestelisää suun kautta (oral rehydration solution - ORS) kotona. Koulutetut äidit antoivat kuitenkin useammin lapsilleen kotona ORS nestettä ja veivät heidät hoitoon terveydenhuollon yksikköön kuin kouluttamattomat äidit. Akuuttia gastroenteriittiä ja rotavirusripulitautia sairastavien lasten joutuminen sairaalahoitoon oli yleisintä 6–11 kuukauden iässä. Myös kuolleisuus oli suurin tässä ikäryhmässä. Rotavirus-positiiviset potilaat olivat nuorempia (mediaani-ikä, 8 vs. 13 kuukautta), heillä oli vakavampi tauti ja he joutuivat sairaalahoitoon merkitsevästi useammin kuin ne potilaat, joiden ulosteviljely oli negatiivinen rotaviruksen suhteen. Rotavirusripulin itsenäisiä riskitekijöitä olivat imeväisikä ja runsas oksentelu. Kahdessatoista Kenialaisessa sairaalassa vuosina 2002-2013 hoidetuista suolentukkeumapotilaista kaksi kolmasosaa oli vauvoja, joilla oli ainakin yksi seuraavista oireista: oksentelu, ripuli tai verta ulosteessa. Suolentukkeuman tapauskuolleisuus oli 6,4%. Verrattuna potilaisiin, jotka toipuivat, menehtyneet potilaat olivat nuorempia, heillä oli kuumetta ja he tulivat hoitoon myöhemmin oireiden puhkeamisen jälkeen. Heitä oli myös hoidettu kirurgisesti useammin kuin taudista selviytyneitä.

Yhteenvetona tämän tutkielman tutkimukset osoittavat, että lasten akuutti ripulitauti ja etenkin rotaviruksen aiheuttama vaikeaoireinen ripuli ovat merkittävä kansanterveysongelma Kenialaisten pikkulasten keskuudessa. Terveydenhuollon piiriin tulevat tautitapaukset ovat kuitenkin vain jäävuoren huippu. Siksi on huolestuttavaa, että monien lasten huoltajat viivyttivät hoitoon hakeutumista ripuliepisodin alettua ja jopa vähensivät nesteen ja ruoan antamista. Myös suolentukkeumaan kuolleiden potilaiden hoitoon hakeutuminen oireiden alkamisen jälkeen oli viivästynyt. Tutkimukset vahvistivat gastroenteriitin, rotavirusripuliin ja suolentukkeumaan liittyvän sairastuvuuden ja kuolleisuuden olevan yleisintä imeväisiässä.

Tulokset tukivat Kenian terveysministeriön päätöstä aloittaa rotavirusrokotusohjelma heinäkuussa 2014. Ne ovat myös linjassa Maailman Terveysjärjestön (WHO) suosituksen kanssa, jonka mukaan rotavirusrokotteet tulee antaa kuuden ja kymmenen viikon ikäisenä. Näin lapset saavat rokotteet ennen kuin taudin ilmaantuvuus on Keniassa huipussaan. Kokonaisuutena väitöskirjan tutkimusten tulokset muodostavat kattavan perustason, johon vertaamalla Kenian rotavirusrokotusohjelman väestötason vaikuttavuutta rotavirustaudin esiintyvyyteen, riskitekijöihin ja komplikaatioiden yleisyyteen voidaan jatkotutkimuksissa täsmällisesti arvioida. Tutkimusten perusteella arvioinneissa ja ehkäisyohjelmissa on erityisesti otettava huomioon havainnot vakavasti sairastuneiden lasten huoltajien terveydenhuoltoon hakeutumisen käytännöistä ja hoidon viivästymisestä. Jatkuva väestöpohjainen seuranta on avainasemassa rotavirusrokotusohjelman kansanterveydellisen vaikuttavuuden osoittamiseksi Keniassa.

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ABBREVIATIONS

AGE	Acute Gastroenteritis
CDC	Centers for Disease Control and Prevention
CGHR	Center for Global Health Research
CI	Confidence Interval
CRF	Case Report Form
GAVI	Global Alliance for Vaccines and Immunization
GEMS	Global Enteric Multicenter Study
GPS	Global Position System
HDSS	Health and Demographic Surveillance System
HUAS	Health Utilization and Attitude Survey
IS	Intussusception
IQR	Inter Quintile Range
IRB	Institution Review Board
KEMRI	Kenya Medical Research Institute
MSD	Moderate-to-Severe Diarrhea
OR	Odds Ratio
ORT	Oral Rehydration Therapy
ORS	Oral Rehydration Salt
PYO	Person-Years of Observation
RVV	Rotavirus Vaccine
RVAGE	Rotavirus Acute Gastroenteritis
SCRH	Siaya County Referral Hospital
SHC	Sentinel Health Center
VA	Verbal Autopsy
WHO	World Health Organization

ORIGINAL PUBLICATIONS

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II. **Omore R,** Khagayi S, Onkoba R, Ochieng JB, Juma J, Munga S, Kibet S, Nuorti JP, Odhiambo F, Mwenda J, Breiman RF, Parashar DU and Tate EJ. Rates of hospitalization and death for all-cause and rotavirus acute gastroenteritis before rotavirus vaccine introduction in Kenya, 2010-2013. *BMC Infectious Diseases* volume 19, Article number: 47 (2019). doi: 10.1186/s12879-018-3615-6

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1 INTRODUCTION

Rotavirus is a major cause of severe dehydrating diarrhea and remains the main cause of hospitalization and death associated with diarrhea among children worldwide, accounting for approximately two million hospitalizations and 215,000 annual global deaths in 2013 among children under five years of age (Tate, Burton *et al.*, 2016). Oral rehydration therapy (ORT) is vital to combating dehydration caused by severe diarrhea (Forsberg *et al.*, 2007). Despite Kenya's presence in the top ten countries for rotavirus-associated mortality (Tate, Burton *et al.*, 2016), the country has seen some of the largest declines in ORT use rates in the world (Forsberg *et al.*, 2007). Vaccination is the best way to prevent severe rotavirus disease and the deadly, dehydrating diarrhea associated with it (WHO, 2013b). Two licensed rotavirus vaccines have shown 85–98% efficacy in large clinical trials conducted in the United States and Europe (WHO, 2013b). These vaccines have since been recommended by WHO for inclusion in national immunization programs, although they are not recommended for infants with a history of intussusception or intestinal malformations that could predispose for intussusception (WHO, 2013b).

A few studies have quantitatively evaluated population-based health care-seeking behavior among caretakers of young children with diarrheal disease in Kenya or other middle-income countries. These studies can provide a rate multiplier that can be used to adjust for and extrapolate disease incidence rates in the source population based on the proportion of diarrhea episodes that were not evaluated at sentinel health centers (SHCs), which is a limitation of most case-control studies and hospital-based surveillance (Burton et al., 2011). Data on intussusception in Kenya are rare and incomplete. If the international community and national, regional, and intergovernmental authorities are to meet the post-2015 millennium development agenda under the Sustainable Development Goals (SDGs), reliable data will be essential (L. Liu et al., 2015). Without such data, governments will not be able to measure progress against the goals or to redesign or maintain relevant policies to make attaining them likely. To ensure that the limited resources in the low- and middle-income countries of sub-Saharan Africa,

where the burden of diarrheal disease is unacceptably high, are not wasted on ineffective interventions, thorough evaluation of new diarrhea interventions such as rotavirus vaccine programs is even more important. Furthermore, monitoring the impact of such interventions requires reliable data collected over a meaningful time frame. For example, describing the baseline rates and epidemiology of intussusception among children under five years old prior to rotavirus vaccine implementation in Kenya could serve as a useful basis for monitoring vaccine safety. Continued documentation of rotavirus epidemiology and estimates from hospital-based surveillance studies for incidence rates of all-cause and rotavirus diarrhea-associated hospitalizations and deaths can provide data for national authorities and programs whose role is to make decisions regarding vaccines; they can serve as a baseline for assessing vaccine impact (WHO, 2008). Data generated from such studies are rarely available globally, a gap that is even more pronounced in Kenya. Even where data exist, there are notable deficiencies, including short study periods that do not take into account seasonality patterns, use of non-standardized methods that do not allow for population inference in estimating disease rates, and unclear denominators for the population under study, which can be useful to estimate and adjust population-based disease burden and to monitor epidemiological trends. Such data could help inform targeted diarrhea interventions by policymakers and programs in both Kenya and similar settings.

In this thesis, we determined the factors associated with seeking health care for childhood diarrhea, estimated rates of hospitalizations and deaths associated with all-cause acute gastroenteritis (AGE) and rotavirus acute gastroenteritis (RVAGE), determined factors associated with rotavirus disease, and described the epidemiology of and factors associated with death among children hospitalized with intussusception in Kenyan referral hospitals prior to the introduction of the rotavirus vaccine.

2 LITERATURE REVIEW

2.1 Diarrheal Disease in Children

2.1.1 Definitions of diarrheal disease

According to the World Health Organization (WHO), diarrhea is defined as the passage of ≥ 3 loose or liquid stools (or more frequent passage than is normal for the individual) within a 24-hour period (WHO, 2005c, , 2018a). Diarrhea, also known as AGE, is usually a symptom of an infection in the intestinal tract. Neither the frequent passing of formed stools nor the passing of loose, pasty stools by breastfed infants (WHO, 2018a) qualify as diarrhea.

From the clinical and epidemiological standpoints, there are three main types of diarrhea: acute watery diarrhea that lasts several hours or days and includes cholera; acute bloody diarrhea (also called dysentery); and persistent diarrhea, which lasts 14 days or longer (WHO, 2005c, , 2018a). Acute diarrhea usually manifests as an increase in the frequency and volume of abnormally loose stools (WHO, 2018a). The majority of diarrhea deaths are caused by dehydration. However, more than 90% of dehydration caused by acute diarrhea of any etiology regardless of patient age can be treated effectively using oral rehydration solution (ORS), except when it is severe (WHO, 2005c). The WHO defines severe dehydration in a child as diarrhea with at least two of the following signs: lethargy or unconsciousness, sunken eyes, difficulty or inability to drink, and a skin pinch that only returns to normal in two seconds or longer (WHO, 2018a).

2.1.2 Rationale for studying etiologies of acute diarrhea

Understanding the etiologies and distribution of acute diarrheal diseases is an important tool for public health management and for advising control interventions in settings where the disease burden is highest (Yongsi, 2008).

Although non-microbes can cause diarrhea, the most important group of microbiologic agents (pathogens) known to cause diarrhea in children under five years old are generally classified as bacterial, viral, and parasitic organisms (WHO, 2018a); see Table 1. While the incubation period after host exposure to ingested non-microbes—mainly chemicals—is only a few minutes, most microbes have been shown to have incubation periods lasting between a few hours and five days, depending on infection dose and host immunity level (WHO, 2005c). Detection of diarrhea pathogens requires specific laboratory analysis, as described elsewhere (Vila *et al.*, 2009); the latest methods such as TaqMan Array Cards (TACs) have even provided opportunities for concurrent genotyping of most etiologic agents for diarrhea (J. Liu et al., 2013).

2.1.3 Predominant pathogens associated with acute diarrhea

2.1.3.1 Bacterial agents

Children in developing countries are exposed to and suffer from a wide range of bacterial pathogens causing diarrhea at a very early age (Bonkoungou et al., 2013). The predominant bacterial pathogens vary with child age, season, secular trends, and geographical variations (Kotloff *et al.*, 2013; Podewils *et al.*, 2004). The diarrheagenic *Escherichia coli Shigella* spp., *Campylobacter* spp., *Vibrio* spp., and *Salmonella* are among the most commonly recognized bacterial causes of diarrhea among infants and young children worldwide (Podewils *et al.*, 2004; Kotloff *et al.*, 2013; J. Liu *et al.*, 2016).

Diarrheagenic *E. coli* is the predominant facultative anaerobe of human colonic flora and has been shown to be capable of colonizing the infant gastrointestinal tract within hours of birth; it remains prevalent in children with acute diarrhea at all age groups (Sanchez-Villamil & Navarro-Garcia, 2015; Bonkoungou *et al.*, 2013). While some *E. coli* strains have been shown to be harmless or even beneficial to their human hosts, several highly adapted clones are capable of causing diarrheal illness (Lomasney & Hyland, 2013; Keskimaki *et al.*, 2001; Nataro & Kaper, 1998). Diarrheagenic *E. coli* may present with different clinical symptoms and frequency in both developed and developing countries (Nataro *et al.*, 2006; Kotloff *et al.*, 2013). In developing countries, *E. coli* accounts for more cases of AGE among infants than any other cause and remains a major cause of travelers' diarrhea worldwide (Nataro & Martinez, 1998; Kotloff *et al.*, 2013).

Shigella has been associated with moderate-to-severe diarrhea (MSD) in children under five, mostly in developing countries, and is the diarrhea pathogen most frequently associated with bloody diarrhea (WHO, 2005c), especially in Asia and sub-Saharan Africa (Kotloff et al., 2013). Toddlers and older children have been shown to be at greater risk of infection than infants and non-breastfeeding children (WHO, 2005b; Lindsay *et al.*, 2015; Kotloff *et al.*, 2013; WHO, 2005c). The four subgroups of *Shigella* capable of causing severe disease are *S. flexneri*, *S. sonnei*, *S. boydii*, and *S. dysenteriae* (Kotloff et al., 2013).

AGE caused by vibrio cholera differs from that with other causes in three main ways: it occurs in large epidemics; it may be spontaneous and involve more cases of both children and adults; it presents with more voluminous watery diarrhea than diarrhea caused by other pathogens, leading rapidly to dehydration that can result in hypovolemic shock and death if not managed in time (WHO, 2005c). Generally, routine use of antimicrobials for treatment of diarrhea in children should be avoided since it is not clinically possible to distinguish diarrhea caused by unresponsive pathogens such as rotavirus or cryptosporidium (WHO, 2005c). However, diarrhea cases with severe dehydration from cholera and bloody diarrhea from possible *Shigella* infection may require appropriate antimicrobial drugs to shorten the duration of the illness and prevent further spread of the pathogens (WHO, 2005c).

2.1.3.2 Viral agents

Enteric viral pathogens are responsible for causing the majority of acute diarrhea episodes in developed countries and remains the main cause of non-bloody diarrhea in developing countries, most commonly due to poor hygiene and sanitation in such settings (Podewils *et al.*, 2004; Kotloff *et al.*, 2013; Cunliffe *et al.*, 1998; J. Liu *et al.*, 2016). Viruses are the most important etiology of MSD and are estimated to account for approximately 70% of AGE episodes in children under five (Webb & Starr, 2005).

Although there are over twenty different types of viruses associated with childhood diarrhea, rotavirus has been shown to be the leading etiologic agent associated with AGE among children under five before rotavirus vaccine introduction in many settings worldwide (Kotloff *et al.*, 2013; Wilhelmi *et al.*, 2003; Walker *et al.*, 2013; Mohan *et al.*, 2017). Furthermore, approximately 39% (range by country, 20–73%) of children under five years old hospitalized with severe diarrhea

in different regions of the world test positive for rotavirus (Widdowson *et al.*, 2009).

2.1.3.3 Parasitic agents

Parasites account for a relatively small proportion of diarrhea cases compared to bacterial and viral agents. *Cryptosporidium parvun* and *Entamoeba histolytica* are the parasites most frequently seen in stool samples from diarrhea cases; by contrast, *Giardia lamblia* has recently been observed to be less common in children with diarrhea than those without diarrhea residing in sub-Saharan Africa and southeast Asia (Kotloff *et al.*, 2013; Bodhidatta *et al.*, 2010). Despite these observations, findings from two recent and highly influential diarrhea studies in the world—the Rotavirus Infection and Disease in a Multisite Birth Cohort (MAL-ED) (Mohan et al., 2017) and the Global Enteric Multicenter Study (GEMS) (Kotloff et al., 2013)—have reaffirmed that, before vaccine programs, rotavirus accounted for the majority of acute MSD in infants and children under two years old in regions with high disease burdens, largely in South America, south east Asia, and sub-Saharan Africa.

Table 1. The most important microbial causes of acute diarrhea in infants and children under five, before the rotavirus vaccine was introduced

Agent	Incidence	Pathogenesis
Viruses		
Rotavirus	Responsible for 15-25% of diarrhea episodes in children aged 6-24 months visiting treatment facilities but only 5-10% of cases in the same age group in the community. Prevalence is worldwide and spreads is by faecal , oral transmission or possibly by airborne droplets. Peak incidence in cold or dry seasons	Causes patchy damage to the epithelium of the small intestine, resulting in blunting of the villi. Illness ranges from asymptomatic infection to acute dehydrating diarrhea that may lead to death.
Bacteria		
Shigella	Causes 10-15% of acute diarrhea in children < 5years and the most common cause of bloody diarrhea. Transmission occurs from person-to-person contact since the infectious dose is low (10 to 100 organisms). Foodborne and waterborne also occurs in warmer seasons	Invades and multiplies within colonic epithelial cells, causing cell death and mucosal ulcers. Occasionally invades the blood stream.
Escherichia coli (E. Coli)	E. Coli causes up to one quarter of all diarrhea in developing countries. Transmission usually occurs through contaminated food and water. Enteroxigenic Escherichia coli (ETEC) are the major cause of acute watery diarrhea in children in developing countries during warm and wet seasons	Two important virulent factors of ETEC are: colonization factors that allow ETEC to adhere to electrocytes of small bowel, and enterotoxins. ETEC produce heat-labile (LT) and/or heat stable (ST) enterotoxins that cause secretion of fluid and electrolytes, resulting in watery diarrhea. ETEC do not destroy the brush border or invade the mucosa.
Campylobacter jejuni	C.jejuni cause 5-15% of diarrhea in infants worldwide, but because it is also found in many without diarrhea, the true proportion of cases due to C.jejuni is unknown. Transmission is mainly from chicken and other animals.	C.jejuni probably produces diarrhea by invasion of the ileum and the large intestine. Two types of toxin are produced: a cytotoxic and a heat-labile enterotoxin.
Vibrio cholera O1 and O139	Cholera is endemic in many countries of Africa, Asia and Latin America, where epidemics often occur annually usually during the hot, wet season. Transmission occurs mainly through contaminated water and food, person-to-person transmission is much less common.	Because of potential for epidemic spread, confirmed or suspected cases of cholera) including severe dehydration in patients should be reported promptly to public health authorities.
Protozoa		
Cryptosporidium	Accounts for 5-15% of childhood diarrhea in developing countries. It`s transmitted through the faecal-oral route.	Cryptosporidium attach to the microvillus surface of enterocytes and produce mucosal damage, which causes mal-absorption and fluid secretion.

Source: (WHO, 2005c).

2.1.4 Risk factors associated with acute diarrhea in children

Although some children with diarrhea failed to show any pathogenic infection in their stool samples in laboratory-based studies, infection with a microbiologic agent causing acute diarrhea remains the primary risk factor for diarrhea occurrence in children (Kotloff *et al.*, 2013; WHO, 2005c; Mohan *et al.*, 2017). Five pathogens (rotavirus, *Shigella*, enterotoxigenic *E. coli* producing heat-stable toxin [ST-ETEC], *Cryptosporidium*, and typical enteropathogenic *E. coli*) account for the majority of MSD cases in children under five in Asia and sub-Saharan Africa (Kotloff et al., 2013). It has been estimated that interventions targeting at least four of these pathogens—rotavirus, *Shigella*, *Cryptosporidium*, and ST-ETEC—were likely to reduce MSD by 40% during the first two years of life (Kotloff et al., 2013). While viral diarrhea appears to be transmitted primarily from person to person, bacterial diarrhea appears to be mainly foodborne (Ethelberg et al., 2006; WHO, 2005c). In general, factors associated with increased risk of diarrhea in children include low socio-economic status (and low education level of parents or caretakers) mediated by poor sanitation (Genser *et al.*, 2006), recent foreign travel, and contact with domestic animals and symptomatic persons (Ethelberg et al., 2006). A lack of rotavirus immunization and having another member of the family with diarrhea have also been linked to increased risk of diarrhea (Mbonye, 2004; Sobel et al., 2004).

2.1.5 Clinical features associated with acute diarrhea in children

Understanding clinical features associated with AGE are important tools for clinicians in establishing possible diagnosis and treatment options for infectious agents in setting with sub-optimal laboratory capacity (WHO, 2005c). The symptoms can be combined in a stepwise manner using clinical history to identify patients with high probability of having either viral, bacterial or AGE caused by other etiologies (WHO, 2018a, , 2005c). While the most predominant clinical characteristic of AGE in children generally include; loose, watery stool and abdominal pain, clinical presentation usually depend on etiology and host factors (WHO, 2018a). For example, non-bloody watery diarrhea presenting with mainly vomiting, and fever have been associated with viral etiologies, most commonly rotavirus (L. J. Liu *et al.*, 2005). However, mucus or bloody stools are routine features of bacterial infection, especially *Shigella* (WHO, 2005c). Symptoms

associated with other diarrhea etiologies are further described elsewhere (WHO, 2005c).

2.2 Diarrhea Epidemiology

2.2.1 Global burden of childhood diarrheal diseases

Globally, there are approximately 1.7 billion episodes annually of diarrhea among children under five (WHO, 2018a). Each year, diarrhea kills approximately 525,000 children under five (WHO, 2018a). Children in sub-Saharan Africa and South Asia face the highest risk of dying before their fifth birthday (UNICEF, 2017); see Figure 1. Despite progress at the global, regional, and national levels following the successes in striving for Millennium Development Goals (MDGs), populations in low- and middle-income countries still continue to bear the greatest burden of infectious diseases — the leading cause of death in children under five worldwide (L. Liu et al., 2015).

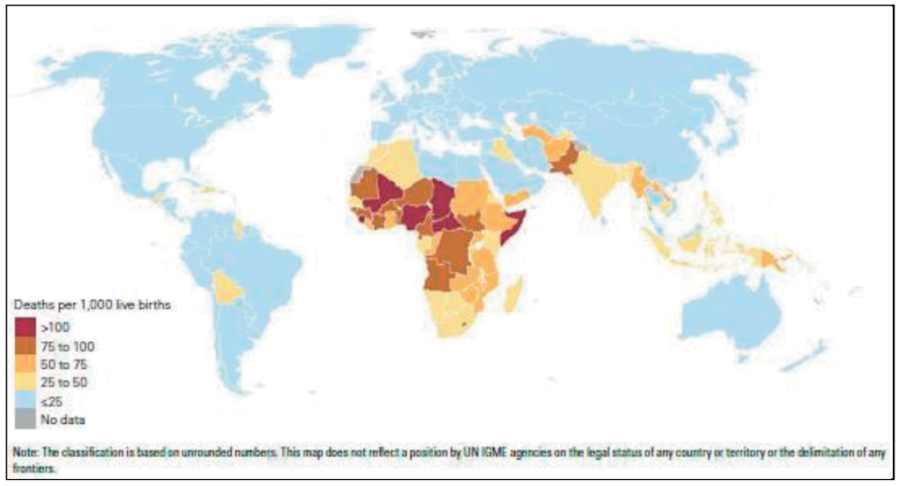

Figure 1. Mortality rates (deaths per 1,000 live births) by country, 2016.

Source: (UNICEF, 2017). Accessed on 25 April 2018 https://www.unicef.org/publications/index_101071.html

Diarrhea has continued to be a leading cause of preventable morbidity and mortality among children under five and, accounts for 8–9% of total global deaths

and approximately 20% of child deaths worldwide (Fischer Walker *et al.*, 2012; Black *et al.*, 2003; Black *et al.*, 2010; L. Liu *et al.*, 2012; UNICEF, 2018). According to UNICEF's 2017 global mortality estimates, diarrhea was the second most common cause of mortality among children under five (UNICEF, 2017); see Figure 2. Children with MSD, unlike those without diarrhea, are likely to encounter linear growth faltering and an increased chance of death within 60 days of an MSD episode (Kotloff et al., 2013). Each episode of diarrhea leads to nutritional insult and causes growth retardation; as a result, diarrhea causes malnutrition, and malnourished children are at increased risk of further diarrhea and resultant death (WHO, 2018a).

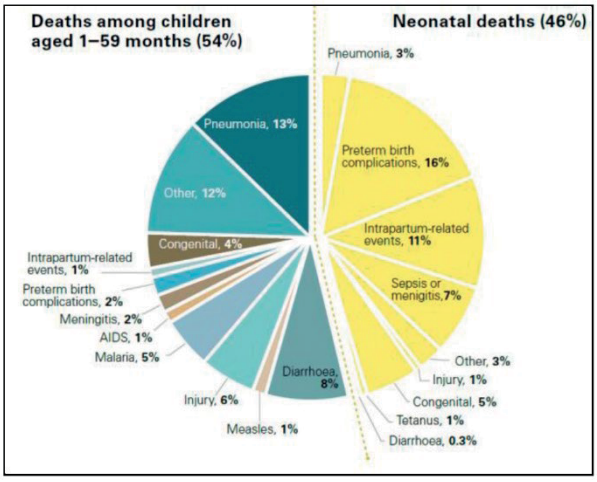

Figure 2. Global distribution of deaths among children under five, by cause, 2016.

Source: (UNICEF, 2017). Accessed on 25 April 2018 https://www.unicef.org/publications/index_101071.html

Understanding the epidemiology of diarrhea among children living in high disease burden regions could contribute to more effective approaches to saving children's lives (Black *et al.*, 2003). Continued efforts to improve diarrhea case management are important to reduce childhood deaths from the disease (Forsberg *et al.*, 2007; Black *et al.*, 2010). Furthermore, expanding effective preventive and curative interventions targeted to high disease burden regions is an important step to accelerate reductions in child morbidity and mortality. Such efforts may be more effective if the interventions focus on the main causes of child morbidity and mortality and on the most vulnerable groups: infants and children under five, especially in high disease burden regions (UNICEF, 2017).

2.2.2 The burden of childhood diarrheal disease in Kenya

In Kenya, diarrhea is the third leading cause of death among children under five, after pneumonia and malaria (UNICEF, 2010). Every Kenyan child under 5 years old has an average of 3 episodes of diarrhea annually; an estimated 86 children die daily from diarrhea, with rotavirus alone killing approximately 7,500 Kenyan children under five annually in the pre-rotavirus vaccine era (UNICEF, 2010). Furthermore, findings from the GEMS study estimated the mean cost of a single episode of diarrhea among children under five to be US$6.24 in Kenya, compared to only US$4.11 in Mali and US$2.63 in The Gambia (Rheingans et al., 2012). This observation suggests that families living in settings like Kenya, where the daily household income is less than a dollar a day, may be forced to forgo purchase of essentials for household at the expense of treating a child with diarrhea.Consistent with the recent global estimates (Tate, Burton *et al.*, 2016), data from Kenya demonstrate that rotavirus is a leading pathogen associated with dehydrating diarrhea in children under five (Kotloff et al., 2013; Tate, Rheingans et al., 2009). Therefore, an improved understanding of the population-based disease burden of diarrhea and the risk factors for rotavirus diarrhea in Kenya is needed to support decisions involving future allocation of the country's limited resources toward diarrhea- and rotavirus-specific interventions. Furthermore, knowledge of the consequences of acute diarrhea and rotavirus disease in children from high disease burden regions of the world like Kenya (Figures 3 and 4) should aid in the design and evaluation of potential interventions to improve child health (Black et al., 2010).

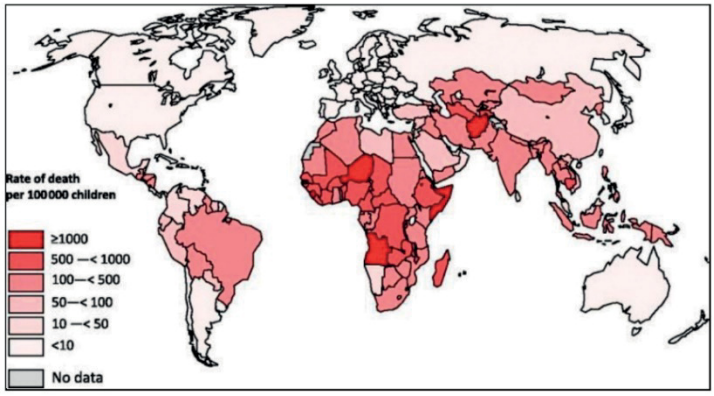

Figure 3. WHO-reported rates of child mortality due to diarrhea, 2013.

Source: (UNICEF, 2017). Accessed on 25 April 2018 https://www.unicef.org/publications/index_101071.html

2.3 Rotavirus Diarrhea in Children

2.3.1 Epidemiology of rotavirus

Rotavirus was first identified as an enteric pathogen by Ruth Bishop and colleagues in 1973 (Bishop, 1973). Since then, it has been widely reported as the most common cause of severe gastroenteritis in infants and children under two years old in many settings worldwide before the introduction of rotavirus vaccine (Kotloff *et al.*, 2013; Tate, Burton *et al.*, 2016; Tate, Burton *et al.*, 2012; Fletcher *et al.*, 2013). Globally, it is recognized that by the age of five, every child in most places worldwide will have been infected with rotavirus at least once (WHO, 2008). Other authors have also observed that at least 1 and up to 3 prior rotavirus infections have the potential to confer up to 74% protection against subsequent infection, even in settings where rotavirus vaccine immunization is not yet in place (Mohan et al., 2017; Velazquez et al., 1996). These findings may in part be related to neonates and children who are infected with rotavirus and remain asymptomatic or less severely symptomatic, especially in settings where diarrhea was a major problem in the pre-vaccine era (Velazquez et al., 1996).

2.3.1.1 Hospitalization associated with rotavirus

The rationale for focusing on hospitalization is that hospital-based data are important in evaluating the need for a vaccine. Once a rotavirus vaccine becomes available, hospital-based surveillance data would permit reliable and rapid assessment of the success or failure of a given vaccine program (WHO, 2008). Hospitalization data make it easier to quantify the occurrence of severe rotavirus diarrhea from a catchment area, especially if the population is well defined, as they are likely to present to a hospital for treatment; even case finding will be easier than in community settings (WHO, 2008). Hospital surveillance also makes it easier to collect and test diarrhea patients' stool samples for rotavirus. Moreover, a system for monitoring hospitalizations attributable to AGE can easily be modified to incorporate intussusception surveillance, since these diseases occur in the same age group and are both likely to result in hospitalization (WHO, 2008).

Before the introduction of rotavirus vaccine in Kenya, rotavirus infection was estimated to cause 19% (~9,000) of hospitalizations and 16% of clinic visits among children under five annually (Tate, Rheingans et al., 2009). Estimates of

hospitalization rates, outpatient care, and health care-seeking patterns are useful since they can help calculate country-specific estimates of the disease burden associated with hospitalization, as demonstrated in Kenya (Tate, Rheingans et al., 2009). However, to update estimates on hospitalizations attributable to AGE and RVAGE prior to vaccine introduction in settings like Kenya requires a defined population that uses specific health care facilities or a single hospital with good or at least free access to health care services for children under five, such as the government hospitals as recommended by the WHO (WHO, 2008).

2.3.1.2 Morbidity and mortality associated with rotavirus

Despite the global decline in all-cause and rotavirus-specific diarrhea, recent data from several key studies show the continued relative importance of rotavirus as a major cause of vaccine-preventable diarrhea in the world's high disease burden regions (Kotloff et al., 2013; Mohan et al., 2017). In previous observations, more than 80% of global rotavirus-related deaths occurred in middle-income countries, with South East Asia and sub-Saharan Africa accounting for 30% and 50%, respectively (Parashar *et al.*, 2006; L. Liu *et al.*, 2012). For example, 700,000 episodes of all-cause diarrhea were reported worldwide in 2011; 72% led to death, with rotavirus the leading cause in 28% of all episodes (Walker et al., 2013). Although Tate and colleagues have recently estimated a decline in global mortality attributed to rotavirus from 528,000 in 2000 to 215,000 in 2013, Kenya remains among the ten countries with the highest number of reported rotavirus deaths (Tate, Burton *et al.*, 2016); see Figures 4 and 5.

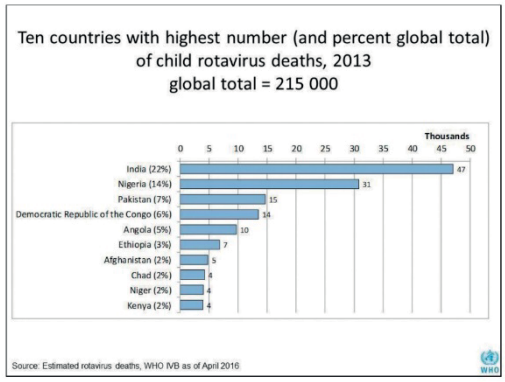

Figure 4. Distribution of rotavirus deaths among children under five in the ten countries with the highest rates, 2000–2013. Source: (WHO, 2018b).

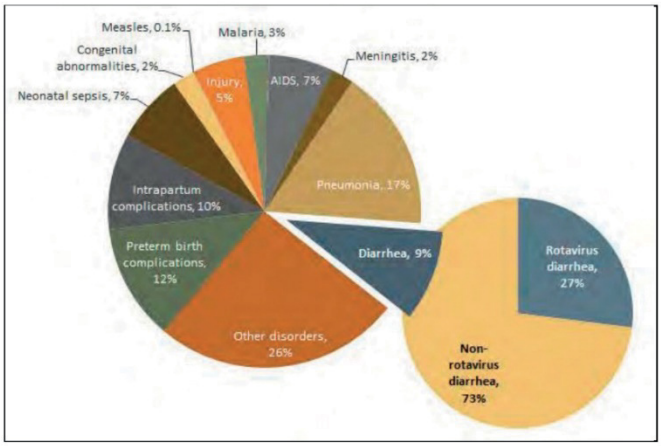

Figure 5. Causes of death among Kenyan children under five, 2010 . Source: (PATH, 2014).

Accessed on 25 April 2018: http://www.path.org/publications/files/VAD_rotavirus_kenya.pdf

2.3.1.3 Economic Impact of rotavirus disease

Although the economic impact of rotavirus diarrhea is expected to decline after the introduction of a rotavirus vaccine, rotavirus diarrhea still places a significant burden on both household and national health infrastructures. For example, during the pre-rotavirus vaccine era in Kenya, rotavirus diarrhea among children under five cost the national healthcare system approximately US$10.8 million annually (Tate, Rheingans et al., 2009). It has been estimated that, in Kenya, a two-dose rotavirus vaccine regimen would prevent 55% and 65% of rotavirus-associated deaths and hospitalizations, respectively, at a cost of US$3 per series and US$2.1 million in total medical costs annually (Tate, Panozzo et al., 2009).

2.3.1.4 Seasonality of rotavirus diarrhea

Understanding the seasonality of leading enteric pathogens such as rotavirus can help guide policymakers and others implementing vaccine intervention to identify periods of high disease transmission and decide on appropriate interventions and approaches to optimize prevention and case management strategies. Rotavirus has been shown to be seasonal in some settings, occurring more commonly during the dry season in sub-Saharan Africa (Ouedraogo *et al.*, 2017; Mayindou *et al.*, 2016;

Ngabo *et al.*, 2014; Khagayi *et al.*, 2014). The pattern of seasonality can even vary by region, peaking in the dry months in northern Africa and the Middle East (Zaraket *et al.*, 2017) and in colder and drier months in tropical countries and South Asia (Levy *et al.*, 2009; Jagai *et al.*, 2012). In fact, rotavirus has been shown to peak in winter in places like Australia (Fletcher et al., 2013), the United States (MacNeil *et al.*, 2009; Tate, Panozzo *et al.*, 2009; de Oliveira *et al.*, 2009), and China (Zeng et al., 2010). These observations support the findings of a study by Patel and colleagues (Patel et al., 2013), which showed that there is no single unifying factor for global rotavirus seasonality patterns. On the other hand, there is increasing evidence that rotavirus vaccination has the potential to change the observed seasonality in a number of locations. For example, in the United States, the rotavirus season has been shown to be delayed, to be shorter, or to disappear altogether after vaccine introduction (Tate, Panozzo *et al.*, 2009; Tate *et al.*, 2011). These observations support the WHO's call for worldwide implementation of rotavirus vaccines (WHO, 2013b).

2.3.2 Clinical features associated with rotavirus infection

Assessing and classifying diarrhea based on etiology and the clinical features presented by patients are useful and simple tools for identifying possible life-threatening AGE (WHO, 2006). These criteria can readily be used by health care workers whose clinical training or access to diagnostic laboratory facilities may be limited, as is common in most low- and middle-income countries like Kenya, where most if not all clinicians do not routinely use laboratory results to guide patient management (Webb & Starr, 2005; WHO, 2005c; F. Odhiambo *et al.*, 2014). Understanding the clinical features associated with rotavirus infection could also help support awareness among caretakers and health care workers of the need to promote timely care seeking and management of patients who have RVAGE. Pre-vaccine data could also help evaluate whether the introduction of rotavirus vaccination in a given area alters the clinical characteristics of RVAGE among children under five years old (Parashar et al., 2015).

Rotavirus has a short incubation period (usually less than 48 hours; (WHO, 2005c). Children presenting with rotavirus compared to non-rotavirus diarrhea more often present with vomiting and severe dehydrating diarrhea preceded by abdominal pain and fever (Webb & Starr, 2005). In Africa, AGE that presents with fever, vomiting, and dehydration is commonly associated with rotavirus infection

(Bonkoungou *et al.*, 2010; Nakawesi *et al.*, 2010). Likewise, in developed countries in Europe and elsewhere, fever, vomiting, and severe dehydration (Aristegui *et al.*, 2016; Schael *et al.*, 2009)—regardless of malnutrition or poverty status (Schael *et al.*, 2009)—are the predominant clinical symptoms among AGE patients with rotavirus infection. In Asia, vomiting and fever have also been found to be associated with rotavirus infection among children with AGE (Dhiman *et al.*, 2015). However, in some settings in Uganda, higher maternal education and breastfeeding, which have been widely reported to offer protection against AGE and RVAGE (Webb & Starr, 2005), have actually been shown to be associated with rotavirus infection (Nakawesi *et al.*, 2010). In general, vomiting, fever, and dehydration are the clinical features most commonly associated with RVAGE illness (Table 2).

Table 2. Risk factors for rotavirus infection among children aged under five: summary of evidence from prospective observational studies.

Reference, Country, World Region	Study setting	Age of study subjects	Study design	Outcomes assessed	Main findings
(Aristegui et al., 2016), Spain, Europe	Out/in-patient	</=3years	Prospective hospital-based study	Factors associated with RVAGE	Fever, vomiting, dehydration, hospitalization, higher cost of treatment was associated with RVAGE than non-RVAGE.
(Schael *et al.*, 2009), Venezuela, Europe	In/out-patient	< 5years	Prospective hospital-based study	Socio-demographic and clinical characteristics of RVAGE	Severe dehydration regardless of malnutrition and poverty and age being infants were associated with RVAGE than non-RVAGE
(Paul *et al.*, 2014), India, Asia	Population-based study	<5 years	Prospective cohort	Risk factors for symptomatic and asymptomatic rotavirus infection	Rotavirus was associated with 15% of mild diarrhea, 40% of moderate diarrhea and 67% of very severe diarrhea
(Salim *et al.*, 2014), India, Asia	In-patient	< 5years	Prospective hospital-based study	Risk factors for symptomatic infection	Vomiting and male gender were risk factors for rotavirus infection. Good nutrition and breastfeeding were protective against rotavirus infection
(Abebe et al., 2014),Ethiopia, sub-Saharan Africa	In-patient	<5years	Prospective hospital-based study	Risk factors for rotavirus disease	Children aged 6-12 months had the highest infection rates and Vomiting was associated with rotavirus infection
(Bonkoungou et al., 2010), Burkina Faso, sub-Saharan Africa	Out/in-patient	< 5years	Prospective hospital-based study	Epidemiology of RVAGE	Fever, vomiting and hospitalization were associated with RVAGE than non-RVAGE.
(Mohan et al., 2017), 8 sites in developing countries	Out/in-patient	< 5years	Prospective longitudinal study	Risk factors for rotavirus and duration of protection	Household overcrowding and high pathogen load were associated with rotavirus infection and disease. Prior rotavirus infection conferred 74% of protection against subsequent infection in the absence of vaccination.

2.3.3 Rotavirus prevention

2.3.3.1 Diagnosis and treatment for rotavirus

Although the currently preferred routine diagnostic test for rotavirus is detection of rotavirus antigen in fecal stool specimens by enzyme-linked immunoassay (EIA), other techniques including electron microscopy and reverse transcription

polymerase chain reaction (RT-PCR), have been used to detect rotavirus in stool samples (WHO, 2013a, , 2008). Children with rotavirus infection commonly present with dehydrating diarrhea, which often needs to be treated with ORS and in severe cases with IV fluid administration; otherwise, they are at risk of dying (WHO, 2005c). Such urgent health care services are often inaccessible, unavailable, or scarce in developing countries where diarrhea case management is also generally poor (Forsberg *et al.*, 2007). Rotavirus prevention through vaccination is thus critical to saving children's lives in such areas (Parashar *et al.*, 2016).

2.3.3.2 Rotavirus vaccines

As the post-2015 MDGs take hold, continued surveillance of the leading pathogens associated with acute childhood diarrhea remains a priority for infectious disease specialists (L. Liu et al., 2015). Moreover, prioritizing implementation of licensed interventions like rotavirus vaccines and instituting follow-up studies to monitor the impact of such interventions are increasingly urgent to help document benefits that can guide new interventions to address emerging needs. Increasing evidence for the efficacy and effectiveness of rotavirus vaccination against morbidity and mortality among children under five from all MDG regions has continued to be reported (Lamberti *et al.*, 2016). The efficacy of rotavirus vaccination against severe rotavirus diarrhea has been shown to range from 90.6% (95% confidence interval [CI]: 82.3–95.0) in developed regions to 88.4% (95% CI: 67.1–95.9) in eastern and south eastern Asia, 79.6% (95% CI: 71.3–85.5) in Latin America and the Caribbean, 50.0% (95% CI: 34.4–61.9) in South Asia, and 46.1% (95% CI: 29.1–59.1) in sub-Saharan Africa (Lamberti *et al.*, 2016).

Given the above evidence and observations from other settings, the epidemiology of AGE and RVAGE disease is expected to change with time (Lamberti *et al.*, 2016; Patel & Parashar, 2009). Monitoring disease trends for several years before and after vaccine introduction in a country with a view to assessing vaccine impact would therefore require active gastroenteritis surveillance and hospitalization surveillance data that would support the realization of the goals detailed in Table 3 (Patel & Parashar, 2009).

Table 3. Objectives and rationale for assessing postlicensure performance of rotavirus.

Objective	Rationale
Demonstrate effectiveness in real world setting of routine use	•Alternative vaccination patterns may be encountered, such as administration of only a partial series or delays in the vaccination schedule •Vaccine will be coadministered with oral poliovirus vaccine, which might result in interference •Efficacy against unusual strains not included in vaccine formulations may vary •The duration of protection could be less in field settings; because as many as 40% of children may develop disease during the second and third year of life, protection through 24–30 months of life would be necessary to maximize the public health impact •Vaccine quality may vary; for example, cold-chain could be compromised, thus impairing vaccine potency, and antigenicity may vary by formulation •Rotavirus vaccine trials were conducted in middle- and high-income countries and not in developing countries with the highest burden of severe rotavirus disease
Establish epidemiological patterns of rotavirus disease after vaccine implementation	•Age distribution of rotavirus disease could change, with increasing risk of severe disease among school-age children and adults •Assessment of herd immunity (ie, reduction in incidence of disease among nonvaccinated populations because of indirect benefits)
Demonstrate impact on morbidity and mortality	Demonstration of absolute reductions in the incidence of severe childhood gastroenteritis through rotavirus vaccination and creation of demand for rotavirus vaccines by demonstrating direct public health benefits of vaccination
Strain surveillance	•Monitor for possible emergence of unusual rotavirus strains that may escape protection from vaccines •Allow for serotype-specific measures of vaccine effectiveness
Encourage in-country and regional vaccine introduction	Poor performance of previous rotavirus vaccine and other oral vaccines (eg, oral poliovirus and cholera vaccines) in developing countries may hinder the acceptance of newer rotavirus vaccines

Source:(Patel & Parashar, 2009)

Vaccines are the best rotavirus prevention tools available today, since the improvements in drinking water, sanitation, and hygiene (including good hand washing) that have been shown to be effective in preventing other forms of gastroenteritis do not adequately prevent the spread of rotavirus (WHO, 2006, , 2005c; Churgay & Aftab, 2012). Efforts to realize the goal of a vaccine started with the first rotavirus vaccine (RotaShield [Wyeth Lederle Vaccines, Philadelphia, USA]) which was approved, licensed, and introduced to all infants as part of routine immunization schedules in the United States in 1998 (Hochwald & Kivela, 1999; Svensson *et al.*, 1999). However, in July 1999, the US Centers for Disease Control and Prevention (CDC) reported 15 cases of intussusception (an intestinal invagination resulting in obstruction) in recipients of RotaShield (CDC, 1999), which informed the subsequent decision to withdraw the vaccine from use and recommend further studies (Kapikian, 2001). Although additional follow-up evaluation data revealed a small excess risk and temporal association between the first dose of RotaShield vaccine and intussusception in infants (Rha *et al.*, 2014; Tate, Yen *et al.*, 2016; Patel *et al.*, 2011), some available data have shown no evidence of an association between increased intussusception and admissions of infants during the period of RotaShield availability in the United States (Simonsen et al., 2001). However, randomized clinical trials (RCTs) have also failed to rule out very small relative risks of an association between two recent rotavirus vaccines—Rotarix® (GlaxoSmithKline Biologicals, UK) and RotaTeq® (Merck Vaccines,

New Jersey, USA)—and intussusception (Soares-Weiser *et al.*, 2010; Buttery *et al.*, 2011; Soares-Weiser *et al.*).

Despite the fact that both RCTs and post-marketing safety monitoring data in both developed and developing countries do not indicate a significant risk of intussusception after vaccination, a low-level risk cannot be ruled out, according to other follow-up studies (Patel *et al.*, 2009; Tate, Steele Ad Fau - Bines *et al.*, 2012; Peter & Myers, 2002), even though the benefits of these two vaccines have been demonstrated to far outweigh the estimated small risks of intussusception (Soares-Weiser *et al.;* Patel *et al.*, 2011). It is worth noting that this risk has not been observed when the vaccine is administered earlier (Oberle *et al.*, 2014), suggesting the need for timely administration of these vaccines.

To limit intussusception risk among vaccine recipients, it is recommended that the first dose of rotavirus vaccine be administered before 12 weeks of age and the series be completed by 24 weeks (Rotarix®) or 32 weeks (RotaTeq®) (WHO, 2002; Wood, 2005). Finally, these two vaccines have now been licensed and recommended for routine use through immunization programs to prevent rotavirus gastroenteritis globally (WHO, 2013b). African countries are increasingly introducing these vaccines with the assistance from GAVI, the Vaccine Alliance (Steele et al., 2012). Monitoring intussusception before and after rotavirus vaccine introduction is important for understanding any epidemiological changes in this medical condition (Huppertz *et al.*, 2006; Escolano *et al.*, 2015). Intussusception surveillance studies in countries introducing rotavirus vaccines are therefore highly recommended to assess the safety of these vaccines and to identify any adverse events that may be associated with them (Soares-Weiser *et al.*, 2012).

2.4 Epidemiology of Intussusception in Children

Intussusception—a condition in which a portion of the intestine invaginates into a distal portion (Lloyd, 2004); see Figure 8)—is the most common cause of intestinal obstruction among children from three months to five years old (Stringer & Holmes, 1992; DiFiore, 1999; Roeyen *et al.*, 1999). Intussusception can take various forms: ileo-ileal, ileo-caecal, ileo-colic, ileocaeco-colic, jejuno-ileal, and colo-colic. It is estimated that approximately two-thirds of all intussusception cases occur in children under a year old, with a peak age of five to seven months and an incidence of 74 per 100,000 (range: 9–328) among infants worldwide (Jiang et al., 2013). While intussusception incidence rates may not be higher in sub-Saharan Africa

than elsewhere (Figure 6), the proportion of children with intussusception who die after presenting to the hospital is substantially higher in sub-Saharan Africa (9.4% to ~13%) than in Asia (0.2%), Central and South America (0.6%), the Eastern Mediterranean (0.8%), Europe (0.1%), North America (0.4%), and Oceania (0%) (Jiang et al., 2013).

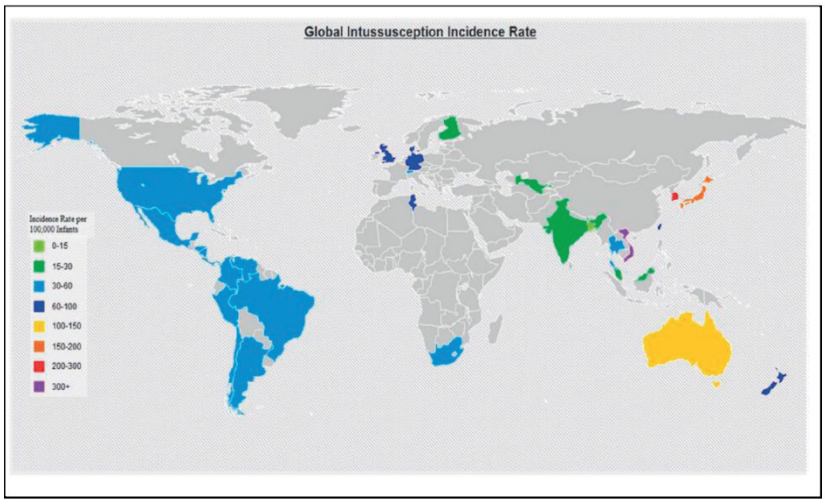

Figure 6. Global distribution of intussusception incidence rates per 100,000 infants

Source: (Jiang et al, 2013).

2.4.1 Seasonality of intussusception

Epidemiological studies conducted in 11 Latin American countries (Saez-Llorens et al., 2013) and in China (Cui et al., 2016), New Zealand (Chen *et al.*, 2005), and Mexico (Velazquez *et al.*, 2004), combined with observations from one of the most recent comprehensive literature review of studies conducted over 18 years in Africa and other parts of the world (Jiang et al., 2013), show that there is no clear global seasonality pattern for intussusception among children. On the other hand, one study conducted over a 10-year period in France did document a seasonality pattern among children diagnosed with intussusception (Serayssol et al., 2014).

2.4.2 Clinical features associated with intussusception in children

Although many cases of intussusception self-resolve, others lead to more elaborate clinical symptoms, especially bowel obstruction that can be fatal if not treated urgently (Yen et al., 2016). Knowing the classic clinical symptoms commonly associated with intussusception is important in designing awareness programs to urge caretakers to seek care promptly (Escolano *et al.*, 2015) and can assist health care workers in identifying potential cases for urgent treatment, if not referral (Bines *et al.*, 2004). Furthermore, since intussusception is a rare disease, describing the most common clinical symptoms of the disease at the local level would inform decision makers and help parents in developing countries better recognize it (Glass et al., 2005). However, clinical presentation in patients with intussusception in many settings often includes a wide range of non-specific clinical symptoms (Waseem & Rosenberg, 2008). Predominant symptoms from the majority of intussusception patients have been shown to include ; vomiting, abdominal pain, and rectal bleeding, blood in stool, and abdominal mass and tenderness from physical examination (Waseem & Rosenberg, 2008; Klein *et al.*, 2004). In other settings, most cases have presented with symptoms that include chronic but not acute abdominal pain and an absence of fever (Ahn *et al.*, 2009).

For a decade now, the most commonly reported clinical signs of intussusception in children from most observational studies in Asia (Cui *et al.*, 2016; Waseem & Rosenberg, 2008; Yousafzai *et al.*, 2017; Yap Shiyi & Ganapathy, 2017), Europe (Huppertz et al., 2006), and sub-Saharan Africa (Carneiro & Kisusi, 2004) have been similar and include vomiting, abdominal mass/pain, and bloody stool or rectal bleeding occurring with abdominal tenderness. It is worth noting that plain radiograph findings in the absence of stool in the ascending colon could also be a predictor of intussusception (Klein *et al.*, 2004; Yousafzai *et al.*, 2017). Still, there remains no reliable prediction model that can accurately identify all patients with intussusception (Klein *et al.*, 2004).

2.4.3 Diagnosis and treatment options for intussusception

Methods used to diagnose and treat intussusception have been shown to vary by global region (Jiang et al., 2013). Outside Africa, 95–100% of cases are diagnosed by radiographic methods like air-contrast enema, ultrasound, or computed tomography (Jiang et al., 2013). Although intussusception diagnosis normally relies first on clinical suspicion (Waseem & Rosenberg, 2008), approximately 70% of

intussusception cases in sub-Saharan Africa are diagnosed at the time of surgery; while a more desirable diagnostic modality that uses contrast enema or ultrasound is involved in diagnosing fewer than one in five cases (Steele et al., 2012). Despite surgery's being the most commonly used treatment in African countries (Steele et al., 2012), other studies in African settings have shown that non-operative treatment of ileo-colic intussusception through ultrasound-guided reduction boasts higher success rates (75–95%) than surgery. In addition, this method carries no radiation risk and is safe, painless, quicker than surgery, and not associated with any complication, death, or recurrence of intussusception among patients (Mensah *et al.*, 2011; Krishnakumar *et al.*, 2006; Tander *et al.*, 2007; Rohrschneider & Troger, 1995).

Other studies have shown that clinical manifestation and surgery are the predominant clinical methods intussusception management in Africa (Kuremu, 2004; Carneiro & Kisusi, 2004). These findings departs radically from other parts of the world, where diagnosis and treatment of intussusception mainly uses modern radiographic methods that are associated with fewer or no fatalities (Jiang et al., 2013; N. Liu et al., 2018; Yousafzai et al., 2017). These observations may help explain the high differential in intussusception-related deaths between most African countries and other parts of the world.

2.4.4 Etiology of intussusception among children

The causes of intussusception in a majority of infants and young children remain unknown. However, some microbiologic infectious agents like respiratory adenovirus (Bines, Liem, Justice, Son, Kirkwood et al., 2006; Minney-Smith et al., 2014; Ukarapol et al., 2016) and other enteric bacterial agents (*Campylobacter* spp., *E. coli* , *Salmonella* spp., and *Yersinia enterocolitica*) have been associated with intussusception in other studies conducted in a variety of locations around the world (Nylund *et al.*, 2010; May *et al.*, 2014). Although viral respiratory infections have been associated with most intussusceptions in population-based studies, a number of studies have also shown that naturally occurring or wild-type rotavirus is not associated with intussusception in India (Bahl et al., 2009), New Zealand (Chen *et al.*, 2005), or South Carlifornia (Chang *et al.*, 2002). The observed geographical variations in these studies is not well defined, but a number of factors like genetic dispositions, circulating pathogens, differentials in feeding practices,

and differences in diagnostics and access to healthcare patterns could account for most of these variations (Jiang *et al.*, 2013; Johnson *et al.*, 2010).

Post-marketing surveillance has identified a small increased risk of intussusception associated with rotavirus vaccines (Velazquez *et al.*, 2012; Patel *et al.*, 2011). For example, an association between RV1 and RV2 in the range of 1–6 excess cases per 100,000 vaccinated infants (Rha et al., 2014) in high- and middle-income countries has been documented, but the risk data from these affluent settings may not translate directly to developing countries. Further characterization of any associated risk following rotavirus vaccination, baseline rates, and death associated with intussusception is therefore desirable for low- and middle-income countries like Kenya (Parashar et al., 2015). As rotavirus vaccines are introduced in more developing countries, intussusception surveillance efforts in diverse settings will provide data that will improve our understanding of the risks and benefits of the vaccine and intussusception epidemiology beyond affluent settings.

It is worth noting that the pattern of age distribution (peaking at ~5–7 months) follows the same pattern in rotavirus gastroenteritis and intussusception disease, as reported in a number of studies (Chouikha *et al.*, 2009; Jiang *et al.*, 2013; Tate *et al.*, 2008; Parashar *et al.*, 2000; Mattei *et al.*, 2017). Similarly, the predominance of the male gender appears to overlap as a factor associated with both conditions in diverse settings (Chouikha *et al.*, 2009; Jiang *et al.*, 2013; Huppertz *et al.*, 2006; Chen *et al.*, 2005). Although these observations may suggest biological plausibility, intussusception occurs with no clear seasonality (Jiang et al., 2013), unlike rotavirus (Velazquez *et al.*, 2004; Nelson *et al.*, 2002; Chang *et al.*, 2002), which undermines any possible association between rotavirus and intussusception and confirms the existing gap in knowledge about the etiology of intussusception.

Table 4. Intussusception-associated etiologies among children aged under five: summary of evidence from prospective observational studies.

Author, year of publication, Country and World Region	Age group of study subjects	Study design	Outcomes assessed	Main findings
(Vega Garcia et al., 2015), Spain, Europe	95 Cases aged <2years	Case-crossover	Association between Intussusception and history of drug administration	Drug administration 2-to-7 days before onset of symptoms in children <2years was associated with development of intussusception
(Chen *et al.*, 2005), New Zealand, Europe	< 3 years	Prospective hospital surveillance	To describe epidemiology of intussusception and its relationship to rotavirus hospitalization	In contrast to rotavirus hospitalized cases, intussusception peaked at younger age and lacked seasonality. Wild-type rotavirus was observed not to have an association or trigger intussusception in young New Zealand children
(Bhisitkul *et al.*, 1992)	3 months-5years	Prospective case-control	Possible relationship between intussusception and Adenovirus 40/41	Association between intussusception and non-enteric adenovirus was observed
(Bahl et al., 2009), India, Asia	Infants	Case-control	To examine association between intussusception and natural rotavirus infection	No association was observed to exist between natural rotavirus infection and intussusception in Indian children
(Ukarapol et al., 2016), Thailand, Asia	40 cases aged	Prospective cohort	Determine association between gastroenteritis viruses and IS	Significant association with adenovirus (subtype C) was observed (OR=8.87, 95%CI: 1.95-12.16)
(Velazquez *et al.*, 2004), Mexico, USA	Infants	A prospective, multi-center case-control	To determine whether natural rotavirus infection or any another enteropathogen is associated with Intussusception	No association between natural rotavirus infection and IS was observed
(Okimoto *et al.*, 2011), Japan	Infants and children aged 4-47 months	Prospective hospital surveillance	To determine association between viral infections with development of IS	Adenovirus infection, especially with the non-enteric types was observed to be a risk factor for developing intussusception among Japanese children , particularly those aged >2 years in Japan.

2.4.5 Factors associated with death among children with intussusception

Data on factors associated with death among children with intussusception are rarely available. However, where they do exist, most data support the position that delay in seeking care for intussusception after symptom onset is a risk factor for death, especially in sub-Saharan Africa (Carneiro & Kisusi, 2004; Gudeta, 1993; Ekenze *et al.*, 2010). Similarly, delays in obtaining diagnosis, admission, and treatment (Ekenze *et al.*, 2010) are the factors most commonly associated with death among some intussusception patients. Delay in seeking care for intussusception has also been observed to increase the chances of open surgery, especially intestinal resection, which is a non-operative diagnosis and treatment

method that is equally associated with death among children with intussusception (Lehnert *et al.*, 2009; Jenke *et al.*, 2011). Unlike surgery, other non-operative methods such as fluid and air enemas and ultrasound have been shown to be highly successful, reducing the chance of death and leading to minimal hospital stays with almost no fatalities (Justice *et al.*, 2006; Al-Malki, 2005; Kruatrachue *et al.*, 2011). Although surgery has also been successful in treating intussusception in some settings (Cui et al., 2016), it continues to be associated with high case fatality in African settings, where it is still used to treat 70–100% of children with intussusception, despite existence of other more efficient methods such as fluoroscopy (Steele *et al.*, 2012; Adamou *et al.*, 2017; Jiang *et al.*, 2013).

2.4.6 Intussusception and rotavirus vaccines

Rotavirus vaccine with an improved safety profile was first recommended when the first and second doses of the three-dose, oral tetravalent rhesus-human reassortant vaccine (RRV-TV) was found to be associated with intussusception in the United States (Murphy et al., 2001). The first dose of the currently licensed rotavirus vaccines is recommended to be administered at 6–15 weeks of age. The lower rate of intussusception in this age group reported in studies to date appears to support the need for timely administration of vaccines to minimize their possible attributable risk. However, due to delays in vaccination that are common in sub-Saharan Africa and other settings, intussusception associated with vaccines could increase. As part of safety monitoring following possible vaccine-associated intussusception, data collected before and after rotavirus vaccine introduction in a given country may be key to helping monitor changes in the epidemiology of intussusception. The risk of intussusception and vaccine program implementation in affluent settings has been shown to vary by region, making reliable regional baseline data even more useful in tracking trends of intussusception (Buttery et al., 2011; Jenke et al., 2011). Furthermore, it remains unknown whether an association between intussusception and currently licensed vaccines will be found after their introduction in low- and middle-income countries, so intussusception surveillance is even more important (Peter & Myers, 2002). An increase in intussusception hospitalization rates in children from 8 to 11 weeks old has been shown to overlap with age when the majority of first doses of vaccine were given in the Unites States (Tate, Yen *et al.*, 2016). This supports the ongoing debate, as more countries prepare to introduce the two presently licensed vaccines, over whether rotavirus

vaccines are linked to a risk of intussusception among children. Age-stratified data on intussusception will be useful for interpreting whether any vaccine-associated risk exists and in calculating the number of cases that could be attributable to vaccines after their use in an immunization program (Yen et al., 2016).

Table 5. Future priorities for rotavirus vaccines and intussusception monitoring: recommendations from a meeting organized by The Rotavirus Organization of Technical Allies (ROTA) Council and its core partners, 23–24 July 2014, Washington, DC

Key messages for risk communications

- Ensure that stakeholders are aware that robust surveillance has demonstrated consistent, strong benefits of rotavirus vaccination, and that risks associated with rotavirus vaccine, including intussusception, remain very low in all post-licensure safety studies to date. Present information about baseline risk of intussusception. Share information with all levels of decision-makers in countries considering vaccine introduction.

Vaccine introduction and sustainability in low- and middle-income countries

- Integrate safety monitoring for rotavirus vaccines into routine vaccine safety monitoring:
  - Ensure that countries have clear risk management and communications plans for adverse events following immunization
  - *Conduct targeted safety monitoring while strengthening capacity for routine vaccine safety monitoring*
- Ensure that, wherever possible, vaccine impact evaluations occur alongside safety monitoring to allow comprehensive assessment of potential risks within the context of benefits:
  - *Leverage existing surveillance networks to increase efficiency*
- Understand the regional epidemiology of intussusception to allow accurate interpretation of findings from safety monitoring within the context of comparable data concerning benefit:
  - *Establish background rates and outcomes of intussusception in select areas for each region*
  - *Focus on low- and middle-income countries for which there are limited data*
- Examine the risk of intussusception associated with vaccination in early introducer, regionally representative countries using feasible methods:
  - *Ensure that findings are shared broadly to inform the experiences of other countries*
- Document use, benefit, and safety of rotavirus vaccines in countries that have implemented the expanded age recommendations for rotavirus vaccine administration.

Gaps in knowledge

- Support research to increase understanding of the pathogenesis and etiology of intussusception. This would include the following areas:
  - Basic science studies to understand better the pathogenesis of and triggers for idiopathic intussusception in young children
  - Epidemiological studies to understand the occurrence of transient (i.e., self-resolving) and persistent idiopathic intussusception in different regions and settings:
    - *Standardize case definitions and methodologies to allow pooling of data*
    - *Share findings with all stakeholders in a timely manner*
- Explore why some studies have detected an increased risk of intussusception following the first dose of vaccine and other studies have not:
  - Role of co-administration of inactivated and oral polio vaccines
  - Differences in immune response and shedding across populations
- Support studies to determine risk-benefit assessments for countries with higher baseline rates of intussusception.

Evaluation of new rotavirus vaccines in development

- Conduct post-marketing surveillance for intussusception in appropriate representative sites also conducting vaccine impact evaluations.
- Continue to monitor the potential association of specific vaccine strains with adverse events following immunization post-licensure.

Source: (Yen et al., 2016).

2.5 Healthcare Seeking for Diarrhea in Children

One fundamental reason for recognizing the predictors of healthcare seeking in a particular population is that they may offer information useful for increasing the uptake of healthcare services and enhancing child disease survival (Bayham et al., 2017). For example, a delay of at least 4 hours in a caretaker's seeking healthcare for a child's diarrhea caused by cholera has been shown to increase the chance of death 17 times in patients in Nigeria ; mortality was especially pronounced among

those not reaching a healthcare facility for appropriate treatment (Djouma *et al.*, 2016).

Dehydration caused by severe diarrhea is a major cause of morbidity and mortality among young children worldwide and even more so in Kenya (KDHS, 2015), even though it can be easily treated with ORT (WHO, 2006). Early detection of dehydration, increasing food and fluid intake (including use of ORS), and seeking prompt medical attention when a child has dehydrating diarrhea are important factors in reducing child deaths (WHO, 2006, , 2005c; KDHS, 2015). Caretakers should prevent dehydration through early administration of increased amounts of appropriate fluids if available at home, including ORS (WHO, 2005c). Appropriate care-seeking behavior among caretakers of children who present at healthcare facilities with diarrhea and intussusception can influence disease outcome for both conditions (Qamar *et al.*, 2016; Ogundoyin *et al.*, 2016).

Community-based surveys for diarrhea can help to determine population-based burden of disease and estimate the proportion of illness episodes that are ultimately either included or missed in hospital-based surveillance data (Burton *et al.*, 2011; Breiman *et al.*, 2014). As demonstrated in other settings (Breiman et al., 2014), since healthcare facility (hospital) surveillance data could underestimate the burden of disease, data from community-based surveys may provide a rate multiplier to adjust hospital surveillance data to account for disease episodes for which care was never sought (WHO, 2002). However, since children suffering from rotavirus diarrhea or intussusception disease cannot be diagnosed at the household level, establishing an active hospital-based surveillance system to provide pre- and post-vaccine data for rotavirus and intussusception could provide baseline data that would be useful in the evaluation of rotavirus vaccine safety (Cui et al., 2016). Current and accurate regional data describing caretakers' healthcare-seeking behaviors for childhood diarrhea, the epidemiology of intussusception, and its burden in children are therefore needed to guide implementation and evaluation of rotavirus vaccines.

2.5.1 Caretaker factors associated with care seeking

Caretakers with higher education levels, people living in middle to higher ranges in the wealth index as suggested by income level and type of assets owned by a household, and mothers who are more alert to recognizing fever and vomiting as danger signs of disease have all been shown to be factors associated with increased likelihood of seeking care for a child's diarrheal illness in Mozambique (Bayham et

al., 2017), Ethiopia (Adane *et al.*, 2017), and several countries in Asia and sub-Saharan Africa, including Kenya (Nasrin et al., 2013). Moreover, caretaker proximity to a healthcare facility, knowledge of community emergency plans, and greater alertness regarding the danger signs associated with severe disease have been shown to influence healthcare seeking for childhood diarrhea in Ethiopia (Bruce et al., 2014) and Kenya (Bigogo et al., 2010). However, qualitative data from India have also revealed that, when caretakers were shown pictures of danger signs like sunken eyes, reduced skin turgor, indrawn chest, rapid breathing, and bulging fontanel, care seeking was influenced by their "local beliefs," which considered such symptoms untreatable by modern medicine alone (Awasthi *et al.*, 2008). The same authors observed that use of traditional and home remedies were reasons for caretaker delays in seeking appropriate and timely medical care at a healthcare facility (Awasthi *et al.*, 2008). Many caretakers of children with diarrhea in Kenya, as in other low- and middle-income countries, do not provide proper treatment to their children: supplying ORS and increasing fluid and food intake (Forsberg *et al.*, 2007; Ram *et al.*, 2008). Despite the fact that sub-Saharan Africa and Asia are the two regions with the greatest burden of diarrheal disease among children (UNICEF, 2017), caretakers in parts of these areas have been shown to seek care for their child's diarrhea only when the condition revealed life-threatening symptoms (Mbonye, 2003). Furthermore, more than half the countries in Asia and sub-Saharan Africa have recently shown either no significant improvement or a reduction in ORT coverage for diarrhea, and Kenya had the largest decrease in ORT use (Boschi-Pinto *et al.*, 2009).

2.5.2 Patient characteristics associated with care seeking

Care seeking for childhood diarrhea has been shown to be more frequent for toddlers than infants and school-age children in Africa and Asia (Nasrin et al., 2013). Young children who present with diarrhea accompanied with high-risk symptoms and clinical features that are perceived by caretakers to suggest severe disease, such as diarrhea with fever, have been shown to inspire care seeking more frequently than their counterparts, even in settings where medical care is free (Amarasiri de Silva *et al.*, 2001; Breiman *et al.*, 2011; Burton *et al.*, 2011). However, in the absence of perceived severe signs of disease in a child with serious acute diarrhea, caretakers still tend to expect the presence of severe signs; otherwise, they

would most likely claim that diarrhea was not severe enough to warrant seeking care, especially in African settings.

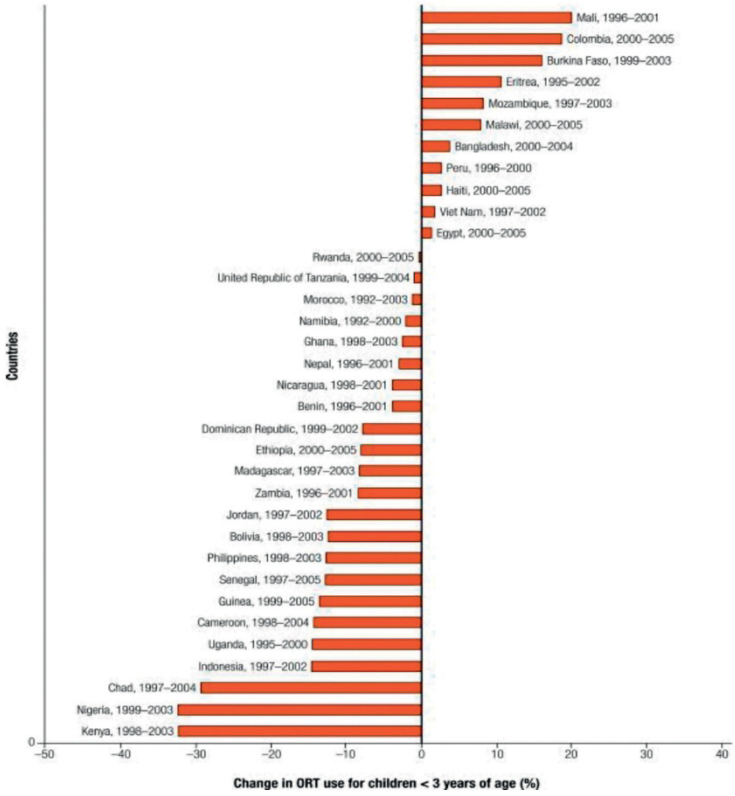

Figure 7. Percentage change in use of ORT during two demographic and health surveys conducted from 1992- 2005.

Source; (Forsberg *et al*., 2007).

Table 6. Factors associated with seeking care for diarrhea among children under five: summary of evidence from observational studies.

Reference, Country, World Region	Age of study subjects	Study design	Outcomes assessed	Main findings
(Nasrin et al., 2013), multisite study in 3 countries in Asia and 4 countries in sub-Saharan Africa	Children aged 0-59 months	Randomized cross-sectional household survey	To estimate the proportion of children with acute diarrhea who would present to sentinel health centers (SHCs) and to characterize healthcare seeking patterns	Among children aged 0-11, 12-23 and 24-59 months, proportions of children with acute diarrhea in 2-weeks prior to survey were; 0.7-4.4%, 0.4-4.7% and 0.2-2.4% and the proportions for diarrhea that sought care from a healthcare facility were; 15-56%, 17-64% and 7-33% across the age groups respectively. Caretakers perceived high cost of care and insufficient knowledge about diarrhea danger signs were associated with lack of any care-seeking
(Adane *et al.*, 2017), multiple surveys in Ethiopia, sub-Saharan Africa	Children < 5years	Five rounds of community-based cross-sectional (house-hold) surveys study using multi-stage systematic sampling method	To assess the status of health facilities utilization and predictors for health-seeking behavior of mothers/caregivers of under-five children with acute diarrhea in slums of Addis Ababa, Ethiopia	Maternal literacy, Caretakers who recognize fever and vomiting as danger diarrhea signs in their child, Household monthly income ≥ US $50, living within 15 minutes walking distance to the healthcare facility were significantly associated with health care-seeking
(Das et al., 2013), Bangladesh, Asia	Children < 5years	A population-based house-hold survey	To characterize caretakers health seeking behaviors for their child's diarrheal illness to inform hospital surveillance study design.	Proportions of children <5years with acute diarrhea in 2-weeks prior to survey was 7% of whom 89% sought care outside home for the diarrhea. In general 50% sought care from a pharmacy and only 22.1% from a hospital or a healthcare facility. Caretakers perception that diarrhea was not severe enough and high cost of treatment were main reasons associated with not seeking care.
(Burton et al., 2011), rural western Kenya, sub-Saharan Africa	Children < 5years	A population-based household survey	To characterize healthcare-use and determine the proportion of diarrhea episodes not captured by health facility-based surveillance	Proportion of under-five with diarrhea in two weeks was 14% of whom 33% sought care for acute diarrhea from at least a healthcare facility. Seeking healthcare at health facilities was more likely for children from households with higher socioeconomic status and with more symptoms of severe illness.

2.5.3 Significance of care seeking for childhood diarrhea

The primary benefit of community-based healthcare utilization surveys is that they can help determine what caretakers do if their children experience an episode of diarrhea, where caretakers take their children with diarrhea for treatment, the proportion of children with acute diarrhea who receive treatment at hospitals, and caretakers' preferred healthcare facilities (WHO, 2008). Despite the relative importance of available diarrhea interventions, recognition of childhood diarrhea as

a cause of severe dehydration by caretakers remains stubbornly poor in low- and middle-income countries (Nasrin *et al.*, 2013; Geldsetzer *et al.*, 2014). This is a major problem for attempts to improve healthcare utilization in such settings (Geldsetzer et al., 2014). Poor healthcare utilization can also work against efforts to improve child survival. Diarrhea surveillance data from Kenya have shown that caretakers' tendency to seek care first from non-licensed care providers can delay opportunities for early optimal intervention in appropriate healthcare facility settings (Breiman et al., 2012). It has been demonstrated that the introduction of rotavirus vaccine can reduce diarrhea-associated healthcare utilization and medical expenditures in other settings like the United States (Cortes et al., 2011). In Kenya, it has been estimated that a two-dose rotavirus vaccination series could avert 55% of deaths, 65% of hospitalizations, and 59% of clinic visits due to the disease (Tate, Rheingans et al., 2009). However, refusal of admission and delay in seeking care for MSD among caretakers of children under five have been shown to be associated with child death in Pakistan (Qamar et al., 2016). Care-seeking patterns in a catchment population is therefore an important indicator of appropriateness of settings for rotavirus surveillance activities to support estimates of AGE and RVAGE disease burdens before and after rotavirus vaccine introduction (WHO, 2008, , 2005a). The most important threat posed by diarrhea in patients, regardless of age, is dehydration (WHO, 2018a). Rotavirus is the most common cause of severe dehydrating diarrhea in children under five (WHO, 2005c) and has been shown to account for the majority of MSD in children living in low- and middle-income countries in Asia and sub-Saharan Africa (Kotloff et al., 2013). During an MSD episode, especially when rotavirus appears in the causal pathway, the rapid loss of water and electrolytes (sodium, chloride, potassium, and bicarbonate) through liquid stools, vomit, sweat, urine, and fast breathing leads to severe dehydration (WHO, 2018a). Since care-seeking behaviors and treatments for children with dehydrating diarrhea can vary considerably in different geographical settings and globally (WHO, 2008; Nasrin *et al.*, 2013), updating knowledge on care-seeking patterns for children with diarrhea in a rotavirus surveillance setting is important. This information can help researchers and diarrhea intervention planners acknowledge the attitudes and practices of the local population regarding pediatric gastroenteritis (WHO, 2008) and provide crucial evidence to inform child survival intervention programs (Geldsetzer et al., 2014).

2.6 Healthcare Seeking for Intussusception in Children

Intussusception is an emergency condition that requires urgent care seeking, diagnosis, and treatment to avoid unfavorable outcomes (Jenke et al., 2011). Symptoms associated with intussusception like vomiting, bloody stool, and abdominal pain are classic indicators of severe disease, as documented in literature reviews (Mpabalwani *et al.*, 2017). Delays in care seeking and prompt medical intervention when a child presents with such symptoms may cause the illness to become more severe and can even lead to death (Gudeta, 1993; Lehnert *et al.*, 2009).

3 AIMS OF THE STUDY

The purpose of this study was to estimate the burden of diarrheal illness among children under five years old before the introduction of rotavirus vaccines in Kenya and to provide baseline information on healthcare seeking, prevalence, hospitalizations, and potential complications of childhood diarrhea to help evaluate the impact of the implementation of a rotavirus vaccine program in Kenya. These data may also guide development of other interventions aimed at reducing morbidity and mortality associated with childhood diarrhea in Kenya.

The specific objectives were:

1. To estimate diarrhea prevalence and describe caretakers' knowledge, attitudes, perceptions of illness, and patterns for seeking care from health facilities for young children with MSD in rural western Kenya and to evaluate factors associated with healthcare-seeking behavior (Study I).
2. To estimate the population-based baseline incidence rates of AGE overall and RVAGE in particular, including associated hospitalizations and deaths among children under five in rural western Kenya (Study II).
3. To assess factors associated with RVAGE among young children with MSD and describe the severity of illness in rural western Kenya (Study III).
4. To describe the pre-rotavirus vaccine epidemiology and to evaluate factors associated with intussusception-related deaths among patients under five treated at emergency referral hospitals in Kenya (Study IV).

4 METHODS

4.1 Study Settings

Kenya is located in East Africa, between 5°S and 5°N latitude and 23°E and 31°E longitude. It has 400 kilometers of shoreline along the Indian Ocean and was divided into eight provinces until a 2010 constitutional reform. Nyanza, one such province, is located in the western part of the country, bordering Uganda to the northwest and Tanzania to the southwest (Figure 8). Studies I–III were conducted in Nyanza within an existing Health and Demographic Surveillance System (HDSS) area operated by the Kenya Medical Research Institute (KEMRI) in partnership with the CDC (Figure 8). The fourth study (IV) was conducted at Kenya's leading referral hospitals, which are mainly operated by the Kenyan Ministry of Health (KMoH) or private hospitals located in the major towns of Nairobi, Mombasa, Kisumu, Nakuru, Eldoret, Kakamega, and Thika (Figure 9).

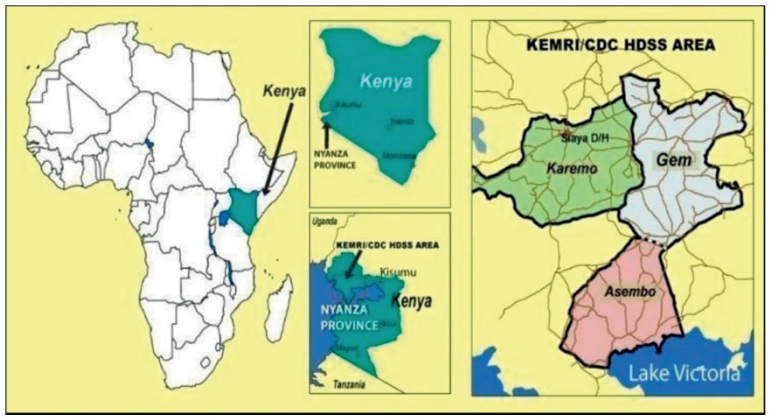

Figure 8. A series of maps showing Kenya's location in Africa, the former Nyanza province location in western Kenya, and the locations of KEMRI–CDC jointly operated HDSS study areas (Asembo, Gem, and Karemo), where Studies I–III were conducted.

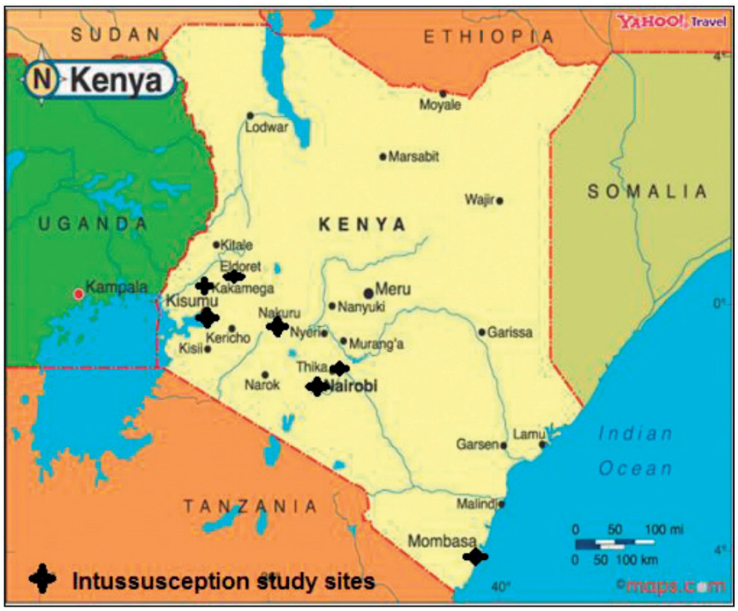

Figure 9. Major towns and locations of the intussusception surveillance study (IV) sites in Kenya.

4.1.1 Health and Demographic Surveillance System (HDSS)

The HDSS study site jointly operated by KEMRI and CDC is situated about 60–65 kilometers west of Kisumu and is managed from the KEMRI and CDC research station located 15 kilometers west of Kisumu (Figure 8). The KEMRI and CDC research partnership began in 1979 as a malaria and vector biology research center, but it has since expanded and currently known as the KEMRI Center for Global Health Research (CGHR). It now includes programs focusing on infectious diseases such as diarrhea, tuberculosis, HIV/AIDS, a refugee health program, and an HDSS. The HDSS initially started in Asembo in 2001, added Gem in 2002, and expanded to Karemo in 2007 (Figure 8). The HDSS area covers approximately 700 km^2 (Asembo ~200 km^2, Gem ~300 km^2, and Karemo ~200 km^2). HDSS surveillance commences with baseline census enumeration, after which field workers visit the enumerated households three times a year to conduct a census of the population and update population denominators that are then used to estimate and extrapolate disease rates. The regular household census visits are used to update data on resident demographics and to capture vital events like births,

deaths, educational attainment changes, ownership of household assets, marital status, immunization status for children, causes of death through verbal autopsy (VA), in and out migration, and other health events such as diarrhea episodes among adults and children under five years old. Asembo, Gem, and Karemo residents comprise a culturally homogeneous population; more than 98% are members of the Luo ethnic group, and most people live in dispersed settlements. Houses are made of mud, cement, or brick with roofs of iron sheets or thatched grass (Ombok et al., 2010). These houses are predominantly clustered in compounds made up of houses for the male head of household, his wives, and his unmarried sons. The compounds are dispersed and lie next to the households' agricultural fields (Adazu et al., 2005). In general, Gem and Karemo are hillier than Asembo, but all the three areas consist of gentle hills drained by small seasonal streams that drain into Lake Victoria (Ombok et al., 2010). Although all houses were mapped using a global positioning system (GPS) as part of the original insecticide-treated bednets (ITNs) trial (Hightower et al., 1998), maps were updated at least annually to take account of new construction; a unique location code was also painted on each house to identify the village, compound, specific house, and individual residents of the household (Adazu et al., 2005). Most HDSS residents earn their living through small-scale business, farming, or fishing (Lindblade et al., 2004). There are few paved or public transport roads in the area, so walking is the main means of transport (Ombok et al., 2010). The primary source of drinking water is the polluted Lake Victoria and nearby streams and rivers (Tate, Rheingans et al., 2009).

4.1.2 Global Enteric Multicenter Study (GEMS)

The GEMS was a prospective, age-stratified, matched case-control study of MSD among children under five years of age residing in well-defined populations at four sites in sub-Saharan Africa and three in South Asia (Levine *et al.*, 2012). Cases with MSD seeking care at SHCs were recruited along with one to three randomly selected matched control children without diarrhea of the same age, gender, and residential location. A GEMS case was defined as a patient enrolled with MSD at a study clinic within 7 days of illness onset; MSD was defined as 3 or more loose stools in 24 hours with at least 1 of these characteristics: sunken eyes, skin tenting, dysentery, IV rehydration, or hospitalization. The GEMS Kenya study was conducted in Asembo and Gem for the first three years and in Asembo and

Karemo in the fourth year. Together, these areas form the jointly operated KEMRI and CDC HDSS study area (Figure 8). The GEMS Kenya setting and the HDSS have been described in detail elsewhere (Adazu et al., 2005; F. O. Odhiambo et al., 2012), as have the GEMS rationale (Levine *et al.*, 2012) and the clinical (Kotloff et al., 2012) and laboratory (Panchalingam et al., 2012) methods employed.

The 2008 mid-year population of the HDSS at the start of our rotavirus surveillance among GEMS cases was 225,064, of whom 16.7% were children under five and 5.3% were adults 65 or older; females comprised 47.1% of cases, with a male-female ratio of 1:1.2 (unpublished data from the KEMRI and CDC jointly operated HDSS).

The GEMS collected clinical and epidemiological data, anthropometric measurements, and fecal samples to identify enteropathogens at enrollment; a single home visit was made approximately 60 (range: 50-90) days later to ascertain vital status, clinical outcome, and interval growth. As part of GEMS and HDSS activity, we conducted healthcare utilization and attitude survey (Study I) in the Asembo and Gem HDSS areas. Rotavirus surveillance among GEMS cases (Study III) was subsequently performed in the Asembo, Gem, and Karemo HDSS areas, where GEMS Kenya MSD cases were enrolled from.

4.1.3 Healthcare delivery and referral system in Kenya

Kenya's healthcare system is structured in a stepwise manner (Figures 10); complicated cases are referred to higher levels in the system (KMoH, 2014). Although some county referral hospitals may have had pediatric surgeons or medical specialists referred to as consultants, it is the top referral hospitals that have long been observed to be well equipped with these specialists and the diagnostic facilities needed to provide specialized care of the kind demanded by intussusception. Therefore, intussusception surveillance (Study IV) was conducted at selected Kenyan referral hospitals (Figures 9 and 10) due to their ability to handle referrals related to pediatrics and the public knowledge that these facilities have resident pediatrician consultant surgeons who deal with child health complications.

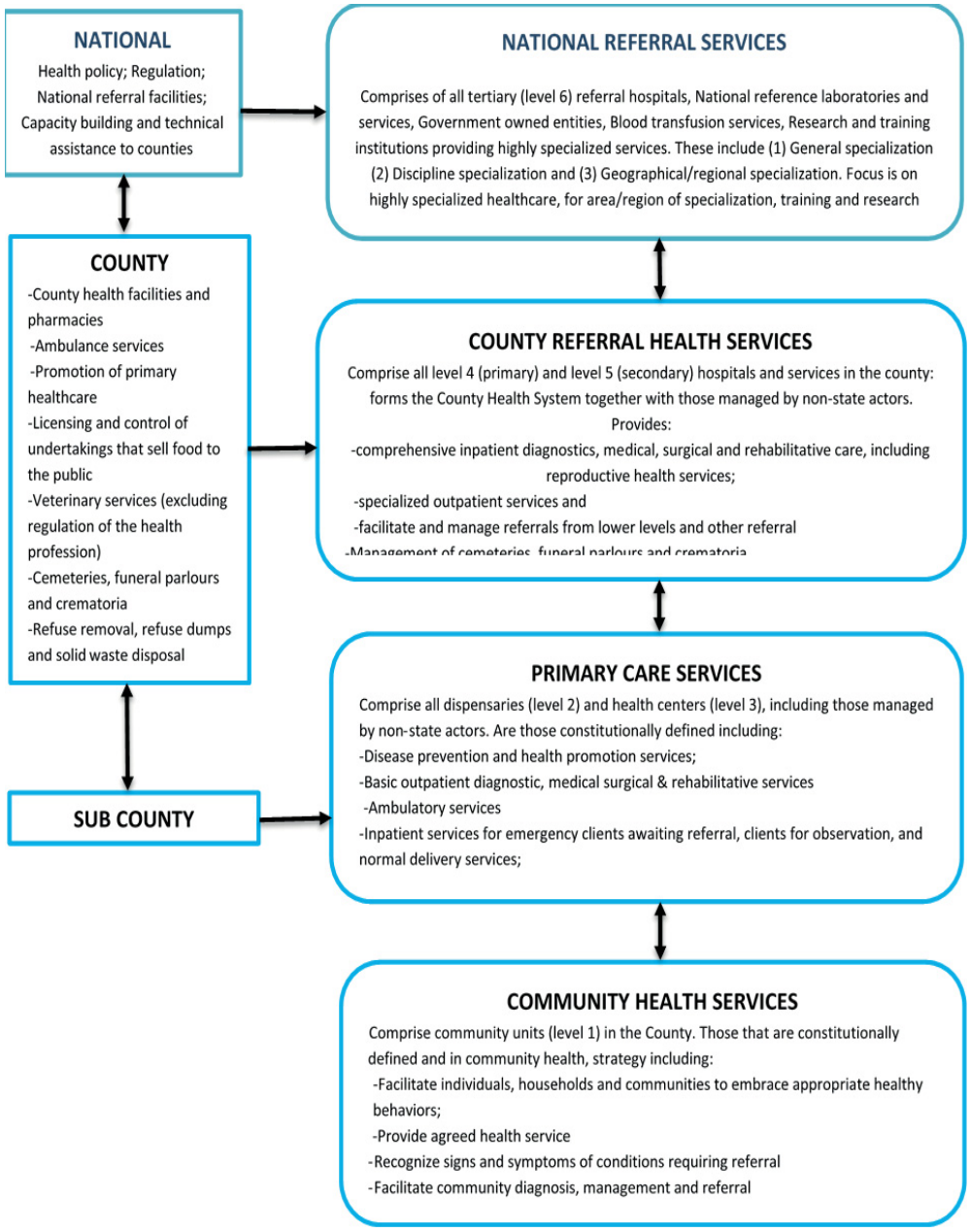

Figure 10. Organization of health service delivery and referral system in Kenya

Source: (KMoH, 2014).

4.2 Epidemiologic Study Designs

The objectives, study settings, targeted population, epidemiological designs (including surveillance periods), and specific case definitions for the investigations conducted in this thesis are summarized in Table 7. Specific details for each study are described in separate sections below.

4.2.1 Survey methods for estimating rates of healthcare seeking and prevalence for diarrhea (Study I)

As part of the GEMS Kenya study, we performed a one-time detailed baseline population randomized sample cross-sectional survey referred to as the healthcare utilization and attitudes survey (HUAS) and repeated a shorter version called HUAS-Lite. The HUAS-Lite was a brief healthcare utilization survey conducted serially three times a year during the 2008–2011 period in concert with each round of the HDSS household census visits, using a whole population survey of resident children aged 0–59 months as denominator. The parent or primary caretaker of each child enrolled in each survey was asked whether the child had experienced a new episode of diarrhea during the preceding seven days, whether any signs and symptoms had presented during the diarrheal illness, whether they sought care outside the home, and, if so, where they sought care, including home management, for the child's diarrhea illness. By pooling the data from serial surveys and based on the number of children in each age-gender stratum in the HDSS population, we calculated the proportion, designated as *r* (the rate multiplier), of children with any diarrhea and MSD (based on the MSD case definition) who were at least taken to a health facility within seven days of diarrhea illness onset during each round of the survey.

4.2.2 Rotavirus surveillance among the GEMS Kenya case population (Study III)

We used the initial HUAS baseline data to identify health facilities where caretakers preferred to seek care for their child's diarrhea illness. We used data from the subsequent HUAS-Lite rounds to monitor the SHCs and healthcare seeking in the HDSS area during the GEMS-based rotavirus surveillance period. We used prospective, hospital-based surveillance to enroll children with MSD who visited

those SHCs for care from 2008 to 2012 to participate in our GEMS Kenya rotavirus surveillance and risk factor study (Study III).

Case definition: a GEMS rotavirus surveillance study case was defined as a child enrolled in a GEMS clinic within 7 days of illness onset, with 3 or more loose stools in 24 hours with at least 1 of these characteristics: sunken eyes, skin tenting, IV rehydration, or hospitalization. This study was conducted in Asembo, Gem, and Karemo (Figure 11).

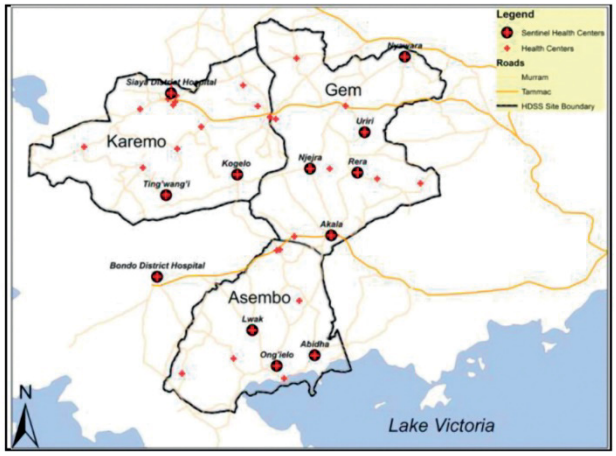

Figure 11. Locations of GEMS Kenya SHCs where the rotavirus surveillance (Study II) was conducted.

4.2.3 Rotavirus surveillance in the HDSS-hospitalized population (Study II)

Siaya County Referral Hospital (SCRH), formerly known as Siaya District Hospital, is the only public inpatient health facility located within easy reach from almost every location in the Karemo HDSS, due to a superior road network. Therefore, as part of the HDSS, we conducted a prospective, hospital-based inpatient surveillance study for rotavirus (Study II) at SCRH. The study targeted children under five admitted to SCRH using the WHO's common protocol for rotavirus surveillance network countries, which has been described in detail elsewhere (WHO, 2008). In our study, AGE cases were defined as residents of the Karemo HDSS study area aged 0–59 months (Figures 8 and 11) who were hospitalized in the SCRH inpatient department with AGE, which was further defined as 3 or more looser-than-normal stools and/or 1 or more episodes of unexplained

vomiting followed by loose stool within a 24-hour period within the 7 days before seeking healthcare. Informed consent was obtained from caretakers of the eligible AGE cases before enrollment during the study period from 1 January 2010 to 31 December 2013.

4.2.4 Intussusceptions among pediatric patients in Kenya (Study IV)

Data on intussusception from across Kenya were obtained retrospectively from 1 January 2002 through 31 October 2013. The study sites were located at 12 geographically dispersed leading referral hospitals in Kenya (Figure 9). We reviewed hospital records for patients diagnosed with intussusception from January 2002 through October 2013. The review at each hospital varied based on when records were available and the filing system for patient records.

An intussusception case was defined as a diagnosis of intussusception confirmed in the records of a patient under five years old who met the Brighton Collaboration level 1 criteria (Bines *et al.*, 2004): "pediatric patients diagnosed with intussusception clinically and confirmed through imaging and/or at surgery at the time of admission or any time during hospital stay at the study sites". Clinical case definition for diagnosis of acute intussusception is further detailed elsewhere (Bines *et al.*, 2004).

4.2.5 Data collection and management

For the initial baseline HUAS and subsequent HUAS-Lite surveys (Study I), we collected demographic, clinical, epidemiological, and household information, including caretaker healthcare-seeking behaviors at enrollment.

In the rotavirus surveillance studies (II and III), we collected clinical, household, environmental, and epidemiological data, along with stool samples, to identify rotavirus at enrollment. In Study III, a single follow-up home visit was made approximately 60 days (the targeted range was 50–90 days) following enrollment to assess each child's health outcome after the acute diarrheal illness, as described elsewhere (Kotloff et al., 2012). For the HUAS-lite (part of study I) and study II at SCRH, we used a paperless questionnaire that was programmed into personal digital assistants or netbooks. The subsequent HUAS-Lite serial surveys were conducted during the GEMS case-control study, along with the routine

census surveys undertaken by the DSS team as described elsewhere (F. O. Odhiambo et al., 2012).

For the initial baseline HUAS part of Study I and the rotavirus surveillance among GEMS Kenya cases (Study III), demographic characteristics, clinical features, and illness history data were recorded on optical character recognition-enabled forms and then scanned and imported into a SAS software package. For the intussusception surveillance (Study IV), paper-based case report forms (CRFs) were used to abstract patients' demographic characteristics, clinical features, illness histories, surgical options, and outcome information from medical records and theater logbooks. Data were collected by the pediatric surgeons who managed the surgical clinics and wards at each study site. After manual accuracy checks, data were entered into a Microsoft Access database and imported into SAS.

4.3 Stool Sample Collection and Laboratory Methods (Studies II and III)

The stool samples from the study participants were collected according to standard microbiology laboratory techniques. Whole stool collection was achieved via sterile plastic containers provided with screwcaps and spoons. Cary Blair Transport Media were used to preserve samples. Rotavirus was detected in the whole stool specimens collected from patients enrolled in Studies II and III by a well-validated commercial enzyme-linked immunosorbent assay (ELISA) (ProSpecT Rotavirus Kit, Basingstoke, Oxford, UK). Detailed laboratory methods for Study II (Khagayi et al., 2014) and Study III (Panchalingam et al., 2012) have been described elsewhere. Laboratory results were then linked to epidemiology data through unique HDSS identifiers before further analysis.

4.4 Statistical Analysis

4.4.1 Descriptive analysis

For each HUAS-Lite survey, we estimated a two-week period prevalence of any diarrhea, MSD, proportion of diarrhea, and MSD seeking care outside the home,

and specifically from at least an SHC for Study III. Proportions and 95% CIs were calculated. The Cochran-Armitage test for trend was used to examine rate differences across rounds (Armitage, 1955). We used chi-square tests to examine associations between the characteristics of the child, caretaker knowledge, caretaker attitude, caretaker healthcare-seeking behaviors, clinical features, environmental factors, occurrence of any diarrhea, seeking care outside the home, use of ORS at home, and seeking care from a health facility. Similarly, we compared child and caretaker characteristics between rotavirus and non-rotavirus cases and occurrence of death preceding intussusception treatment and survival among children under five. Unadjusted odds ratios (ORs) and 95% CIs were used to assess the strength of the associations between categorical variables. We used Fisher's exact test to compare characteristics of intussusception patients who died with those who survived. Medians were compared using the Wilcoxon rank sum test. For all statistical tests, a 2-sided $p < 0.05$ was considered statistically significant.

4.4.2 Analysis of severity of diarrheal disease associated with rotavirus infection

For Study II, we adapted the 20-point full scale analysis developed by Ruuska and Vesikari (Ruuska & Vesikari, 1990) to assess the severity of rotavirus diarrhea. For rotavirus severity analysis from GEMS rotavirus surveillance study cases in Study III, we applied a 17-point scoring system, referred to in this analysis as the GEMS-modified Vesikari score system, which was adapted from the 20-point scale. Scores were calculated based on symptoms of diarrheal illness and the child's characteristics at enrollment.

4.4.3 Calculation of hospitalization and mortality rates for all-cause AGE and RVAGE

4.4.3.1 Hospitalization rates for AGE and RVAGE

As described elsewhere (Breiman et al., 2014), we used the person-years of observation (PYOs) contributed by all children under five who were residents of the Karemo region during the study period as the denominator. We limited our rate calculations to the Karemo area of the HDSS, as it has been shown to be

representative of the entire HDSS area and the immediate catchment population of SCRH, where our participants were enrolled. PYOs were calculated by totaling person-time for all children aged 0–59 months who met the HDSS residency requirement during the 4-year study period from 1 January 2010 or date of enrollment (if later) until they exited or lost their residency status through out-migration or death; alternatively, they ceased being observed due to loss to follow-up or reached the end of the observation period, set in this analysis at 31 December 2014. HDSS residents who moved out of the HDSS area for four consecutive months were excluded from both the denominator and numerator. However if a new resident moved into or a former resident moved back to the study area and lived there for at least four consecutive months, that person was re-enrolled to participate in the HDSS as a resident, and his or her PYOs were counted in this study.

The crude incidence rates of AGE-associated hospitalization were calculated by dividing the total number of AGE hospitalizations by the PYOs contributed by children 0–59 months for the period that they met residency criteria for the HDSS, multiplied by 100,000 (and thus presented as cases per 100,000 PYOs). The crude rate of rotavirus-associated hospitalization was calculated by dividing the total rotavirus-positive AGE hospitalizations for those under five by the PYOs during the study period.

We used two incidence rate adjustments. First, to account for possible bias arising from missed AGE case detection, we multiplied the crude rate of AGE and RVAGE by the proportion of all inpatients who met the stool collection criteria, whether a sample was collected or not. The second adjustment accounted for children with AGE or possibly RVAGE and who did not reach a healthcare facility, as reported from repeated healthcare utilization and diarrhea attitude surveys that were conducted alongside census household visits during the hospital surveillance study period. For this adjustment, we further multiplied the rate of AGE and RVAGE hospitalizations by the proportion of those who sought care for AGE from a healthcare facility, as reported from the household healthcare utilization survey. The products are reported as the final adjusted incidence rates for AGE and RVAGE. The 95% CIs were calculated around crude rates using the PEPI software method (Abramson, 2011) and around adjusted rates using the Delta method (Long, 2005 ; WHO, 2008). We categorized the participants as 0–5 months, 6–11 months, 12–23 months, 24–59 months, 0–11 months, and 0–59 months.

4.4.3.2 AGE and RVAGE mortality rates

Deaths were recorded at the household level through regular interviews with HDSS residents. Diarrhea as a cause of death was derived from VA, using a validated VA methodology (Byass et al., 2015). The VA methodologies, coding, and interpretation used in our study are described elsewhere (Byass et al., 2012). Upon the death of an HDSS resident, a village-based reporter sent a notification. After allowing for a mourning period of at least three weeks, an interviewer approached the most appropriate interviewee who was closest to the deceased to administer a detailed questionnaire on the deceased's final disease, signs, symptoms, and medical history. The data were collected electronically, validated, and processed using an Inter-VA program, which is a probabilistic computer-based expert opinion algorithm that determines the most probable cause of death (Byass et al., 2012). We calculated the number of deaths attributable to rotavirus by multiplying the total deaths among HDSS residents under five years old in the study area by the proportion of deaths attributable to diarrhea by VA and the proportion of hospitalized AGE episodes attributable to rotavirus in that specific age group, as shown below.

Number of deaths attributable to RV = (Total under-five deaths among HDSS residents in study area) * (proportion of deaths attributable to diarrhea) * (proportion of hospitalized AGE episodes attributable to RV)

Mortality rates associated with RVAGE were obtained by dividing the number of deaths attributed to rotavirus by the total PYOs in each age group, as adopted from the WHO (WHO, 2005a) and described above.

4.5 Ethical Considerations

The HUAS and HUAS-Lite (Study I) and prospective health facility-based rotavirus surveillance among GEMS cases (Study III) were sub-studies conducted under the GEMS protocol, which was reviewed and approved by the institutional review boards (IRBs) of KEMRI, the University of Maryland School of Medicine (UMB), and the CDC through deferral to UMB (KEMRI IRB Protocol #1801/1155; CDC IRB Protocol #3308; UMB IRB Protocol #HP-00040030). The HDSS hospital (inpatient) rotavirus surveillance (Study II) was approved by the KEMRI and CDC IRBs as part of the KEMRI HDSS protocol (KEMRI IRB

Protocol #1801). The intussusception study protocol (Study IV) was reviewed and approved by the IRB of the Kenyatta National Hospital (Protocol #P514/09/2012). For each study, written informed consent was obtained from every parent or primary caretaker of each case child who met eligibility criteria before any research activity was performed. In cases where the parent or primary caretaker was illiterate, an impartial third party witnessed the consenting process and signed the consent document after the caretaker made an informed decision.

Table 7. Descriptive summary of Studies I–IV, 2007–2013.

Investigation (Study)	Study Objective	Study setting	Targeted population	Study design	Data source	Case definition as per study protocol	Key variables studied
Study I	To estimate diarrhea prevalence and describe caretakers' knowledge, attitudes, perceptions of illness and patterns for seeking care from health facilities for young children with moderate-to-severe diarrhea in rural western Kenya and to evaluate factors associated with the healthcare seeking behavior	KEMRI and CDC operated HDSS (Gem and Asembo) study area	Household resident children Aged 0-59 months	Community-based one-time comprehensive baseline cross sectional survey, followed by repeated short cross-sectional surveys	Household interview data from 2007-2010	HDSS resident Child aged 0-59 months from Asembo/Gem household interview reporting diarrhea defined as; ≥3 loose stools within the previous 24 hours. Moderate-to-severe diarrhea (MSD) case; was defined further as diarrhea with ≥1 of the following characteristics: sunken eyes more than usual, loss of skin turgor, dysentery (blood in stool), receipt of intravenous rehydration, or required hospitalization as reported by caretaker.	**Demographic and Household information:** Residency, patient age, sex, # of children <5 years in the same household **Medical history:** diarrhea occurrence and duration in the 2-weeks prior to interview **Socio-economic characteristics:** Household functional assets, caretakers educational level **KAPB variables§§**
Study II	To estimate the population-based baseline incidence rates of acute gastroenteritis overall and rotavirus gastroenteritis, including associated hospitalizations and deaths among children < 5years of age in rural western Kenya	KEMRI and CDC operated HDSS (Karemo) study area	In-patient children aged 0-59 months	Prospective, hospital-based, in-patient rotavirus surveillance study as part of WHO generic protocol for rotavirus	In-patient data from 2010-2013	Resident Child aged 0-59 months from Karemo HDSS presenting in Siaya county referral hospital with acute gastroenteritis (AGE) , defined as; ≥ 3 looser than normal stools and/or ≥ 1 episode of unexplained vomiting followed by loose stool within 24 hours period. Rotavirus case was defined as a child with acute gastroenteritis whose stool sample tested rotavirus positive by ELISA	**Demographic characteristics§** **Medical history:** AGE occurrence, clinical features presented with AGE, pathogens detected in stool along with or without rotavirus,, and dates for each of the above events
Study III	To assess factors associated with rotavirus gastroenteritis among young children with moderate-to-severe diarrhea describe the severity of illness in rural western Kenya	KEMRI and CDC operated HDSS (Gem, Asembo and Karemo) study area	Children Aged 0-59 months	Prospective, health facility-based rotavirus surveillance study in GEMS	Out-patient (OPD) and In-patient (IPD) data from 2008-2012	diarrhea case was defined as; a HDSS resident child aged 0-59 months presenting at the study clinic with ≥3 loose stools within the previous 24 hours. Moderate-to-severe diarrhea (MSD) case; was defined further as diarrhea case with ≥1 of the following characteristics: sunken eyes more than usual, loss of skin turgor, dysentery (blood observed in stool) as reported by caretaker or assessed by study clinician, receipt of intravenous rehydration, or required hospitalization as assessed by study clinician. Rotavirus case was defined as a child with MSD and whose stool sample tested rotavirus positive by ELISA	**Demographic characteristics§** **Medical history:** diarrhea history, clinical features presented with MSD, pathogens detected in stool along with or without rotavirus, illness outcome
Study IV	To describe the pre-rotavirus vaccine epidemiology and to evaluate factors associated with intussusception-related deaths among patients < 5years of age treated at emergency referral hospitals in Kenya	Kenyan leading referral hospitals	Children Aged 0-59 months	Retrospective hospital-based record review of Intussusception patient charts	In-patient data from theatre logbooks, in-patient records and emergency patient logbooks from 2002-2013	Intussusception ("definite" cases) case was defined as patients aged 0-59 months who visited Kenyan main referral hospitals during the study period and whose records met Level 1 of Brighton Collaboration criterion , defined further as; Demonstration of invagination of intestine at surgery (in absence of another primary cause such as volvulus or pyloric stenosis); OR Demonstration of invagination of intestine by air or liquid contrast enema; OR Demonstration of an intra-abdominal mass by abdominal ultrasound with specific criteria, that is proved to be reduced by hydrostatic enema on post-reduction ultrasound; OR Demonstration of invagination of intestine at autopsy.	**Demographic characteristics§** **Medical history:** Illness history, days from illness symptoms onset to seeking care, referral history. **Assessments, diagnosis and treatment and illness outcome:** signs and symptoms assessed by the surgeon. Diagnostic tools used and final diagnosis, treatment options used, illness outcome

§§Caretakers knowledge, attitudes, belief and care seeking practices for their child's diarrhea, including antibiotic and ORT use, days diarrhea lasted, willingness to use vaccines, who makes decision for care seeking if the child is sick, care received within and outside home for the child`s diarrhea episode, what caretaker offered the child to drink and eat during the child`s diarrheal illness.

§ Demographic characteristics: residence location, patient age and sex, and referral status, event dates

5 RESULTS

5.1 Healthcare Utilization and Knowledge, Attitude, and Practice Surveys (Study I)

5.1.1 Baseline prevalence of diarrhea among children under five in the HUAS population (Study I)

During the initial baseline HUAS conducted between April and May 2007, 1,043 caretakers of children under five participated in the survey (Figure 12). Our weighted analysis of the baseline HUAS estimates showed that, of the approximately 20,000 children under five living in the HDSS during that study period, 4,612 (22%) had any diarrhea and that 3,155 (68%) of those cases met the MSD case definition. Figure 12 details the enrollment flow for the HUAS study.

5.1.2 Caretaker knowledge of, attitudes about, and perceptions of illness

In the 2 weeks preceding the survey, 275 children had any diarrhea reported by their caretakers; of those, 82.2% had 3–6 loose stools per day. We asked the caretakers of all 1,043 children who participated in the survey what they would look for to see whether a child was dehydrated; 716 (68.6%) indicated that they would look for lethargy, 481 (46.1%) sunken eyes, 369 (35.4%) wrinkled skin, 297 (28.5%) dry mouth, and 297 (28.5%) thirst. In total, only 206 (19.8%) of the 1,043 caretakers said they would look for both thirst and dry mouth to see whether a child was dehydrated. Furthermore, when we asked the 1,043 caretakers about who makes the decision to take a sick child to a healthcare facility, 809 (78%) of 1,041 respondents at baseline responded with the child's mother, while 232 (22%) said other relatives, including the child's father, make the decision. We asked all 1,043 caretakers who participated in the baseline HUAS if they thought that vaccines were important to their child's health; 99% answered in the affirmative.

We asked caretakers of children with any diarrhea what they offered the child to eat and drink during the diarrheal illness. Of the 275 children with any diarrhea, 41 (15%) of caretakers said they offered the child more to drink than usual, 51 (19%) reported offering the usual amount, and 183 (67%) reported that they offered the child less than usual to drink. Of those offered less than usual, 96 (52%) were offered somewhat less, 69 (38%) much less, and 18 (10%) were offered nothing to drink during their diarrheal illness. Of 269 caretakers who reported what they offered their child to eat during the diarrheal episode, 3 (1%) offered more than usual, 43 (16%) the usual amount, and 223 (83%) less than usual. Of those who offered less than usual, 74 (33%) offered somewhat less, 67 (30%) offered much less, and 82 (37%) offered nothing to eat during the diarrhea illness. According to their caretakers, 66 (37%) of the 180 and 77 (35%) of the 220 children who were offered less than usual to drink and eat, respectively, had vomiting accompanying the diarrhea episode. We estimated that 2,822 (89%) of children with MSD (3,155) in the HDSS sought care outside the home, 1,683 (60%) of whom reached a healthcare facility as a source of care for that MSD episode.

5.1.3 Symptoms in children with any diarrhea and illness outcomes

Most caretakers (86.2%) of the 275 children said that those who had an episode of any diarrhea in the preceding 2 weeks had 3 to 6 loose stools per day. The main symptoms they reported included lethargy (n = 225, 81.8%), fever (n = 201, 73.1%), being very thirsty (n = 193, 70.7%), mucus or pus in stool (n = 194, 70.6%), dry mouth (n = 188, 68.4%), rice-watery stool (n = 163, 59.7%), sunken eyes (n = 162, 58.9%), decreased urination (n = 102, 40.2%), wrinkled skin (n = 92, 33.7%), vomiting (n = 89, 32.7%), coma or loss of consciousness (n = 67, 24.6%) and blood in stool (n = 34, 12.4%). Overall, 6.7% of children with any diarrhea were hospitalized, and 47% of the hospitalized cases received IV fluids. Seeking healthcare outside the home for diarrheal illness was less common for infants than for children aged 24-59 months (aOR 0.33, CI: 0.12-0.87).

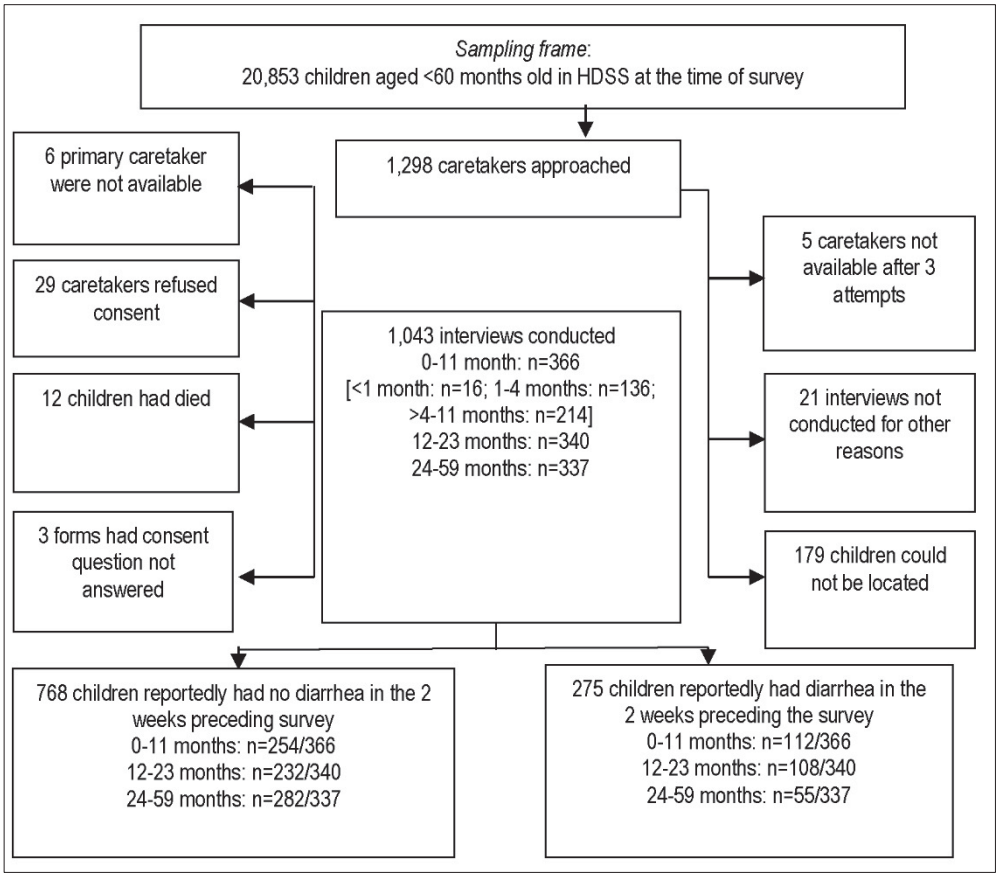

Figure 12. Study enrollment flow diagram for the initial cross-sectional HUAS of caretakers of children under five in western Kenya, 25 April–9 May 2007.

5.1.4 Factors associated with children seeking care for diarrhea from a healthcare facility (Study I)

Factors that were associated with seeking care for diarrhea from any healthcare facility are shown in Table 8. In summary, seeking care for any diarrhea from a healthcare facility was observed to be significantly more common among infants than school-age children, children whose caretakers had formal education, children whose caretakers offered no remedies at home, and those who presented with severe symptoms, particularly lethargy, during the diarrhea episode.

Table 8. Factors associated with seeking care from a health facility for children under five with any diarrhea in the HUAS in western Kenya, 2007* [N = 214].

Variable†	Sought care outside home for any diarrhea at a health facility		Unadjusted Odds Ratio (95% CI§)	Adjusted Odds Ratio‡ (95% CI)
	n/N	Weighted %		
Child's age group				
0-11 months	53/76	69.7	2.30 (1.08–4.93)	5.06 (1.88–13.61)
12-23 months	46/90	51.8	1.08 (0.52–2.22)	1.35 (0.57–3.21)
24-59 months	24/48	49.98	Reference	Reference
Child's gender				
Male	77/123	54.7	1.03 (0.59–1.80)	0.65 (0.32–1.34)
Female	46/91	54.5		
Caretakers education				
≥Primary school (some formal education)	67/104	65.1	2.35 (1.25–4.44)	3.32 (1.56–7.07)
<Primary school (no formal education)	56/110	44.2		
Caretakers looks to see if the child is thirsty to assess dehydration				
Yes	34/65	43.3	0.52 (0.27–1.03)	0.21 (0.09–0.47)
No	89/149	59.4		
Caretaker perceives that blood in stool can cause harm or death in a child				
Yes	112/186	57.9	2.95 (1.15–7.60)	3.25 (1.16–9.09)
No	11/28	31.8		
Caretaker never endures circumstances that make it difficult to reach their health facility of choice				
Yes	32/42	69.7	2.25 (0.93–5.44)	3.90 (1.47–10.35)
No	91/172	50.6		
Lethargy as a symptom during diarrheal illness				
Yes	112/185	57.6	2.41 (0.92–6.30)	5.73 (1.79–18.42)
No	11/29	36.1		
Child was offered ORS at home for diarrheal illness				
Yes	43/56	75.5	3.50 (1.57–7.84)	6.99 (3.01–16.22)
No	80/158	46.8		
Child was offered no special remedies at home for diarrheal illness				
Yes	22/27	79.1	3.73 (1.17–11.86)	10.17 (2.84–36.37)
No	101/187	50.4		

*Weighted analysis. †Based on the inclusion criteria, 14 variables were initially included in the model with results shown for the significant variables, controlling for age and gender. §Confidence interval. ‡Adjusted OR, whereby all ORs control for other factors in the model.

5.1.5 Factors associated with ORS use among children with any diarrhea (Study I)

Most (89.5%) caretakers of children with diarrhea indicated that ORS works well in treating it. However, only 63 (22.9%) of the 275 children with diarrhea of any severity were offered ORS at home, according to their caretakers. A higher proportion of children with MSD (46 of 182, 25.3%) than those with just any diarrhea (17 of 93, 18.3%) were offered ORS at home ($p > 0.05$).

We examined factors associated with the use of ORS at home for the child's diarrheal illness. In the multivariate weighted analysis from the baseline HUAS, caretakers were less likely to use ORS at home for infants than for older children (aOR 0.35, CI: 0.14–0.89). However, they were more likely to use ORS at home if the primary caretaker had some formal education than those whose caretakers had informal education (aOR 3.01, CI: 1.41–6.42), if the caretaker perceived that dehydration could result in harm or death (aOR 5.54, CI: 2.23–13.73), if the child had vomiting ≥ 3 times per day during their diarrheal episode (aOR 3.33, CI: 1.56–7.11), if the caretaker knew of a child who had died of bloody diarrhea (aOR 2.73, CI: 1.20–6.20), if the child was offered the usual or less than usual amount to eat during the diarrheal episode (aOR 8.24, CI: 1.80–37.73), and if the caretaker believed that breastfeeding prevents diarrheal illness (aOR 16.19, CI: 1.32–199.21).

5.1.6 HUAS-Lite

From 22 May 2009 through 31 August 2011, we conducted seven whole population-based cross-sectional surveys, repeated at least two or three times each year as part of the HUAS extension (Study I; see Table 9). The enrollment flow is detailed in Figure 13. In brief, a 2-week period prevalence of any diarrhea in the HDSS decreased from 22% at the baseline HUAS in 2007 to 3% in 2011, while that of MSD increased significantly from 68% to 73%, and the proportion of children seeking care for MSD from a healthcare facility increased from 60% to 79% during the same surveillance period. The overall proportion of children aged 0–59 months seeking care for MSD from a healthcare facility during the hospital surveillance (Studies II and III) was 64%. The HUAS-Lite data further revealed that the rate of seeking care for MSD from a healthcare facility was highest for children aged 6–11 months (70%), followed by 0–5 months (69%), 12–23 months (66%), and 24–59 months (57%) during the rotavirus hospital-based surveillance (Studies II and III) period. The proportion and trends of any diarrhea, MSD, and healthcare seeking for MSD are further detailed in Table 9.

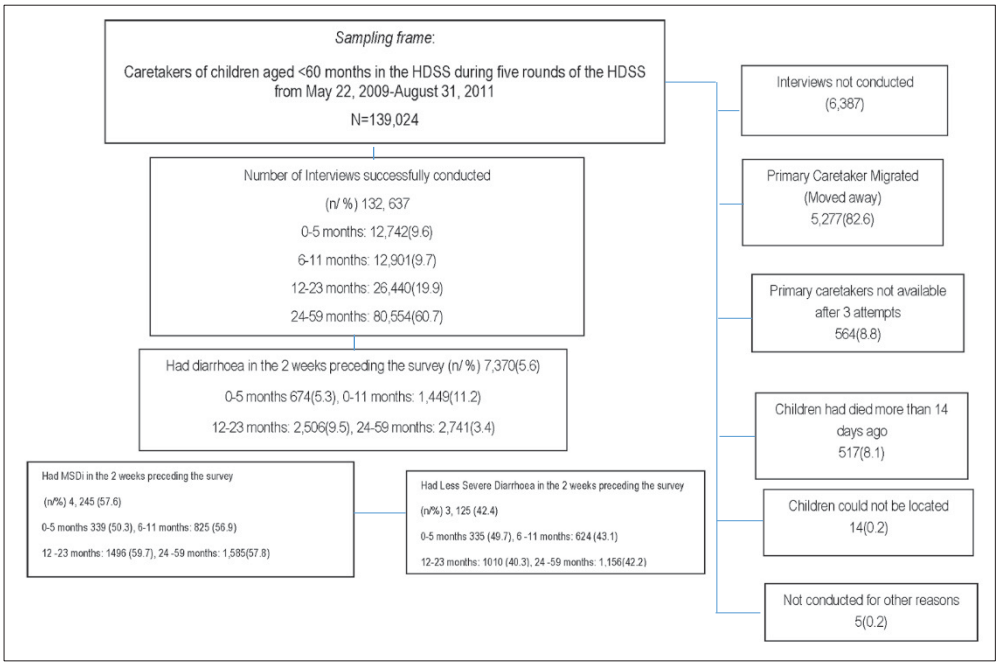

Figure 13. HUAS-Lite study enrollment profile in western Kenya, 22 May 2009–31 August 2011.

Table 9. Two-week prevalence of any diarrhea or MSD and proportions of caretakers seeking care from a healthcare facility in the HUAS-Lite study by round, western Kenya, 22 May 2009–31 August 2011

Characteristic	Round 1	Round 2	Round 3	Round 4	Round 5	Round 6	Round 7	Overall (Round 1-7)	P-value for trend
	May 22-Aug 31, 2009	Sep 15-Dec 3, 2009	Jan 28-Apr 30, 2010	May 27-Aug 31, 2010	Sep 14-Dec 31, 2010	Jan 26-Apr 30, 2011	May 20-Aug 31, 2011	May 22, 2009-31 Aug 2011	
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%, 95%CI)	
No. of HDSS resident children <5yrs of age approached	20256	20928	20687	19691	19755	20486	17221	139024	
No. of HDSS resident children <5yrs of age with interviews conducted	19221/20256 (94.9)	19733/20928 (94.3)	19735/20687 (95.4)	18916/19691 (96.1)	18887/19755 (95.6)	19608/20486 (96.7)	16537/17221 (96.0)	132637/139024 (95.4,94.9-95.9)	<.0001
Had diarrhoea in the 2 weeks preceding the survey	**2070/19221 (10.8)**	**1017/19733 (5.2)**	**1116/19735 (5.7)**	**898/18916 (4.7)**	**738/18887 (3.9)**	**791/19608 (5.0)**	**560/16537 (3.4)**	**7370/132637 (5.6, 5.4-5.7)**	**<.0001**
MSD	**1137/2070(54.9**	**539/1017(53.0)**	**641/1116(57.4)**	**518/898(57.7)**	**427/738 (57.9)**	**572/791(58.9)**	**411/560(73.4)**	**4245/7370 (57.6,56.4-58.8)**	<.0001
Sought care outside home for MSD	915/1137(80.5)	425/539(78.8)	537/641(83.8)	444/518(85.7)	354/427(82.9)	512/572(89.5)	360/411(87.6)	3547/4245 (83.6,82.4-84.7)	**<.0001**
Sought care for MSD from a health facility	**627/915(68.5)**	**276/425(64.9)**	**354/537(65.9)**	**221/444(49.8)**	**179/354(50.6)**	**347/512(67.8)**	**284/360(78.9)**	2288/3547(64.5,61.9-67.2)	0.7636
Overall seeking care for MSD from any Health Facility (0-59)	627 /915(68.5)	276/425 (64.9)	354/537 (65.9)	221/444(49.8)	179/354 (50.6)	347/512 (67.7)	284/360(78.9)	2288/3547 (64.5,61.9-67.2)	0.7636
0-5 months	45/65 (69.2)	23/32(71.9)	33/44(75.0)	20/36(55.6)	18/31(58.1)	36/47(76.6)	15/19(78.9)	190 /274 (69.3,60.2-79.9)	0.5817
6-11 months	127/169 (75.1)	58/84(69.0)	79/107(73.8)	49/89(55,1)	29/57(50.9)	80/102(78.4)	66/87(75.9)	488/695 (70.2,64.3-76.7)	0.2536
12-23 months	221/324 (68.2)	110/152(72.4)	128/189(67.7)	78/155(50.3)	72/136 (52.9)	114/159(71.7)	103/150(81.1)	826/1242 (66.5,62.1-71.2)	0.0434
24-59 months	234/357 (65.5)	85/157(54.1)	114/197(57.9)	74/164(45.1)	60/130(46.5)	117/204(57.4)	100/143(78.7)	784/1336 (58.7,58.7-62.9)	0.1345

5.2 All-Cause- and Rotavirus Diarrhea-Associated Hospitalization and Mortality Rates (Study II)

From 1 January 2010 to 31 December 2013, 7,760 all-cause hospitalizations for children aged 0–59 months living in the 3 HDSS areas were registered at SCRH. The enrollment flow for the rotavirus surveillance in Study II is shown in Figure 14. In general, the proportion of all-cause hospitalizations associated with AGE decreased in each subsequent year of the study. However, the proportion of AGE decreased with increases in child age (Table 10). RVAGE-associated hospitalizations were highest in 2010 and increased by decreases in child age in a pattern very similar to the reduction in AGE-associated hospitalizations (Table 10 and Figure 21).

In brief, our prospective hospital-based rotavirus surveillance data (Study II) showed that 21% of the overall hospitalizations in children were due to AGE of all causes and that 26% of hospitalized AGE patients were rotavirus-positive (RVAGE) during the study period. Consistent with the data presented in Table 10, our data further revealed that both all-cause AGE- and RVAGE-specific hospitalizations were most commonly observed in infants and that rotavirus infection was less likely in older children.

Table 10. Characteristics of children under five hospitalized at SCRH with all-cause morbidity, AGE, and RVAGE in the Karemo HDSS area in western Kenya, 2010—2013.

Characteristics	All Cause Hospitalizations from Karemo DSS (N=3793)	AGE Hospitalizations (N=805)	AGE specimen collected and tested for RV [r] (N=544)	Proportion tested RV Positive (N=143)
Sex	n	n (row%)	n (row%)	n (row%)
Male	2066	461 (22%)	312 (70%)	87 (28%)
Female	3793	344 (20%)	232 (67%)	56 (24%)
Year				
2010	920	224 (24%)	149 (67%)	43 (29%)
2011	1335	313 (23%)	207 (66%)	53 (26%)
2012	822	147 (18%)	93 (63%)	26 (28%)
2013	716	121 (17%)	95 (79%)	21 (22%)
Age (Months)				
0-5	536	205 (38%)	143 (70%)	45 (31%)
6-11	781	285 (36%)	204(72%)	57 (28%)
12-23	1110	205 (18%)	139 (68%)	30 (22%)
24-36	687	70 (10%)	40 (57%)	9 (23%)
37-59	679	40 (6%)	18 (45%)	2 (11%)

[r]Three samples were not tested due to inadequate stool.

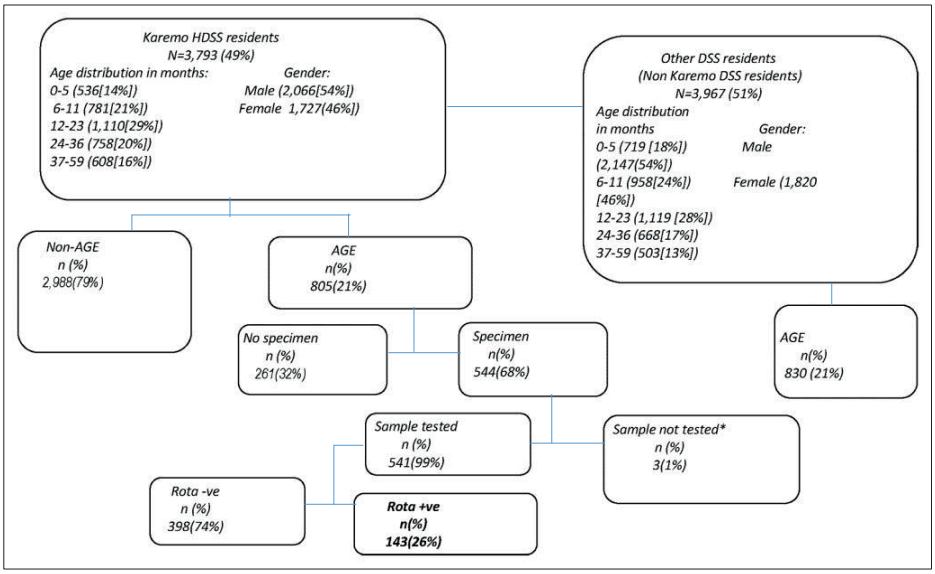

Figure 14. Flow diagram of Karemo DSS residents under five who were hospitalized and enrolled in the study from SCRH, western Kenya, 2010–2013.

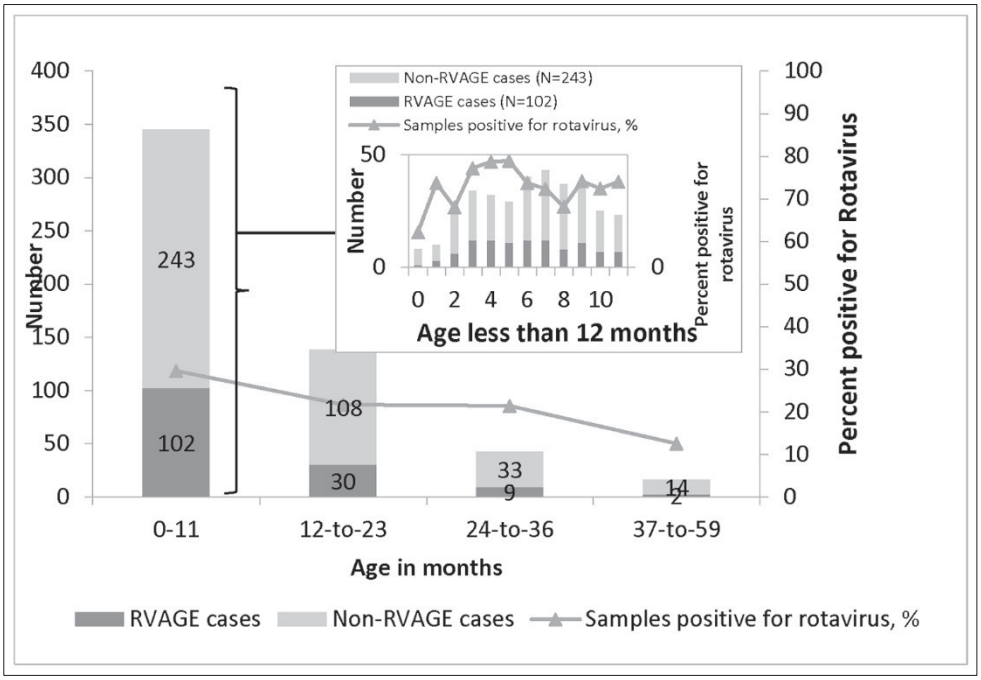

Figure 15. Rotavirus-positive cases among AGE-hospitalized children under five among Karemo HDSS residents population seeking care from SCRH, western Kenya, 2010–2013.

We calculated all-cause and rotavirus diarrhea-associated hospitalization rates using PYOs from the HDSS. We further adjusted the rates by using population-based data on healthcare utilization and the proportion of stools collected from patients who met the case definition at the surveillance hospital. Mortality rates for RVAGE were calculated by applying the percentage of those positive for rotavirus among AGE hospitalizations to estimated diarrhea deaths. The overall adjusted incidence rate of all-cause AGE-associated hospitalization was 2,413 cases per 100,000 children, while RVAGE accounted for 429 cases per 100,000 children aged 0–59 months (Tables 11 and 12, respectively). Infants and especially children aged 6–11 months experienced the highest AGE hospitalization rates of 7,798 cases per 100,000 hospitalizations and 558 cases per 100,000 deaths. Although infants in general had the highest hospitalization rates due to all-cause AGE, children aged 6–11 months experienced the greatest burden of all-cause AGE hospitalization. The highest annual rate of hospitalizations due to all-cause AGE (per 100,000) was observed in 2011 (3,782), followed by 2010 (2,718), 2012 (1,745), and 2013 (1,437). The rates of hospitalizations due to all-cause AGE during the

study period and by specific age groups are shown in Table 11. Infants aged 6–11 months had the highest RVAGE incidence: 1,560 cases per 100,000 person-years in the HDSS. When estimates of hospitalizations due to RVAGE were compared by year, the highest rates were observed in 2011, followed by 2010 and 2012, with the lowest rate in 2013 (Table 12).

Table 11. Unadjusted and adjusted† rates and 95% CIs of hospitalization attributed to AGE per 100,000 person-years among inpatients aged 0–59 months and residing in the rural Karemo HDSS in the pre-vaccine introduction era in Kenya, 2010–2013. (The estimates in brackets are the 95% CIs).

Year	Unadjusted Rates and 95% Confidence interval † of Hospitalization attributed to AGE					
	0-5 months	**6-11 months**	**0-11 months**	**12-23 months**	**24-59 months**	**0-59 months**
2010	5942 (5313-6572)	5928 (5299-6556)	5934 (5305-6563)	5107 (4523-5690)	353 (199-506)	1740 (1399-2080)
2011	6506 (5818-7193)	8622 (7831-9413)	7639 (6894-8384)	8643 (7851-9435)	528 (332-724)	2421 (2001-2840)
2012	3963 (3278-4649)	3793 (3122-4463)	3868 (3191-4545)	3226 (2607-3844)	208 (51-365)	1117 (753-1481)
2013	2487 (1912-3062)	3735 (3030-4439)	3158 (2510-3806)	1954 (1444-2463)	272 (82-461)	919 (570-1269)
2010-2013	4696 (4064-5329)	5459 (4776-6141)	5112 (4451-5772)	4696 (4064-5329)	340 (170-510)	1544 (1181-1907)
Year	**Adjusted Rates and 95% Confidence interval † of Hospitalization attributed to AGE**					
	0-5 months	**6-11 months**	**0-11 months**	**12-23 months**	**24-59 months**	**0-59 months**
2010	8612 (7854-9370)	8468 (7717-9220)	8478 (7726-9230)	7622 (6909-8335)	619 (416-822)	2718 (2292-3144)
2011	9428 (8601-10256)	12317 (11371-13263)	10913 (10023-11803)	12900 (11932-13868)	927 (667-1186)	3782 (3258-4306)
2012	5744 (4918-6569)	5418 (4617-6220)	5526 (4716-6335)	4815 (4599-5570)	365 (157-573)	1745 (1290-2200)
2013	3604 (2912-4296)	5335 (4493-6178)	4512 (3737-5286)	2916 (2294-3539)	476 (225-728)	1437 (1000-1874)
2010-2013	6806 (6045-7568)	7798 (6983-8614)	7302 (6513-8091)	7010 (6236-7783)	597 (371-822)	2413 (1959-2866)

†Adjusted by applying the proportion of samples collected from all AGE admissions to the hospital and health-seeking behavior in the HDSS for children with reported diarrhea at home

Table 12. Unadjusted and adjusted† rates and 95% CIs of hospitalization attributed to RVAGE per 100,000 person-years among inpatients aged 0–59 months and residing in the rural Karemo HDSS in the pre-vaccine introduction era in Kenya, 2010–2013. (The estimates in brackets are the 95% CIs).

Year	Unadjusted Rates and 95% Confidence interval † of Hospitalization attributed to RVAGE by age and year					
	0-5 months	6-11 months	0-11 months	12-23 months	24-59 months	0-59 months
2010	1486 (1373-1598)	1078 (982-1174)	1263 (1159-1367)	429 (368-489)	25 (11-40)	334 (280-387)
2011	1208 (1105-1311)	1853 (1725-1981)	1554 (1437-1671)	445 (382-508)	74 (48-99)	410 (350-470)
2012	922 (827-1016)	584 (508-659)	733 (649-817)	236 (188-284)	25 (9-40)	198 (154-241)
2013	533 (476-590)	915 (840-990)	738 (671-806)	76 (55-98)	12 (4-21)	160 (128-191)
2010-2013	1031 (938-1123)	1092 (997-1187)	1064 (970-1158)	294 (245-343)	34 (17-51)	274 (227-322)
Year	Adjusted Rates and 95% Confidence interval † of Hospitalization attributed to RVAGE by age and year					
	0-5 months	6-11 months	0-11 months	12-23 months	24-59 months	0-59 months
2010	2153 (2017-2289)	1540 (1425-1654)	1804 (1680-1928)	640 (566-714)	44 (25-64)	522 (455-589)
2011	1751 (1627-1875)	2648 (2495-2800)	2220 (2080-2360)	664 (588-741)	129 (96-163)	640 (565-716)
2012	1336 (1222-1449)	834 (744-923)	1047 (946-1148)	352 (148-410)	43 (23-63)	309 (254-363)
2013	772 (703-841)	1307 (1217-1396)	1055 (974-1135)	114 (87-140)	22 (10-33)	249 (210-289)
2010-2013	1494 (1383-1606)	1560 (1446-1673)	1520 (1408-1632)	439 (379-499)	60 (37-82)	429 (369-488)

†Adjusted by applying the proportion of samples collected from all AGE admissions to the hospital and health-seeking behavior in the HDSS for children with reported diarrhea at home.

Mortality rates due to all-cause AGE were highest among infants and decreased with increasing age. Although the overall mortality rate increased from 2010 to 2011, with a small drop in 2012, we observed an increase in overall rates from 2011 to 2013, with a notable threefold increase in mortality rates among children aged six to eleven months from 2012 to 2013 (Table 13).

Table 13. Crude rates of mortality attributed to all-cause AGE per 100,000 person-years by age group and year in rural Karemo during the pre-vaccine era in Kenya, 2010–2013. (The estimates in brackets are the 95% CIs).

Year	Mortality rates and 95% Confidence interval by child age in months					
	0-5 months	6-11 months	0-11 months	12-23 months	24-59 months	0-59 months
2010	434 (393-474)	475 (432-517)	450 (409-492)	238 (140-117)	100 (80-120)	172 (146-198)
2011	342 (306-378)	558 (512-604)	452 (411-494)	353 (316-389)	90 (72-109)	214 (185-242)
2012	444 (403-486)	314 (280-349)	369 (331-407)	117 (96-138)	43 (30-56)	118 (97-140)
2013	368 (331-406)	928 (869-988)	649 (599-699)	225 (195-254)	68 (52-84)	207 (178-235)
2010-2013	401 (362-441)	558 (511-604)	479 (436-521)	210 (181-238)	75 (58-92)	176 (150-202)

Although the overall annual mortality rates per 100,000 person-years due to RVAGE increased slightly between 2010 and 2012, we observed a substantial increase in the rate between 2012 and 2013, with the increase highest among children aged 6–11 months, before the rotavirus vaccine was introduced in Kenya (Table 14).

Table 14. Mortality rates attributed to RVAGE per 100,000 person-years, by age group and year in Karemo during the pre-vaccine era in Kenya, 2010–2013. (The estimates in brackets are the 95% CIs).

Year	Mortality rate and 95% Confidence interval by child age in months					
	0-5 months	6-11 months	0-11 months	12-23 months	24-59 months	0-59 months
2010	165 (140-190)	119 (97-140)	144 (121-168)	42 (29-55)	33 (22-44)	46 (33-59)
2011	99 (80-119)	156 (132-181)	131 (109-154)	63 (48-79)	18 (10-26)	50 (36-64)
2012	138 (115-161)	91 (72-110)	111 (90-131)	30 (20-41)	3 (0-6)	56 (41-70)
2013	92 (73-111)	297 (263-331)	188 (161-215)	25 (15-34)	13 (7-20)	33 (22-44)
2010-2013	124 (103-146)	156 (132-181)	144 (120-167)	46 (33-59)	14 (7-22)	45 (32-59)

5.3 Rotavirus Infection by Wealth Quintiles and Age (Study III)

In our hospital-based rotavirus surveillance (Study III), we found that 15% of children under five years old with MSD presenting at our study SHCs were infected with rotavirus. Moreover, the proportion of children with MSD who were infected with rotavirus from rich and poor households was similar (Figure 16).

However, the proportion of those positive for rotavirus was significantly higher among infants than school-age children (Figure 17). We observed that the proportion of positives increased from birth to 20% at one month and remained at more or less at the same level through eight months, with a sharp drop-off in infants aged nine through eleven months (Figure 17).

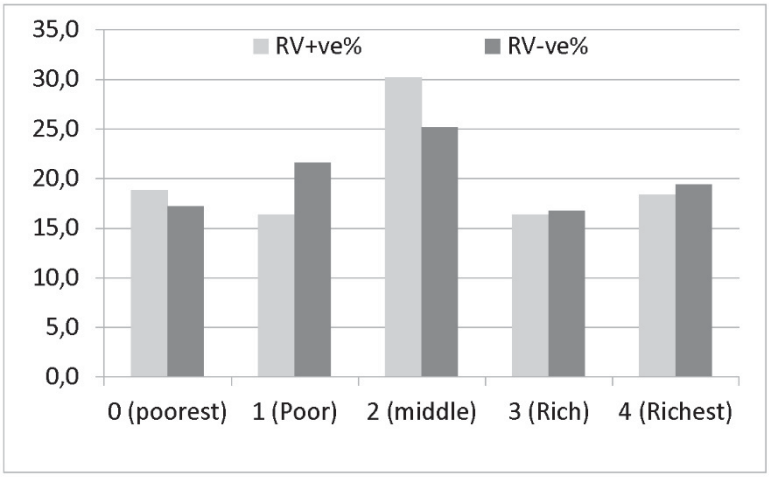

Figure 16. Wealth quintiles for rotavirus-positive vs. rotavirus-negative MSD cases from rotavirus surveillance (Study III) in western Kenya, 2008–2012.

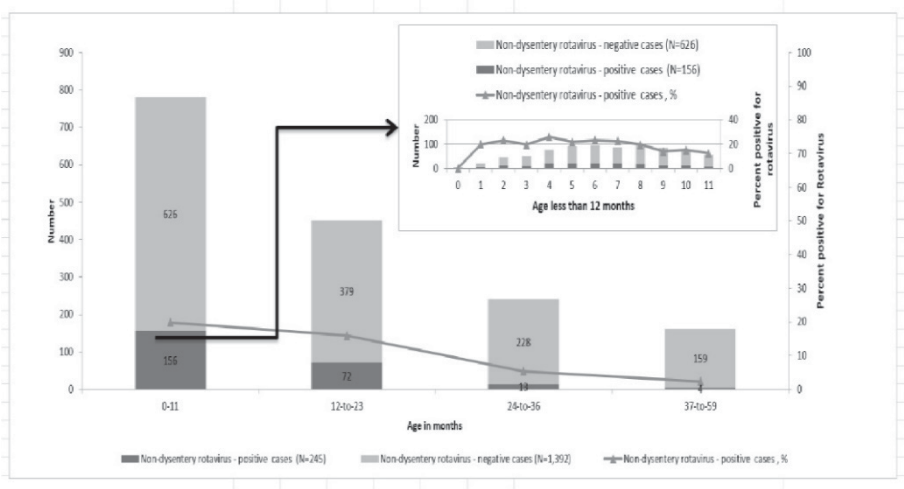

Figure 17. Rotavirus-positive and -negative cases among children with non-dysenteric MSD; number and percentage by age group, western Kenya, 2008–2012.

5.3.1 Factors associated with rotavirus diarrhea

Compared with non-rotavirus cases, rotavirus MSD cases were more likely to present with a history of vomiting and to be treated with IV fluids. The factors associated with rotavirus infection in univariate and multivariable analysis are shown in Tables 15 and 16, respectively. Hospitalization was more commonly observed among MSD patients under one year of age who were rotavirus-positive than rotavirus-negative (67.6% [25/37] vs. 46.3% [62/134], $p < 0.035$) and among all rotavirus-positive vs -negative MSD cases, regardless of age (15.1% [37/245] vs. 9.6% [134/1,392], $p < 0.013$). Our data showed that children with rotavirus diarrhea presented with conditions suggesting more severe disease than those with non-rotavirus diarrhea. The difference in severity between rotavirus and non-rotavirus diarrhea is further described using a GEMS-modified Vesikari score, as detailed in Table 17. The stool samples collected during warm and dry months were twice as likely to be rotavirus-positive than those collected in typically cool and rainy months (142/691 [20.5%] vs. 70/673 [10.4%]; OR = 2.16, 95% CI: 1.58–2.96).

Table 15. Clinical characteristics of rotavirus-positive and -negative cases with non-dysentery MSD enrolled in GEMS rotavirus surveillance (Study III), western Kenya, 2008–2012.

	Rotavirus positive N = 245		**Rotavirus negative N = 1,392**		**unadjusted odds ratio, 95%Confidence interval (OR, 95%CI)**	
Variable	n	%	n	%	OR	95%CI p-value
Child`s age stratum (in months)						
0-11	156	63.7	626	45.0	5.67	
12-to-23	72	29.4	379	27.2	4.32	
24-59	17	6.9	387	27.8	Ref	
Median age in months	8 [IQR 5-14]		13 [IQR 7-25]		N/A	
Gender						
Female	120	49.0	591	42.5	1.3	
Male	125	51.0	801	57.5	Ref	
Clinical symptoms in the child at enrollment						
Vomiting ≥3 times/24hrs						
Yes	171	69.8	627	45.0	2.82	
No	74	30.2	765	55.0	Ref	
Maximum no. of loose stools/24hrs						
≥ 7/24hrs	78	31.8	333	23.9	1.49	
≤ 6/24hrs	167	68.2	1059	76.1	Ref	
Child was admitted to hospital						
Yes	37	15.1	134	9.6	1.67	
No	208	84.9	1258	90.4	Ref	
IV fluid given						
Yes	43	17.6	155	11.1	1.7	
no	202	82.4	1237	88.9	Ref	
Dehydration						
Moderate-to-severe	55/241	22.8	250/1333	18.8	1.28	
Mild	186/241	77.2	1083/1333	81.2	Ref	

Table 16. Factors associated with rotavirus positivity among children under five with non-dysentery MSD enrolled in GEMS rotavirus surveillance (Study III), western Kenya, 2008–2012.

Characteristic †	**Rotavirus positive N=245 (n/N, %)**	**Rotavirus negative N= 1,392 (n/N, %)**	**Odds ratio (OR) for rotavirus detected in the stool [95% confidence interval (CI)]**	
			Unadjusted Odds Ratio	Adjusted Odds Ratio ‡
			[OR] (95%CI)	[aOR] (95%CI)
Child age stratum				
0-11 months	156 (63.7)	626 (45.0)	5.67 (3.38-9.51)	5.41 (3.21-9.11)
12-23 months	72 (29.4)	379 (27.2)	4.32 (2.50-7.47)	4.09 (2.36-7.10)
24-59 months	17 (6.9)	387 (27.8)	Ref.	Ref.
Child`s Gender				
Female	120 (49.0)	591 (42.5)	1.30 (0.99-1.71)	1.38 (1.04-1.83)
Male	125 (51.0)	801 (57.5)	Ref.	Ref.
Clinical symptoms child presented at the clinic/ enrollment visit				
Vomited ≥ 3 times/24hrs				
Yes	171 (69.8)	627 (45.0)	2.82 (2.10-3.78)	2.66 (1.98-3.58)
No	74 (30.2)	765 (55.0)	Ref.	Ref

‡Adjusted for variables in the model. Six variables were initially entered in the model, of which two (above) were associated with rotavirus positivity. The four variables dropped were child offered IV fluid, dehydration, maximum stool in 24 hours, and gender.

Table 17. Numerical GEMS-modified Vesikari score system for severity of diarrhea among rotavirus-positive and -negative children with non-dysenteric MSD, western Kenya, 31 January 2008–30 September 2012.

Child characteristics	Points assigned	Rotavirus-positive		Rotavirus-negative		p-value
	(N=17)	N=245		N=1,392		
		n	%	n	%	
Duration of diarrhea (days)						
1-4	1	221	90.2	1,247	89.6	0.954
5	2	14	5.7	85	6.1	
≥6	3	10	4.1	60	4.3	
Max no. diarrhea /24 hrs.						
3-6	2	167	68.2	1,059	76.1	0.010
≥7	3	78	31.8	333	23.9	
Vomited 3+ times/24 hrs.						
Yes	3	171	69.8	627	45.0	<0.001
No	0	74	30.2	765	55.0	
Fever †						
<37.0	0	82	33.5	550	39.5	<0.001
37.1-38.4	1	128	52.2	534	38.4	
38.5-38.9	2	17	6.9	112	8.1	
>=39	3	18	7.4	195	14.0	
Dehydration††						
Moderate/Severe‡‡	3	55	22.8	250	18.8	0.156
Mild‡	2	186	77.2	1,083	81.2	
Treatment						
Out-patient without IV fluid	0	198	80.8	1,215	87.3	0.023
Out-patient with IV fluid	1	10	4.1	43	3.1	
Hospitalization with or without IV fluid	2	37	15.1	134	9.6	0.013
Median Score †††	N/A	9 [IQR] 8-10		8 [IQR] 6-10		<0.001

†Denominator = 1,636. ††Denominator = 1,574. †††Median calculated for children without missing information (rotavirus-positive = 241; rotavirus-negative = 1,332). ‡A child was considered mildly dehydrated if two or more of the following were present: restless or irritable on arrival or admission; sunken eyes; thirsty; drank eagerly; skin pinch returns to normal slowly (one or two seconds). ‡‡A child was considered moderately to severely dehydrated if two or more of the following were present: lethargic or unconscious on arrival or admission; sunken eyes; drank poorly or unable to drink; skin pinch returns to normal very slowly (longer than two seconds).

5.4 Pre-Rotavirus Vaccine Epidemiology and Factors Associated with Intussusception-Related Deaths Among Children Under Five in Kenya (Study IV)

5.4.1 Background characteristics of study participants

The records of 305 patients treated for intussusception from 1 January 2002 to 31 December 2013 at the 12 leading referral hospitals in Kenya were screened for eligibility and enrollment (Figure 18). We found that approximately sixty percent of

patients under five treated for intussusception in those hospitals were originally referred to other hospitals, mainly district-level hospitals (Table 18).

A total of 280 (91.8%) of the 305 records screened for possible intussusception cases were included in our analysis, as shown in Figure 18. Most patients were infants. Our analysis showed that intussusception peaked at approximately six months of age and that disease occurrence declined with an increase in child age (Figure 19). A majority (40%) of intussusception cases were aged 6–11 months and were (67%) predominantly males (Table 19). Intussusception occurred throughout the year, without a clear seasonality pattern (Figure 20).

Table 18. Cases of intussusception retrospectively identified among pediatric patient records at 12 referral hospitals in Kenya, 2002–2013.

Hospital / Study Centre	Period that records were reviewed	Screened Children†		Eligible Children†		Referral from other district level hospital Yes n/N (%)††	
		(N=305)	(%)	(N=280)	(%)	(n=165)	58.9
Coast Provincial General Hospital	2002-2013	76	24.9	67	23.9	29	43.3
Kenyatta National Hospital	2008-2013	56	18.4	56	20.0	32	57.1
Moi Teaching and Referral Hospital	2009-2013	55	18.0	49	17.5	40	81.6
Nakuru Provincial General Hospital	2002-2013	40	13.1	40	14.3	19	47.5
Jaramogi Oginga OdingaTeaching and Referral Hospital	2009-2013	23	7.5	23	8.2	20	86.9
Gertrude's Children's Hospital	2009-2013	22	7.2	19	6.8	19	100
Kijabe Mission Hospital	2008-2013	11	3.6	9	3.2	2	22.2
Thika District Hospital	2003-2013	8	2.6	6	2.1	1	16.7
Kiambu District Hospital	2009-2013	5	1.6	3	1.1	0	0
Nyeri Provincial General Hospital	2010-2013	4	1.3	4	1.4	1	25.0
Embu Provincial General Hospital	2010-2013	3	1.0	3	1.1	2	66.7
Kakamega Provincial General Hospital	2009-2013	2	0.7	1	0.4	0	0
Year of consultation (Number of hospitals reporting data)-Eligible cases							
2002 (2 hospitals)	N/A	N/A		6	2.1	N/A	N/A
2003 (3 hospitals)	"	"		11	3.9	"	"
2004 (3 hospitals)	"	"		7	2.5	"	"
2005 (3 hospitals)	"	"		7	2.5	"	"
2006 (3 hospitals)	"	"		8	2.9	"	"
2007 (3 hospitals)	"	"		14	5.0	"	"
2008 (5 hospitals)	"	"		30	10.7	"	"
2009 (10 hospitals)	"	"		40	14.3	"	"
2010 (12 hospitals)	"	"		38	13.6	"	"
2011 (12 hospitals)	"	"		48	17.1	"	"
2012 (12 hospitals)	"	"		40	14.3	"	"
2013§ (12 hospitals)	"	"		31	11.1	"	"

Note: †Denominator is the sum from all sites, unless otherwise indicated. ††The percentages shown above are individual hospital proportions of eligible cases referred (i.e., "yes") to that site. §Data collected only from January through November 2013.

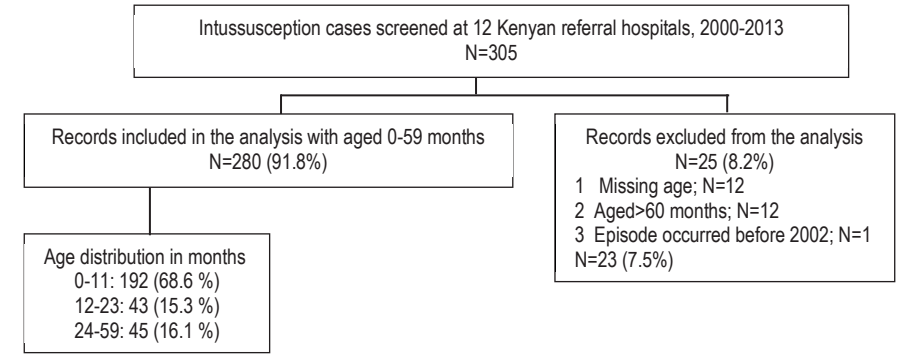

Figure 18. Flow diagram of retrospective intussusception cases identified among pediatric patient records presenting at selected Kenyan referral hospitals, 2002–2013.

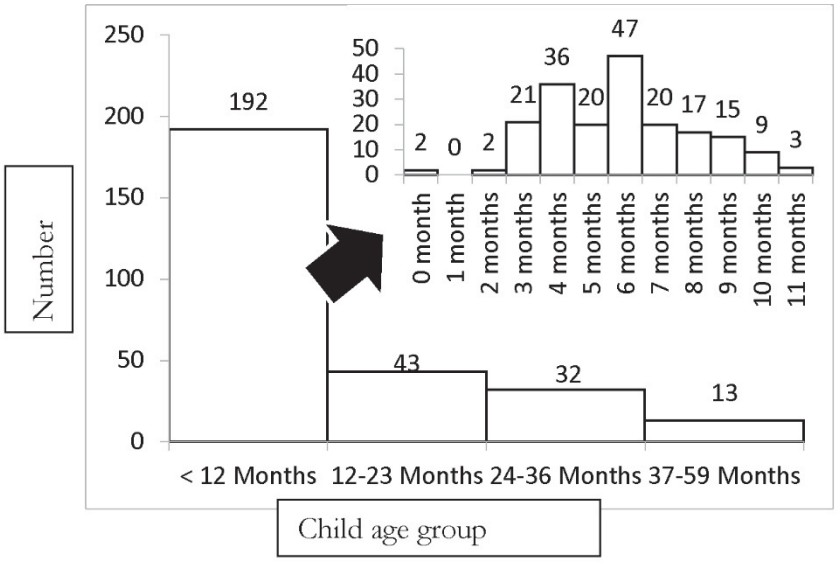

Figure 19. Number of intussusception cases by age (in months) among pediatric patients under 5 years old treated at 12 referral hospitals in Kenya (N = 280), 2002–2013.

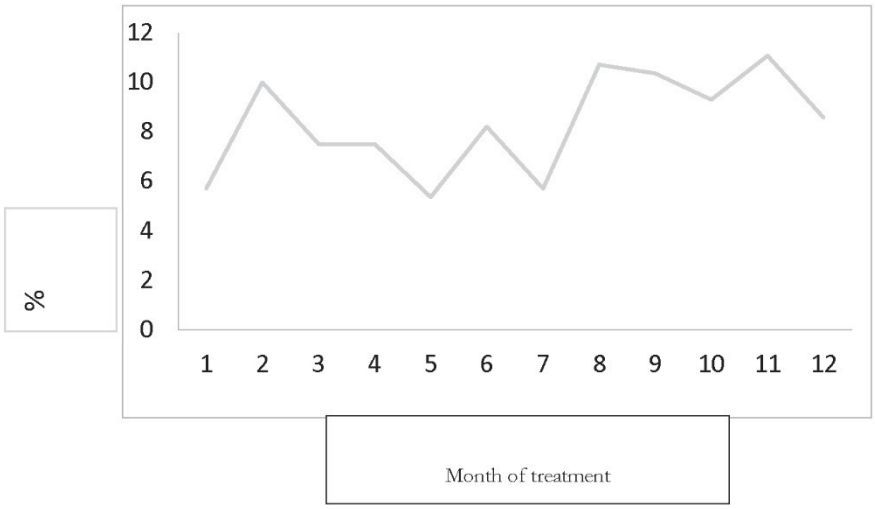

Figure 20. Distribution of intussusception cases by month of treatment among pediatric patients treated at the 12 referral hospitals in Kenya (N = 280), 2002–2013.

5.4.2 Clinical presentations in intussusception patients and care seeking

Most intussusception cases (75–88%) presented with vomiting, blood in stool or rectal bleeding, and abdominal distension (Table 19). As to seeking care, 3.7%, 16%, 33%, and 50% of patients sought care within 1 day, 2 days, 3 days, and 4 days after illness symptom onset, respectively (data not shown). The median number of days until seeking care was 3 (interquartile range: 2–6) days after illness onset. Further clinical features, diagnosis, treatment, and characteristics of the intussusception patients are detailed in Table 19.

5.4.3 Survival in intussusception patients by demographic and clinical characteristics

Eighteen (6.4%) patients died during hospitalization or on discharge after seeking care, most of whom (15, or 83%) were infants, generally aged 0–5 months. Compared with intussusception patients who survived, patients who died were more likely to be young infants, those for whom care was sought late after symptom onset, those who had a reported history of fever, those who had clinical fever on admission, and those who had bowel surgery. However, treatment

through manual reduction was inversely associated with fatal outcomes. The differences and factors associated with death among intussusception patients under 5 years old who were treated at the 12 leading referral hospitals in Kenya from 2002 to 2013, prior to rotavirus vaccine introduction, are shown in Table 19.

Table 19. Characteristics of children aged 0–59 months with intussusception who died vs. those who survived at the 12 referral hospitals in Kenya, 2002–2013.

Background Characteristics	All		Case fatality proportion, n/N (%)		Survived n/N (%)		P-value
Demographic characteristics	N=280 [N (%)]		(N=18)		(N=262)		
Child age in months							
0-5	81	28.9	9	50	72	27.4	0.195
6-11	11	39.6	6	33.3	105	40.1	
12-23	43	15.4	2	11.1	41	15.7	
24-59	45	16.1	1	5.6	44	16.8	
Median age of patients in months (IQR)	7.0 (5-14)		5.5 (4.0-9.0)		7.0 (5.0-14.0)		0.04
Gender††							
Male	186	66.7	11	61.1	175	67	0.611
Female	93	33.3	7	38.9	86	33	
Median days to seeking care (IQR)	3 (2-6)		5 (3-9)		3 (2-5)		0.04
Median days to death/ discharge upon recovery after admission (IQR)	5 (3-8)		2 (1-6)		6 (4-8)		0.01
Clinical features (% yes)							
Fever	177	63.2	17	94.4	160	61.4	<0.01
Temperature§							
< 37.0	38	17	1	6.2	37	18	0.01
37.0-38.4	125	56.1	5	31.2	120	58	
38.5-38.9	21	9.4	3	18.8	18	8.7	
≥ 39.0	39	17.5	7	43.8	32	15.5	
Vomiting	247	88.2	17	94.4	230	87.8	0.71
Diarrhea	209	74.6	13	72.2	196	74.8	0.78
Blood in stool	227	81.1	13	72.2	214	81.7	0.35
Abdominal Pain	178	63.6	10	55.6	168	64.1	0.46
Abdominal distension	210	75	16	88.9	194	74	0.26
Abdominal mass	111	39.6	5	27.8	106	40.5	0.33
Rectal mass	80	28.6	4	22.2	76	29	0.79
Type of Intussusception							
Ileocolic	132	47.1	10	55.6	122	46.6	0.76
Colocolic	40	14.3	5	27.8	35	13.4	
Ileo-ileal	22	7.9	2	11.1	20	7.6	
Diagnosis methods, ‡							
Ultra-Sound	91	32.5	10	55.6	81	30.9	0.04
Abdominal X-ray	152	54.3	14	77.8	138	52.7	<0.05
Treatment method (operative)							
Bowel resection	91	32.5	12	66.7	79	30.2	<0.01
Manual reduction	128	45.7	4	22.2	124	47.3	<0.05
Ileostomy	5	1.8	1	5.6	4	1.5	0.28
Treatment method (Non-operative)							
Air reduction	0	0	0	0	0	0	N/A
Contrast Fluid enema	5	1.8	0	0	5	1.9	1
Unknown treatment method	73	26.1	1	5.6	72	27.5	0.049

††One child's gender was missing. §N = 223. IQR = interquartile range, ‡Multiple diagnosis methods possible. CFR = Case fatality proportion.

6 DISCUSSION

In this chapter, the key findings from our studies are summarized. Next, the strengths and limitations of our studies are discussed, and our findings are compared with those from other studies and then interpreted. Finally, conclusions from our findings and practical implications for future research are presented.

6.1 Summary of Key Findings

Our finding that caretakers were less likely to seek healthcare outside the home for infants than for older children with diarrhea is important because severe AGE- and intussusception-related mortality are more likely in the younger group. Timely access to healthcare can lead to life-saving rehydration for diarrhea (Geldsetzer et al., 2014; WHO, 2006), and possible use of non-invasive interventions for treatment of intussusception (Mpabalwani *et al.*, 2017; Menke & Kahl, 2015). Our study also showed that fewer than half of children with diarrheal disease received care at a licensed healthcare facility and that a substantial proportion of children with diarrhea were given less food and drink than normal; only 23% were offered ORS at home. Moreover, caretakers who did not report looking for thirst as a sign of dehydration were less likely to seek care from a healthcare facility for a child's diarrheal illness.

However, sunken eyes and lethargy as symptoms during diarrheal illness were both associated with seeking care outside the home. Caretakers with formal education were more likely than those without it to seek care from a healthcare facility for a child's diarrhea and to give ORS. Children who were offered antimicrobial drugs and those who were not offered ORS at home for diarrheal illness were more likely to have care sought from a healthcare facility. Seeking care for MSD from a healthcare facility was most common for infants aged 6–11 months. Taken together, these observations suggest that deficiencies in the caretaker management of children's diarrhea illness at home could be associated with severe disease and adverse outcomes. These findings are particularly

important for infants— an age group that accounted for more than 70% of hospitalizations due to all-cause AGE and more than 60% of rotavirus infections among children with MSD in our study. Moreover, our study showed that infants accounted for more than 70% and 80% of all intussusception case-patients who were enrolled and died, respectively. Infants with rotavirus-associated MSD were twice as likely to be hospitalized as those with non-rotavirus MSD and tended to have more severe disease, as measured by GEMS-modified Vesikari scores. The intussusception case fatality rate was 6.4%. Mortality among intussusception patients was associated with late care seeking, presentation with fever, and undergoing bowel surgery. However, in assessing these outcomes, our study was unable to control for likely confounding factors, such as severity at presentation to care, as demonstrated by Chrsti and colleagues (Chisti et al., 2014).

6.2 Methodological Considerations

6.2.1.1 Strengths of the study

Studies I–III used reliable, age-specific population denominators from a well-updated HDSS (F. O. Odhiambo et al., 2012). Surveillance systems with accurate population denominators are necessary for estimating disease burden and evaluating the impact of interventions such as vaccines. Such HDSS platforms are rare in the developing world (WHO, 2005a; Baschieri *et al.*, 2019). Furthermore, due to its longitudinal nature, an HDSS has the additional advantage over other common study designs in tracking and monitoring the health indicators that could be relevant for estimating progress like the achievement of MDGs or SDGs as described from most of the low-middle-income countries where they exists (Arthur *et al.*, 2013; F. O. Odhiambo *et al.*, 2012; Kabudula *et al.*, 2017; Sankoh *et al.*, 2014; Sankoh, 2014). Our baseline and repeated HUAS (Study I) helped to characterize healthcare seeking in our catchment population. We first established baseline rates of diarrheal disease by using a comprehensive population-based study, followed by a short version of HUAS that supported conducting efficient hospital-based surveillance (Studies II and III). To our knowledge, this study is the first comprehensive, age-stratified, complete population-based healthcare utilization survey using a standard protocol. Furthermore, it was conducted over the longest time period in a well-defined population compared to similar studies in sub-Saharan Africa (Kenya, Mozambique, Mali, and The Gambia) and Asia (India,

Bangladesh, and Pakistan) before rotavirus vaccine introduction in these settings (Nasrin et al., 2013).

Our hospital-based rotavirus surveillance study (II) calculated population-based incidence rates of all-cause and rotavirus diarrhea hospitalizations and deaths. Reliable estimates of the proportion of children with all-cause and rotavirus diarrhea from the HDSS who were seen at the SHCs provided the basis for using a rate multiplier, as recommended by the WHO (WHO, 2008). The accurate age-specific assessment of the rotavirus disease burden before rotavirus vaccine introduction presented in our study provides a baseline for robust future assessment of long-term direct and indirect effects of the vaccination program in Kenya (WHO, 2008).

The hospital-based surveillance study design as applied in Studies II–IV provided detailed epidemiologic, seasonality, and risk factor data for rotavirus infection and intussusception-associated mortality. Another unique aspect of Study III was that most hospital-based studies lack a follow-up component to evaluate treatment outcomes. To obtain data beyond the acute period, we incorporated a 60-day follow-up home visit after enrollment to monitor illness outcomes beyond the acute phase.

The laboratory procedures used in hospital-based surveillance (Studies II and III) included using whole and fresh stool samples and avoiding the use of rectal swabs. Use of rectal swabs and other non-EIA methods to detect rotavirus has been discouraged since they have been associated with up to a 50% decrease in sensitivity of detecting rotavirus (WHO, 2002, , 2008). Furthermore, adoption of whole, fresh stool sample collection and the use of the ELISA method for testing rotavirus supports comparison of our findings to those from similar studies (WHO, 2002, , 2008).

Our studies incorporated WHO-recommended standard case definitions for diarrhea, MSD, and intussusception (WHO, 2005c, , 2006; Bines, Liem, Justice, Son, Carlin *et al.*, 2006). Use of standard case definitions as recommended by the WHO (WHO, 2008) enhanced data quality and reliability and enabled comparison of our findings with those from other settings across the world. Furthermore, this effort will ensure effective comparison of disease burden before and after rotavirus vaccine introduction in Kenya when assessing possible vaccine impact. Our studies provide high-quality baseline data collected over an extended period of time (a range of 4–10 years) before rotavirus vaccine introduction in Kenya. These data account for seasonal variations and cover children aged 0–59 months. Finally, our studies contribute to fulfilling the call by WHO and Gavi, the Vaccine Alliance for

timely and quality pre-vaccine baseline surveillance data. This information could form the basis for monitoring systems to assess vaccine impact and safety that are needed to inform post-vaccine era decisions, as detailed elsewhere (WHO, 2013a; Patel & Parashar, 2009; WHO, 2008).

6.2.1.2 Limitations of the study

Our HUAS relied on caretakers' recall of the occurrence of a child's diarrhea episode during the preceding two-week period. In classifying diarrhea as MSD, we assumed that caretakers were sufficiently familiar with the signs and symptoms of diarrhea, an assumption that may have resulted in misclassification. Many rotavirus-associated fatalities are likely associated with delay in healthcare seeking (WHO, 2013), as our study also showed. Furthermore, the lack of a qualitative component in the study prevented a deeper understanding of factors associated with diarrhea management and care seeking, as detailed in Table 20. The VA method used in Study II relies on signs, symptoms, and circumstances prior to death to assign a cause of death. As applied in our study, the VA method is thus subject to misclassification error and may have led to over- or underestimation of diarrhea-associated mortality (WHO, 2005d).

Our methodology for estimating diarrhea deaths attributable to rotavirus was based on three assumptions: (i) in the absence of treatment, the hospitalized severe cases would not have survived; (ii) the treatment effect on survival of severe diarrhea is equal for rotavirus and non-rotavirus diarrhea; and (iii) the rotavirus-attributable fractions of severe diarrhea observed in the sentinel hospital are generalizable to the source population within each age stratum (WHO, 2005d). Interpreting these estimates with caution is important since such assumptions may affect the validity and generalizability of the estimates to the general population. However, there are currently no reliable data for the direct measurement of the proportion of diarrhea deaths that are attributable to rotavirus (WHO, 2005d, , 2008), especially in the high disease burden regions that are largely found in low- and middle-income countries (Tate, Burton *et al.*, 2016). We believe that our methodology is reasonably robust and applicable as recommended by the WHO (WHO, 2005d, , 2008). Moreover, previous observations suggest that patients seeking care from our surveillance hospital reasonably represent the HDSS area, which was our source population (Khagayi et al., 2014).

The GEMS-modified Vesikari score system in Study III should be interpreted with caution. The information on the duration of vomiting and the maximum

number of vomiting episodes over a 24-hour period was not collected as a continuous variable but a categorical one. Although we resolved this by modifying the Vesikari score based on a reconstructed 17-point scoring system, the incomplete capture of information did not allow us to calculate traditional full 20-point Vesikari scores (Ruuska & Vesikari, 1990).

Our hospital-based rotavirus diarrhea surveillance (Study III) nested in the GEMS was not originally equipped to assess risk factors for rotavirus infection, which may have influenced our results one way or the other. As described elsewhere (WHO, 2013b), approximately 90% of all rotavirus-associated fatalities occur in low- and middle-income countries, mostly in Africa. As suggested by our HUAS (Study I), most of our enrolled cases in Studies II–IV may have had illnesses that were severe enough to worry their caretakers into seeking care from healthcare facilities. Furthermore, our intussusception surveillance (Study IV) may also have underreported baseline rates of the disease due to the possibility of delays and low care-seeking patterns that are commonly seen in Kenya. These observations suggest the possibility that some children may have died without seeking hospital care for MSD or intussusception at the sites under surveillance. Hospital-based studies tend to capture information on the most severe illnesses among patients who have access to healthcare—a characteristic that could prompt questions about generalizability of Studies II–IV (Crump *et al.*, 2008).

6.3 Comparison of Main Results with Previous Studies and Interpretation of the Findings

6.3.1 Comparison of Main Results with Previous Studies

The inappropriate caretaker practices in home management of childhood diarrhea that could lead to poor outcomes, such as not giving ORS and decreasing fluid and food intake, are vitally important. Considered in addition to the observed delays in seeking care for severe diarrheal illness, caretakers who do not know the classic symptoms of intussusception, as we observed in our study, remain a pressing problem in Kenya (KDHS, 2015, , 2010; Kuremu, 2004). These findings are similar to those reported by previous studies conducted in rural and urban Kenya (Ram *et al.*, 2008; Breiman *et al.*, 2011) and are not unlike other findings from sub-Saharan Africa showing that diarrhea is often inadequately managed at home in these

settings (Forsberg *et al.*, 2007; Ram *et al.*, 2008). Furthermore, other studies have shown that caretaker delays in seeking care for a child's acute diarrhea (Nasrin et al., 2013) and intussusception (Mpabalwani *et al.*, 2017) are common problems in many settings in sub-Saharan Africa.

On the other hand, over-prescription of antimicrobial drugs and their inappropriate use by caretakers at home before seeking care has previously been reported in many studies from Kenya (Shapiro *et al.*, 2001; Brooks *et al.*, 2006; Njuguna *et al.*, 2013; F. Odhiambo *et al.*, 2014). Our finding that 14% of children who reached a healthcare facility had already been given a non-prescribed antimicrobial drug is comparable with those reports. Inappropriate use of antimicrobials is associated with emergence of resistance: a previous study in our study setting found that approximately 70% of children under five visiting healthcare facilities for diarrhea episodes were prescribed antimicrobial drugs, regardless of etiology (Beatty et al., 2009). Moreover, up to 100% of clinicians in Kenya reportedly do not routinely use laboratory results to guide diarrhea case management (F. Odhiambo et al., 2014), despite recommendations to that effect (WHO, 2005b).

The findings of another qualitative study conducted in our HUAS study area suggest that most caretakers of children who die from diarrhea-related complications visited a traditional healer first and returned to them repeatedly, only visiting a healthcare facility later, after the child`s condition became more severe (Garg *et al.*, 2001). When caretakers did not report barriers to care seeking, the median duration from symptom onset to seeking care was two days, regardless of whether the source of care was traditional or a healthcare facility (Garg *et al.*, 2001). In other parts of Kenya, most children under five with diarrhea had care sought late from a healthcare facility and had more severe symptoms upon reaching the facility. In the same study, about half the caretakers cited a lack of money as the reason for delay in care seeking (Breiman et al., 2011). A study that applied complementary (qualitative and quantitative) methodology in Pakistan found that caretaker delays in seeking care and refusal of admission for children under five with dehydrating diarrhea were associated with death (Qamar et al., 2016).

Findings from intensive qualitative studies involving focus group discussions and in-depth interviews with caretakers of children with diarrhea in sub-Saharan Africa showed that there are many factors that could influence care seeking for childhood diarrhea. These include diverse cultural beliefs (especially regarding traditional medicine), perceived illness severity, and the efficacy and cost of treatment (Cunnama & Honda, 2016; Scott *et al.*, 2014) including caretaker

concerns over frequent drug stock-outs and the distance to healthcare facilities (Bedford & Sharkey, 2014). Another qualitative study in Ethiopia showed that mothers stated a preference for using the health facility, but they were unable to do so because of objections or alternative care-seeking preferences of gatekeepers, often mothers-in-law and husbands (Shaw et al., 2016). On the other hand, a qualitative intervention study observed an increase in healthcare seeking after intensive community mobilization and use of community health worker peer support groups (Langston et al., 2014). These studies demonstrate the value of undertaking qualitative studies when more detailed data on factors influencing healthcare seeking may be warranted (see Table 20), due to the common limitations inherent in using quantitative data to study factors associated with care seeking. However, these observations reaffirm the quantitative findings from systematic reviews (Geldsetzer et al., 2014) that caretakers' poor recognition of symptoms, inappropriate home management, and delays in seeking care for children with severe disease in low- and middle-income countries continue to pose major challenges for child survival efforts in these settings. Taken together, all these observations suggest significant barriers to compliance with the current WHO recommendations for diarrhea management in Kenya and similar settings in Africa (WHO, 2005c, , 2006, , 2018a).

Table 20. Factors associated with seeking care for diarrhea among children under five: summary of evidence from qualitative observational studies.

Reference, Country, World Region	Age of study subjects	Study design	Outcomes assessed	Main findings
(Colvin et al., 2013) sub-Sahara Africa	Children < 5years	Meta-analysis of literature reviews on qualitative data	Qualitative evidence on the factors influencing household recognition and response to child diarrhea, pneumonia and malaria in sub-Saharan Africa	Factors observed to influence household care seeking include: cultural beliefs and illness perceptions; perceived illness severity and efficacy of treatment; rural location, gender, household income and cost of treatment
(Scott *et al.*, 2014), Sierra Leone, west Africa	Children < 5years	A rapid community-based ethnographic assessment	Qualitative factors associated influencing caretakers healthcare seeking patterns	When a child becomes sick, households work within their geographic, social and financial context to seek care from sources including home treatment, herbalists, religious healers, drug peddlers and facility-based providers.
(Bedford & Sharkey, 2014), Kenya, Nigeria and Niger, Sub-Saharan Africa	Children < 5years	Multi-country qualitative approach using thematic in-depth interviews and FGDs of caretakers and health care service providers	To determine the barriers caregivers face in accessing treatment for these conditions; to identify local solutions that facilitate more timely access to treatment; and to present these findings as a platform from which to develop context-specific strategies to improve care-seeking for childhood illness	Despite that, a national policy exists that provided free treatment for children under 5 years at any point of delivery in all government health facilities, caretakers claimed no knowledge about that, hence did not find that policy as motivator to seeking care. Belief in traditional medicine, unaffordable cost of treatment, frequent drug stock-outs, distance to health care facility
(Cunnama & Honda, 2016), South Africa	Children < 5years	Qualitative FGDs with mothers of children < 5 year, healthcare service providers, community members	To qualitatively examine the beliefs surrounding and perceived quality of healthcare accessed for children's acute diarrhea	Seeking healthcare from traditional practitioners was found to be deeply ingrained in the culture of the society. People's beliefs about the causative agents of diarrhea are at the heart of seeking care from traditional practitioners, often in order to treat supposed supernatural causes. A combination of care-types is acceptable to the community, but not necessarily to modern practitioners, who are concerned about the inclusion of unknown ingredients and harmful substances in some traditional medicines, which could be toxic to children.
(Langston et al., 2014), Rwanda	Children < 5years	Qualitative and quantitative analysis of Demographic and Health Surveys in 6 districts in Rwanda	To evaluate factors and strategies that can improve healthcare seeking	Intensive supervised and monitoring of community Health Worker peer support groups and community mobilization was observed to increase healthcare seeking significantly
(Shaw et al., 2016), Ethiopia	Children < 5years	Qualitative using rapid ethnographic approach	To elicit a country-wide perceptions and experiences of caregivers to better understand reasons for low utilization of the integrated community case management of childhood illness strategy by Health extension workers to treat children in rural health posts	Although many mothers stated a preference for using the health post, they unable to do so due to objections or alternative care-seeking preferences of gatekeepers, often mothers-in-law and husbands

In our study, the highest morbidity and mortality associated with all-cause diarrhea and rotavirus-specific diarrhea was among infants aged 6–11 months. The risk of rotavirus infection was highest among infants and decreased in older children. Rotavirus was also associated with more severe dehydrating diarrhea than non-rotavirus infection. These findings are consistent with other pre-rotavirus vaccine

data from studies in sub-Saharan Africa, as well as other settings in Asia and South America—regions that are known to experience the highest diarrhea disease burdens in the world (Mohan *et al.*, 2017; Kotloff *et al.*, 2013; UNICEF, 2017).

Our study found that before rotavirus vaccine introduction in Kenya, children under one year of age experienced the greatest burden of intussusception-associated morbidity and mortality, and that the disease peaked at four to seven months of age. These findings are similar to observations from other settings in Africa showing intussusception peaks between three and nine months (Steele *et al.*, 2012; Ngendahayo *et al.*, 2014) and a literature review of observational intussusception studies conducted in sub-Saharan Africa, which also found that the peak age for intussusception was 5–8 months (Mpabalwani *et al.*, 2017). In addition, according to global estimates, two-thirds of intussusception cases occur among children under a year old with a peak age of five to seven months (Jiang et al., 2013). Intussusception without a history of vaccination has been shown to be rare in the first three months of life in Bangladesh (Zaman et al., 2009) and globally (Jiang et al., 2013); it has been reported to begin occurring between two and four months of age in sub-Saharan Africa (Mpabalwani *et al.*, 2017).

Knowledge of clinical symptoms associated with intussusception in a setting like Kenya is important to ensure awareness among caretakers of the need for prompt care seeking (Escolano *et al.*, 2015) and can assist local healthcare professionals in prioritizing potential cases for urgent treatment or referral (Bines *et al.*, 2004). Most observational studies conducted in Asia (Cui *et al.*, 2016; Waseem & Rosenberg, 2008; Yousafzai *et al.*, 2017; Yap Shiyi & Ganapathy, 2017), Europe (Huppertz et al., 2006), and sub-Saharan Africa (Carneiro & Kisusi, 2004) has shown that vomiting, abdominal pain, rectal bleeding, blood in stool, and abdominal mass and tenderness are the predominant traditional symptoms associated with childhood intussusception in almost all these areas (Waseem & Rosenberg, 2008; Klein *et al.*, 2004). Consistent with these observations, our study showed that 71–92% of intussusception patients presented with at least one of the following: vomiting, diarrhea, blood in stool, and abdominal distension accompanied by fever. Taking into consideration that there are some existing arguments that these signs are mostly associated with late presentation of intussusception (Levinson *et al.*, 2019), these findings—together with an observed average duration of three days from symptom onset to healthcare contact in our study—may also suggest late presentation. These findings may help explain frequent surgery through intestinal resection, as further observed in our study. Other research has also shown that symptoms lasting more than a day before

seeking care for intussusception are associated with increased likelihood of surgery, particularly intestinal resection (Meier *et al.*, 1996; Ekenze *et al.*, 2010; Carneiro & Kisusi, 2004; Kaiser *et al.*, 2007).

Although our study did not assess surgery outcomes, its use may be advisable when radiological reduction is contraindicated (DiFiore, 1999). However, despite its well-documented association with poor prognosis and increased mortality, surgery continues to be the most common method of intussusception management in sub-Saharan Africa (Jiang *et al.*, 2013; Mpabalwani *et al.*, 2017). On the other hand, recent studies from China (N. Liu et al., 2018) and elsewhere in Asia (Yap Shiyi & Ganapathy, 2017), where more than 70% of intussusception patients are managed through air enema, have reported a case-fatality rate close to 0%. Furthermore, a recent systematic literature review of global estimates showed that mortality in intussusception cases in sub-Saharan Africa continues to be higher at 1 death per 10 hospital admissions than in the rest of the world, where it ranges from 1 death per 100 to 1 death per 200 hospital admissions (Clark et al., 2019).

6.3.2 Interpretation of the Findings

Our household survey data indicated that a mother's level of education has an important influence on the likelihood of a child's being offered ORS at home and seeking care from a healthcare facility. A similar observation that children of mothers who lack education are 2.6 times more likely to die before their fifth birthday than children of mothers with secondary or higher education has recently been published (UNICEF, 2018). Furthermore, data presented in this thesis showed that infants accounted for; >70% of hospitalizations due to all-cause AGE, >60% of rotavirus infections among children with MSD, and >70% and >80% of all intussusception case-patients who were enrolled and died respectively. Moreover, infants with rotavirus associated MSD were twice more likely to be hospitalized than those with non-rotavirus MSD and tended to have more severe disease as measured by Vesikari scores. These findings reaffirm that infants are at increased risk of diarrhea and intussusception morbidity and associated mortality ,and that their delay in seeking care from healthcare facilities can result in severe dehydration— the most critical life-threatening condition.(WHO, 2018a; KDHS, 2010; WHO, 2013b). Furthermore, these findings reaffirm rotavirus as a leading pathogen associated with diarrheal disease leading to hospitalization among

children under five years old in Kenya as also observed from other similar settings before rotavirus vaccine introduction (WHO, 2005c; Kotloff *et al.*, 2013; Mohan *et al.*, 2017; WHO, 2013b).

As confirmed by our data, the burden of acute diarrhea and rotavirus disease is usually high in low- and middle-income countries (Webb & Starr, 2005; WHO, 2018b). In these enteric pathogen-endemic settings, infants receive passive protection from trans-placental and breast milk antibodies for the first six months of life (Walker *et al.*, 2013). As this passive immunity wanes, the child's first exposure to a rotavirus infection often results in severe disease. Subsequent infections are generally milder, and the illness is less likely to result in severe dehydration, admission to hospital, and death, according to data from recent studies conducted in countries with high disease burdens (Mohan *et al.*, 2017; Kotloff *et al.*, 2013). Our study finding that the case-fatality proportion among children hospitalized with rotavirus diarrhea was not significantly different from children with non-rotavirus diarrhea suggests that rotavirus diarrhea may not be associated with increased mortality in hospital-based studies, as described elsewhere (WHO, 2005c). This finding supports the assumption that prompt care seeking for rotavirus diarrhea from a healthcare facility enables access to appropriate rehydration, reducing the risk of death (WHO, 2005c).

The reasons for some caretakers preferring use of antimicrobials instead of ORT for a child with diarrhea are complex, according to qualitative studies (see Table 20), and data that might answer the question are limited, so more research may be warranted. Furthermore, this practice may increase the cost and duration of treatment, contribute to treatment failure, and waste household and national resources, as observed from other quantitative data from Kenya (Sang *et al.*, 2012; Beatty *et al.*, 2009; F. Odhiambo *et al.*, 2014). These observations suggest that more rigorous policies and strategies governing the use of antimicrobial drugs in Kenya for treatment of diarrhea diseases are urgently needed.

The common use of intestinal resection for treatment of intussusception and its association with high case-fatality as observed in our current study may be related to the delay in seeking care and slow referral in Kenya (KMoH, 2014) . Such delay in presentation with intussusception increases the chance for bowel rupture, as commonly observed from excessive pressure (Mercer & Carpenter, 1982), limiting chances of reduction of the intussusception through non-operative procedure. Instead such delay necessitates surgery , particularly in infants who have higher risk of perforation as observed in our current study consistent with data from other

settings mainly from sub-Saharan Africa (Kincaid *et al.*, 2004; Ekenze *et al.*, 2010; Kruatrachue *et al.*, 2011; Carneiro & Kisusi, 2004)

It is worth noting that even studies in countries where case-fatality rates among children with intussusception remain below 1% have shown that success rates with non-operative treatment also decrease with increases in the amount of time from symptom onset to care seeking for appropriate intervention (Jenke *et al.*, 2011; Carneiro & Kisusi, 2004; Kruatrachue *et al.*, 2011). These observations suggest that prompt care seeking for childhood intussusception—as for diarrhea—may be a key factor in treatment outcome and child survival.

In summary, the sub-optimal caretaker practices when their children had diarrhea and its associated consequences as demonstrated from data presented from these studies demonstrate that severe diarrhea are important problems during pre-rotavirus vaccine introduction era in Kenya and are mainly due to; poor recognition of danger signs and delay in presentation for appropriate management of these illnesses.

6.4 Public Health Implications of the Research

From the program perspective, our HUAS findings suggest that improving caretaker knowledge of home management of diarrhea could prevent progression of the illness and reduce severe adverse outcomes. Our findings also suggest that community education is needed to ensure that parents provide appropriate food and drink and avoid unnecessary, unprescribed antimicrobials for children—particularly infants—with diarrhea. Engaging complementary qualitative and quantitative research methods may be useful in generating data that could help reveal in greater detail the factors associated with caretakers' low use of ORT and care-seeking patterns in this setting after vaccine introduction. Furthermore, creating awareness in parents and mobilization of healthcare workers and surgeons to recognize signs and symptoms of intussusception could help improve early care seeking and prompt decisions for appropriate referral for, diagnosis of, and treatment of intussusception in Kenya. Such efforts could lead to better outcomes, especially with possible frequent use of alternative non-operative approaches that have been shown to be associated with fewer or even no fatalities in other settings (Jiang et al., 2013; N. Liu et al., 2018). From the research perspective, the data presented from these studies could provide the basis for evaluating future national prevention and treatment guidelines for all-cause and rotavirus diarrhea and

intussusception among children under five years old in Kenya. Moreover, our study findings support the need for continued surveillance for both AGE- and rotavirus-specific diarrhea to support measuring the impact of introducing the rotavirus vaccine in Kenya. The existing HDSS platforms, including rotavirus and intussusception disease surveillance networks in Kenya and other locations in sub-Saharan Africa as described in this thesis, may present a rare opportunity for investigating the etiology of intussusception and post-vaccine introduction changes in the diarrhea landscape among children under five. Furthermore, similar platforms and surveillance networks could offer powerful data to appraise and prioritize future needs; they could even measure the impact of other vaccines, such those for norovirus and even *Shigella*, targeted at reducing further childhood enteric disease in such settings.

Future strategies, policies, and interventions to reduce childhood diarrheal disease should take into consideration that the current generation of caretakers in Kenya (and perhaps similar settings) are not familiar with the critical importance of appropriate home management of diarrhea, especially for infants who may be at the highest risk of poor outcomes. Therefore, future research and intervention programs that target reductions in the morbidity and mortality associated with childhood diarrheal disease may need to step up efforts to address caretaker knowledge gaps around the lack of ORT use and poor recognition of the danger signs of severe disease. The studies presented in this thesis have demonstrated that estimates of the proportion of children with diarrheal disease for whom care was sought at the SHCs provide a basis for using a rate multiplier to adjust incidence rates to account for cases that may have been missed in the hospital surveillance methodology. This methodology could be applicable in future studies looking at the post-rotavirus vaccine disease burden to account for children not seeking care due to the inherent factors observed in our current study and those that may apply in other similar settings. Although it remains beyond the scope of our current studies, stool samples from our hospital-based surveillance offer the potential opportunity for analysis for additional pathogens in efforts to look for co-infections and their contribution to rotavirus-associated disease including rotavirus genotype distribution. Similarly, future studies may be developed to assess nutritional constituents that limit or exacerbate disease. Moreover, given the recent advances in understanding the human microbiome, future studies may need to investigate its contribution to clinical outcome. Collectively, these mechanistic studies may also indicate which factors contribute to vaccine efficacy in Kenya.

Finally, the baseline data from studies presented in this thesis could be used to support evaluation of the impact and safety of rotavirus vaccine introduction in Kenya in several ways. For example, a comparison of the proportion of stool samples from our hospital-based surveillance system that are rotavirus-positive and the use of Vesikari score analysis from rotavirus cases before and after vaccine introduction could provide a better understanding of any possible short- or long-term decline in rotavirus disease, changes in seasonality, and disease severity in Kenya, as demonstrated by Tate and colleagues (Tate, Patel *et al.*, 2016). Moreover, regular census home visits and surveillance platforms as described in this thesis can provide opportunities to gather age-specific data on diarrhea, healthcare seeking, nutrition, and child survival variables that can be linked to vaccination data confirmed from either caregiver-held child health cards or hospital vaccination registers and causes of death ascertained by VA. Such a database could then be used to estimate trends in morbidity and vaccine impact on all-cause and rotavirus-specific diarrhea before and after vaccine introduction, as further demonstrated elsewhere (WHO, 2008). Similarly, intussusception rates before and after rotavirus vaccine introduction could be evaluated as already described by Tate and colleagues (Tate, Yen *et al.*, 2016), and the association between the vaccine and intussusception could also be assessed and monitored further using the case-series approach as further described (Tate & Parashar, 2019).

7 CONCLUSIONS

Enteric viruses account for approximately 70% of episodes of acute infectious diarrhea in children under five worldwide. Rotavirus has been shown to be the leading cause of severe AGE before rotavirus vaccine introduction almost everywhere in the world. The work described in this thesis contributes to the understanding of the epidemiology and burden of diarrhea illness and provides baseline information on healthcare seeking, incidence, hospitalizations, and complications associated with all-cause and rotavirus-specific diarrhea and intussusception among children under five before rotavirus vaccine introduction in Kenya.

The four main research questions we address in this thesis are as follows:

1. What are the factors associated with (i) home management of childhood diarrhea and (ii) caretakers' healthcare seeking for a child's diarrheal illness among children under five from a healthcare facility located in a well-defined population?

The results presented in this thesis demonstrate that caretakers' perceptions and knowledge of diarrhea, including their educational level, may influence their decisions regarding management of and care-seeking behaviors for their child`s diarrheal illness. We also found that a child's age, clinical presentation, severity of diarrhea episode, and mother's education were all independent factors that influenced caretakers' decisions on illness management options and seeking care outside the home at a healthcare facility.

2. (i) What are the age-specific population-based incidence rates for hospitalization and death due to all-cause and rotavirus-specific diarrhea among children under five, and (ii) which age group has the highest incidence rates in a setting with a censused population?

Our results showed that adjusted population-based incidence rates for hospitalization and deaths due to AGE and RVAGE among children under five were high in the study setting. Our data showed that infants had the highest incidence rates for hospitalizations and death compared with children aged 12–23 and 24–59 months. Most important, even among the infant age group, both hospitalization and death rates were highest in infants aged 6 to 11 months.

3. What are the factors associated with (i) the risk of rotavirus infection and (ii) the severity of rotavirus disease among children under five seeking care for non-dysenteric MSD diarrhea from healthcare facility settings located within a population whose demographic characteristics are well defined?

Our results showed that independent factors associated with rotavirus infection were age (with risk decreasing as age increases) and vomiting. Furthermore, hospitalizations were more commonly observed among MSD patients under a year old who were rotavirus-positive versus -negative and among all rotavirus-positive versus -negative, regardless of age—an observation that was not biased since the clinicians who admitted these children were blinded of their rotavirus infection status. Our study demonstrated that rotavirus MSD presented with significantly higher median GEMS-modified Vesikari scores than non-rotavirus MSD; it was further characterized by clinical presentation of vomiting and maximum number of stools within 24 hours, including treatment with IV fluid, which were all associated with rotavirus compared to non-rotavirus MSD when assessed using the GEMS modified Vesikari score system.

4. What are the epidemiology and factors associated with death among intussusception patients under five treated at referral hospitals in Kenya before rotavirus vaccine introduction?

Our results showed that common signs of intussusception included diarrhea, blood in stool, abdominal distension, and vomiting, which were reported in more than 70% of intussusception cases treated at the 12 referral hospitals during the 2002–2013 period. Compared with intussusception patients who survived those who died were more likely to be young infants, to have had care sought late after symptom onset, to have a history of fever on admission, and to have been treated through bowel surgery.

In summary, the results presented in this thesis demonstrate that before rotavirus vaccine introduction in Kenya, children and specifically infants aged six to eleven months had the greatest burden of AGE-, RVAGE-, and intussusception-associated hospitalization and death. The findings of this thesis offer powerful support of the KMoH's decision to introduce the rotavirus vaccine into the Kenyan public immunization program in July 2014, following the two-dose schedule at six and ten weeks of age as recommended by the WHO (WHO, 2013b), before peak disease incidence in terms of age. While the benefits of rotavirus vaccines have been documented in other African countries like Ghana (Armah et al., 2016) and South Africa (Groome et al., 2014), the population-level benefits of these vaccines are yet to be demonstrated in Kenya. Furtermore, evaluation of the impact of interventions such as rotavirus vaccine using hospital-based studies without a defined source population, as described recently by Wandera and colleagues (Wandera *et al.*, 2018; Wandera *et al.*, 2017), renders such findings limited in terms of their generalizability beyond the hospital study population. This dissertation has demonstrated that household surveys for diseases such as diarrhea, when complemented with active sentinel surveillance studies, can provide useful data to guide the interpretation of future changes in the epidemiology, seasonality, severity, risk factors, hospitalization, and mortality incidence rates associated with all-cause and rotavirus-specific diarrhea following rotavirus vaccine introduction in Kenya.

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PUBLICATION I

Health care-seeking behavior during childhood diarrheal illness: Results of health care utilization and attitudes surveys of caretakers in western Kenya, 2007-2010

Omore R, O'Reilly CE, Williamson J, Moke F, Were V, Farag TH, van Eijk AM, Kotloff KL, Levine MM, Obor D, Odhiambo F, Vulule J, Laserson KF, Mintz ED, Breiman RF.

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Health-Seeking Behavior During Childhood Diarrheal Illness: Results of Healthcare Use and Attitude Surveys of Caretakers in Western Kenya, 2007–2010

Richard Omore, Ciara E. O'Reilly, John Williamson, Fenny Moke, Vincent Were, Tamer H. Farag, Anna Maria van Eijk, Karen L. Kotloff, Myron M. Levine, David Obor, Frank Odhiambo, John Vulule, Kayla F. Laserson, Eric D. Mintz, and Robert F. Breiman*

Kenya Medical Research Institute/Centers for Disease Control and Prevention, Kisumu, Kenya; Centre for Global Health Research, Kenya Medical Research Institute, Kisumu, Kenya; Division of Foodborne, Waterborne and Environmental Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; University of Maryland, School of Medicine, Center for Vaccine Development, Baltimore, Maryland; Liverpool School of Tropical Medicine, Liverpool, United Kingdom; Centers for Disease Control and Prevention–Kenya, Nairobi, Kenya

Abstract. We interviewed caretakers of 1,043 children < 5 years old in a baseline cross-sectional survey (April to May 2007) and > 20,000 children on five separate subsequent occasions (May of 2009 to December 31, 2010) to assess healthcare seeking patterns for diarrhea. Diarrhea prevalence during the preceding 2 weeks ranged from 26% at baseline to 4–11% during 2009–2010. Caretakers were less likely to seek healthcare outside the home for infants (versus older children) with diarrhea (adjusted odds ratio [aOR] = 0.33, confidence interval [CI] = 0.12–0.87). Caretakers of children with reduced food intake (aOR = 3.42, CI = 1.37–8.53) and sunken eyes during their diarrheal episode were more likely to seek care outside home (aOR = 4.76, CI = 1.13–8.89). Caretakers with formal education were more likely to provide oral rehydration solution (aOR = 3.01, CI = 1.41–6.42) and visit a healthcare facility (aOR = 3.32, CI = 1.56–7.07). Studies calculating diarrheal incidence and healthcare seeking should account for seasonal trends. Improving caretakers' knowledge of home management could prevent severe diarrhea.

INTRODUCTION

Diarrhea causes an estimated 1.87 million deaths among children < 5 years old annually, representing ~19% of all child deaths[1]; 78% of the deaths occur in Africa and Asia.[1] Recognizing the potential for dehydrating diarrheal illness to rapidly progress to death led to the introduction of oral rehydration solutions as the cornerstone of life-saving treatment in 1979.[2] Early recognition of dehydration, home use of oral rehydration solutions (ORSs), increased fluids and continued feeding, promotion of breastfeeding, and timely medical attention for children with dehydration and diarrhea are important determinants for reducing childhood deaths from diarrhea.[3] Few studies have evaluated patterns of healthcare use and home rehydration for young children with diarrhea in Kenya.[4–6] As part of a multicenter, case-control study of acute diarrhea in children 0–59 months of age called the Global Enteric Multicenter Study (GEMS),[7] we conducted a one-time comprehensive cross-sectional Healthcare Utilization and Attitudes Survey (HUAS) in 2007 followed by five additional abbreviated surveys from May of 2009 to December 31, 2010. The surveys were administered to caretakers of young children residing in western Kenya within the Health and Demographic Surveillance System (HDSS) area operated through collaboration between the Kenya Medical Research Institute and US Centers for Disease Control and Prevention (KEMRI/CDC). The baseline comprehensive HUAS was designed to estimate diarrhea prevalence and examine caretakers' knowledge, attitudes, and healthcare-seeking behaviors for children with diarrhea before the GEMS case-control study. The abbreviated surveys were carried out to provide additional information from different seasons and over time.[8] The HUAS-lite information allows adjusted attributable fraction data for individual pathogens and moderate-to-severe diarrhea (MSD) incidence rates from sentinel health facilities to be extrapolated to the entire HDSS population.[9]

METHODS AND MATERIALS

Study area and study population. The KEMRI/CDC began implementing the HDSS in western Kenya in 2001.[10,11] The HUAS and the five abbreviated surveys (called HUAS-lite surveys) were conducted in Asembo and Gem areas, which are part of the HDSS study area, representing an area of ~500 km^2 and a population of ~135,000 persons (population density ~300 persons/km^2), about 50–65 km west of Kisumu city (Figure 1). The altitude is about 1,100 m, average monthly temperature is 24.5°C, and annual rainfall is 1,358 mm.[12] Rainy seasons generally occur in March to May and October to November.[10,11,13] Residents, predominantly of the Luo ethnic group,[14] earn their living through small-scale business, farming, and fishing.[15] The main source of cooking fuel is firewood,[12] and the main source for drinking water is Lake Victoria, streams, and rivers.[14] This region reports the highest adult human immunodeficiency virus (HIV) prevalence rates (approximately 15%) in Kenya.[16,17] Malaria transmission is high and holoendemic.[10,18] In 2007, 20,853 children < 5 years old (53% female) resided in 217 villages within the Asembo and Gem HDSS areas.

Definitions. A resident of the HDSS area was defined as a person who has lived in the HDSS area for at least 4 consecutive months or a newborn child of such a person.

Diarrhea was defined as more than or equal to three loose stools within the previous 24 hours.

MSD was defined as diarrhea with one or more of the following characteristics: sunken eyes, loss of skin turgor, dysentery (blood in stool), receipt of intravenous rehydration, or required hospitalization.

Less severe diarrhea (LSD) was defined as diarrhea with absence of any characteristic of MSD (above).

* Address correspondence to Robert F. Breiman, Emory Global Health Institute, Emory University, Atlanta, GA 30322. E-mail: rfbreiman@emory.edu

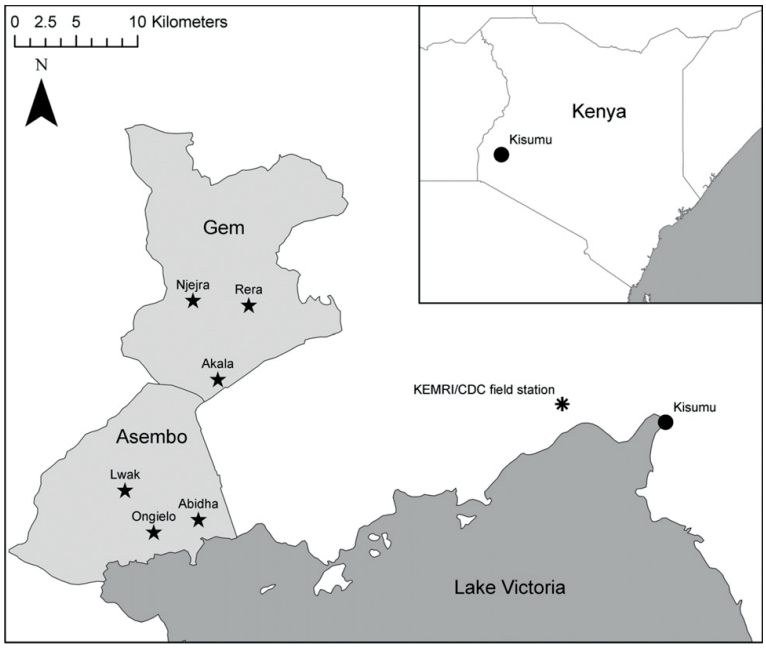


FIGURE 1. Location of the Asembo and Gem HDSS areas in western Kenya. The stars located in Asembo and Gem designate the locations of the GEMS sentinel health facilities.

Other definitions for this study have been detailed elsewhere.[8]

Sample size considerations. *HUAS.* The sample size considerations for the HUAS have been described elsewhere.[8]

HUAS-lite. The HUAS-lite aimed at enrolling the entire population of caretakers of children < 5 years old registered as residents in the HDSS area during every round (N ~20,000–22,000).

Sampling procedure. *HUAS.* From a sampling frame of ~20,853 children < 5 years old registered in HDSS at the time of the survey, we sought to complete interviews with a minimum of 333 caretakers of children in each of three age strata: 0–11, 12–23, and 24–59 months old.

In total, 1,425 children were randomly selected to participate in the HUAS. To ensure that sufficient numbers of neonates < 1 month and children 1–4 months were represented, using the most updated census data collected through the HDSS, we supplemented the sample with a list of 100 pregnant mothers (collected from HDSS data from the most recent round; i.e., January to April of 2007) and 130 randomly selected children 1–4 months old from the most recently completed HDSS census round (January to April of 2007). All other children were randomly selected from the previous census round (September to December of 2006), including 230 children 5–11 months old, 370 children 12–23 months old, and 370 children 24–59 months old. To account for an estimated 20% loss in enrollment because of outmigration, death, and children being over age, we randomly selected an additional 75 children per age stratum. Among 1,425 children randomly selected, 553 children were ages 0–11 months (125 neonates, 155 1- to 4-month old children, and 255 5- to 11-month-old children), 445 children were ages 12–23 months, and 445 children were ages 24–59 months. Children who had moved from their residence, could not be traced, died, or were over age were replaced with a child in the appropriate age group. There was no replacement of children who had traveled (but still resided within the HDSS), refused to participate, or were not available after three attempts were made to contact their caretakers. In total, 1,298 caretakers were approached for interview (Figure 2A).

HUAS-lite. The KEMRI/CDC HDSS collects census and surveillance data through house-to-house interviews by trained staff on a regular basis through three rounds in each calendar year (January to April, May to August, and September to December).[10] The HUAS-lites were conducted from May of 2009 to December 31, 2010 in conjunction with each of these data collection rounds (Figure 2B).

Data collection. *HUAS.* The baseline survey was carried out from April 25 to May 9, 2007 (the HUAS study period). Trained community interviewers located the households and interviewed the primary caretakers of the randomly selected children. Reinterviews were carried out in 10% of households.

After obtaining caretaker's written consent, community interviewers administered to the caretakers of all selected children a pre-tested questionnaire written in English and translated into the local dialect (Dholuo). Through 65 questions (administered over 30 minutes if the child had diarrhea), we collected information on demographics, child morbidity, parents' perception of illness and use of healthcare facilities, diarrhea history during the past 2 weeks (including signs and symptoms), home and health facility management of the child's diarrheal illness (including use of ORS), healthcare use, healthcare expenses, attitudes to healthcare and diarrhea,

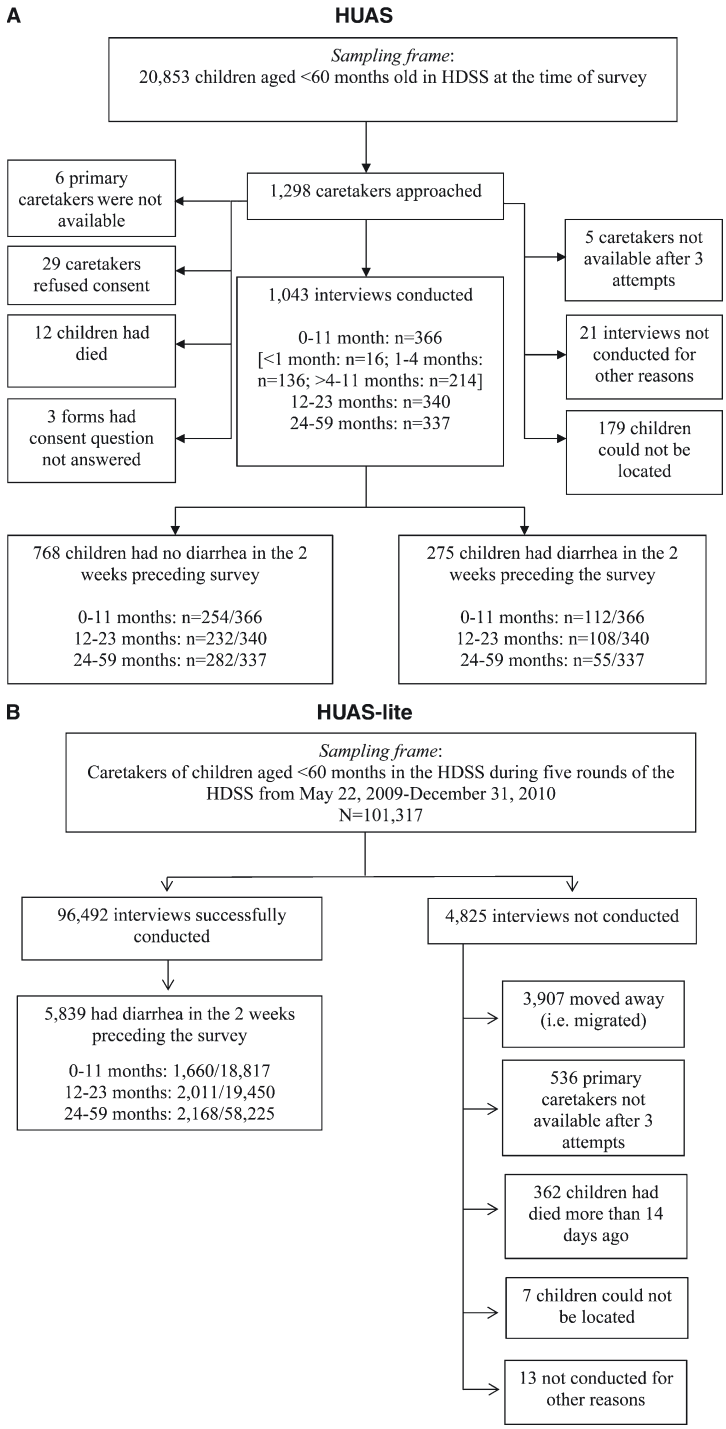


FIGURE 2. (**A**) Study enrollment procedures for the cross-sectional HUAS of caretakers of children < 5 years old in western Kenya in 2007. (**B**) Study enrollment procedures for the HUAS-lite among children < 5 years old in western Kenya from May 22, 2009 to December 31, 2010.

and hypothetical use of enteric vaccines should they become available. For children without diarrhea, the HUAS survey took, on average, 10 minutes.

HUAS-lite. The HUAS-lite used a condensed version of the HUAS questionnaire with 21 questions; the child's primary caretaker was interviewed about information on demographics, the child's diarrhea history, and healthcare use. The first two questions screened caretakers to determine if that person was the child's primary caretaker and if the child had an illness with diarrhea during the last 14 days. If the child had diarrhea, then the additional HUAS-lite questions were asked; if not, the HUAS-lite interview was complete. For children with diarrhea, the HUAS-lite survey took, on average, 10 minutes to administer.

Data management. *HUAS.* Data were recorded on optical character recognition-enabled forms. After manual accuracy checks, the forms were electronically transmitted from KEMRI/CDC to the GEMS Data Coordinating Center (DCC) at the Perry Point Veterans Administration Hospital in Maryland, where data were captured by DataFax software (Clinical DataFax Systems Inc., Ontario, Canada). Cleaned data were exported to an SAS dataset (SAS Institute Inc., Cary, NC).

HUAS-lite. The HUAS-lite survey form was developed and deployed to a handheld device (Personal Digital Assistant [PDA]; HTC Advantage X7500, HTC Corporation, Taoyuan City, Taiwan) running on Windows mobile 6.5 platform. The HUAS-lite questionnaire was developed and deployed to the PDA using Visual Studio.net 2005 and Microsoft SQL server 2005. For data quality, validation rules were programmed to avoid inconsistent or out of range values; repeat interviews were conducted in 3% of compounds per village, and supervisory oversight was conducted on at least 2% of weekly interviews. Weekly data were downloaded in the field to programmed netbooks, from which data inconsistency checks were undertaken. Data cleaning was performed using SAS version 9.2 (SAS Institute Inc., Cary, NC) on download at the KEMRI/CDC HDSS data section. Data were transmitted weekly to DCC through a web-based secure file transfer protocol server, where additional data cleaning and data validation were completed. Databases for each of the five HUAS-lite surveys were exported to SAS datasets.

Statistical analysis. *HUAS.* We used χ^2 tests to examine the association between the characteristics of the child and the caretakers' knowledge, attitude, and health-seeking behavior (predictor factors) and any diarrhea, seeking care outside the home, use of ORS at home, and seeking care from a health facility (outcomes of interest). For all statistical tests, a two-sided $P < 0.05$ was considered statistically significant. Unadjusted odds ratios (ORs) and accompanying 95% confidence intervals (CIs) were used to assess the strength of the associations between categorical predictor factors and outcomes of interest.

Logistic regression was used to model separately for each outcome to evaluate the effect of specific variables and control for confounding. Variables with $P \leq 0.1$ from the bivariate χ^2 tests level were initially entered into the multivariable models. We used a backward stepwise regression method to arrive at our final models. All variables that were significant at $P < 0.05$ remained in the models. Adjusted odds ratios (aORs) for each variable are reported from the logistic regression model, controlling for the other variables in the model. The analyses were conducted taking stratification and sample weighting into account. The weighting accounted for child sex and age.

HUAS-lite. For each survey, we estimated the 2-week period prevalence of any diarrhea, MSD, proportion of the diarrhea group seeking care outside the home, and proportion of the MSD group seeking care outside the home to one of the designated GEMS case-control study sentinel health facilities. Proportions and 95% CIs were calculated, controlling for correlation at the compound level, because more than one child may have been surveyed from the same compound. The Cochran–Armitage test for trend was used to examine differences across rounds.[19] Analyses were performed using SAS statistical software version 9.2 (SAS Institute Inc, Cary, NC).

Scientific ethics. For the HUAS, written informed consent was obtained in the local dialect from all participating caretakers before interview. For the HUAS-lite, verbal consent was sought as consent for data collection, because data collection elements for the HUAS-lite were already approved under the existing HDSS protocol (KEMRI Protocol #1801/CDC Protocol #3308).

The study protocols for the HUAS and HUAS-lite were reviewed and approved by the Scientific and Ethical Review Committees of the KEMRI (KEMRI Protocol #1155) and the Institutional Review Board (IRB) of the University of Maryland, School of Medicine, Baltimore, MD (UMD Protocol #H-28327). The IRB for the CDC, Atlanta, GA, deferred its review to the UMD IRB (CDC Protocol #5038).

RESULTS

Estimated prevalence for diarrhea in the HDSS from the HUAS. Based on the weighted analysis, the estimated prevalence of any diarrheal episode during the past 2 weeks at baseline was 22.3% (CI = 19.5–25.0) among 20,853 children living in the HDSS area at the time of the HUAS survey.

Diarrhea prevalence in the HDSS from the HUAS-lite. The prevalence of reported diarrhea in the past 2 weeks among children < 5 years old in the HDSS ranged from the highest rate of 10.8% (May 22 to August 31, 2009) to the lowest rate of 3.9% (September 14 to December 31, 2010) (Table 1). Among children with diarrhea in the past 2 weeks in the five rounds of the HUAS-lite, the proportion with MSD ranged from 53% (September 15 to December 3, 2009) to 58% (September 14 to December 31, 2010) (Figure 3).

HUAS study enrollment and background characteristics. During the baseline HUAS, we successfully interviewed caretakers of 1,043 children 0–59 months of age; 275 (26%) children were reported to have had diarrhea during the 2 weeks preceding the interview (Figure 2A). The children with diarrhea included 112 (41%) infants, 108 (39%) toddlers (12–23 months), and 55 (20%) children (24–59 months).

We used data on household asset ownership to rank household wealth from poorest to wealthiest using five quintiles. Overall, 34.3% of 1,043 respondents surveyed lived in households within the two lowest wealth quintiles; the highest proportion of children with diarrhea (33%) fell within the poorest wealth quintile (Figure 4). Other characteristics of the households of children with diarrhea in the 2 weeks preceding the study were similar to the characteristics of all households interviewed (Table 2). Among caretakers interviewed, 922 (88.4%) caretakers were mothers,

TABLE 1

Prevalence of diarrhea in the last 2 weeks among children < 5 years old and healthcare-seeking pattern for diarrhea by HUAS-lite round from May 22, 2009 to December 31, 2010 in western Kenya

Characteristic	Round 1: May 22 to August 31, 2009 (*n*/*N*; %)	Round 2: September 15 to December 3, 2009 (*n*/*N*; %)	Round 3: January 28 to April 30, 2010 (*n*/*N*; %)	Round 4: May 27 to August 31, 2010 (*n*/*N*; %)	Round 5: September 14 to December 31, 2010 (*n*/*N*; %)	Overall (rounds 1–5); May 22, 2009 to December 31, 2010 (*n*/*N*; %; 95% CI)	*P* value for trend (rounds 1–5)
No. of HDSS resident children < 5 years approached	20,256 (19.99)	20,928 (20.68)	20,687 (20.42)	19,691 (19.44)	19,755 (19.50)	101,317	< 0.0001
No. of HDSS resident children < 5 years with interviews conducted	19,221/20,556 (94.89)	19,733/20,928 (94.29)	19,735/20,687 (95.40)	18,916/19,691 (96.06)	18,887/19,755 (95.61)	96,492/101,317 (95.24, 95.07–95.41)	< 0.0001
Any diarrhea	2,070/19,221 (10.77)	1,017/19,773 (5.15)	1,116/19,735 (5.65)	898/18,916 (4.75)	738/18,887 (3.91)	5,839/96,492 (6.05, 5.88–6.23)	< 0.0001
MSD	1,137/2,070 (54.93)	539/1,017 (52.99)	641/1,116 (57.41)	518/898 (57.68)	427/738 (57.86)	3,262/5,839 (55.87, 54.54–57.19)	0.0351
Sought care outside home	915/1,137 (80.47)	425/539 (78.85)	537/641 (83.78)	444/518 (85.71)	354/427 (82.90)	2675/3632 (82.00, 80.63–83.38)	< 0.012
Sought care from a health facility	627/915 (68.52)	276/425 (64.94)	354/537 (65.92)	221/444 (49.77)	179/354 (50.57)	1,657/2,675 (61.94, 59.98–63.91)	< 0.0001
Sought care from a GEMS sentinel health facility	227/627 (36.20)	87/276 (31.52)	122/354 (34.46)	77/221 (34.84)	73/179 (40.78)	586/1657 (35.37,32.82–37.91)	0.496
LSD	933/2,070 (45.07)	478/1,017 (47.00)	475/1,116 (42.56)	380/898 (42.32)	311/738 (42.14)	2,577/5,839 (44.13, 42.81–45.46)	0.0351
Sought care outside home	609/933 (65.27)	307/478 (64.23	354/475 (74.53)	269/380 (70.79)	195/311 (62.70)	1,734/2,577 (67.29, 65.39–69.18)	0.2711
Sought care from a health facility	330/609 (54.19)	157/307 (51.14)	186/354 (52.54)	145/269 (53.90)	111/195 (55.92)	929/1734 (53.58, 51.07–56.08)	0.6290
Sought care from a GEMS sentinel health facility	94/330 (28.48)	51/157 (32.48)	71/186 (38.17)	39/145 (26.90)	38/111 (34.23)	293/929 (31.54, 28.29–34.79)	0.3695

65 (6.2%) caretakers were fathers, 33 (3.2%) caretakers were grandmothers, and 23 (2.2%) caretakers were other relatives.

Caretakers knowledge, attitudes, and perceptions of illness and health seeking. We asked caretakers what they would look for to determine if a child is dehydrated; 716 (68.6%) caretakers indicated that they would look for lethargy, 481 (46.1%) caretakers answered sunken eyes, 369 (35.4%) caretakers answered wrinkled skin, 297 (28.5%) caretakers answered dry mouth, and 297 (28.5%) caretakers answered thirst. In total, 206 (19.8%) caretakers said that they would look for both thirst and dry mouth to see if a child is dehydrated.

According to caretakers, the majority (86.2%) of 275 children who had an episode of any diarrhea in the preceding 2 weeks had three to six loose stools per day. Reported accompanying symptoms included lethargy (N = 225, 81.8%), fever (N = 201, 73.1%), being very thirsty (N = 193, 70.7%), mucus or pus in stool (N = 194, 70.6%), dry mouth (N = 188, 68.4%), rice watery stool (N = 163, 59.7%), sunken eyes (N = 162, 58.9%), decreased urination (N = 102, 40.2%), wrinkled skin (N = 92, 33.7%), vomiting (N = 89, 32.7%), coma or loss of consciousness (N = 67, 24.6%), and blood in stool (N = 34, 12.4%). Caretakers reported overall that 6.7% of children with diarrhea were hospitalized and that 6.6% received administered intravenous (IV) fluids for rehydration; 47% of the children hospitalized with diarrhea received IV fluids.

We asked caretakers what they offered their child to drink and eat during the child's diarrheal illness. Of 275 children with diarrhea, 41 (15%) caretakers said they offered the child more drink than usual, 51 (19%) caretakers reported offering the child the same amount, and 183 (67%) caretakers reported that they offered less than usual to drink during the child's diarrheal episode. Of those caretakers who offered less than usual, 96 (52%) children were offered somewhat less, 69 (38%) children were offered much less, and 18 (10%) children were offered nothing to drink during their diarrheal illness. Of 269 caretakers who reported what they offered their child to eat during their diarrheal episode, 3 (1%) caretakers offered more than usual, 43 (16%) caretakers offered the usual amount, and 223 (83%) caretakers stated that they offered less than usual to eat. Of those caretakers who offered less than usual, 74 (33%) caretakers offered somewhat less, 67 (30%) caretakers offered much less, and 82 (37%) caretakers offered nothing during the diarrheal illness. According to their caretakers, 66 (37%) of 180 and 77 (35%) of 220 children who were offered less than usual to drink and eat, respectively, had vomiting accompanying their diarrheal illness.

Healthcare was sought outside the home for 214 (77.8%) of 275 children with diarrhea. For any episode of diarrhea, the places visited as the first source of healthcare outside the home included licensed (62%) and unlicensed (11%) providers and pharmacies (27%). Seeking care outside the home was similar among caretakers of children with bloody compared with non-bloody diarrhea (27 [79%] of 34 versus 187 [78%] of 241, $P > 0.05$) and more common among caretakers of children who were very thirsty and had a dry mouth compared with children who did not have both conditions (142 [77%] of 184 versus 17 [46%] of 37, $P < 0.05$). Of 61 caretakers who did not seek care outside their home for their children with diarrhea, the main reasons that they gave were that the child did not seem to need care (44.3%), the cost of treatment was too high (32.8%), the clinic was

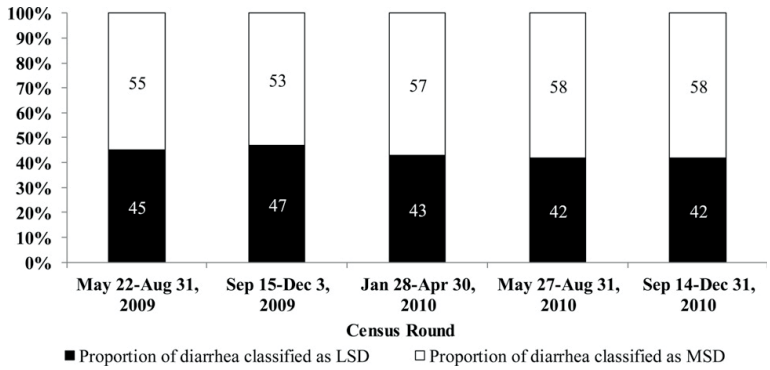


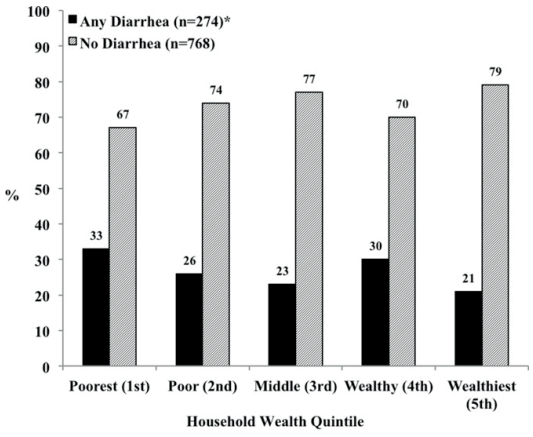
FIGURE 3. Prevalence of MSD and LSD in the last 2 weeks among children < 5 years old by the HUAS-lite round from May 22, 2009 to December 31, 2010, in western Kenya.

too far from home (9.8%), and they were unable to find transportation (8.2%).

The most common means of transportation to the nearest health facility of choice was walking (74%) followed by commercial transportation (which included riding on the back of a bicycle; 13%) and personal transport (generally a bicycle; 4%).

We asked caretakers how long it would usually take to reach the health facility of choice; 770 (74%) of 1,035 respondents estimated that it would usually take less than 1 hour. The main circumstances that make it difficult for caretakers to reach their nearest health facility of choice were that it cost too much money (49%) followed by heavy rainfall or flooding (45%) and lack of transportation (24%).

We asked caretakers about who makes the decision to take the child to a health facility when sick; 809 (78%) of 1,041 respondents said that the child's mother makes the decision, whereas 232 (22%) said other relatives, including the child's father, make this decision. We asked all 1,043 caretakers who participated in this survey if they think that vaccines are important to their child's health; 99% said they think that vaccines are important.



*1 child with diarrhea was missing wealth quintile classification

FIGURE 4. Wealth quintile ranking of caretakers of children < 5 years old participating in the HUAS in western Kenya in 2007.

Risk factors for diarrheal illness. The weighted multivariate analysis of risk factors for any diarrheal illness showed that children ages < 12 months (30.5%, aOR = 2.19, CI = 1.50–3.21) and 12–23 months (31.4%, aOR = 2.24, CI = 1.53–3.30) compared with children ages 24–59 months (16.2%) were at increased risk of having an episode of diarrhea (regardless of severity) during the 2 weeks preceding the survey (Table 3). Also, caretakers who knew of a child who had died of bloody diarrhea (aOR = 2.30, CI = 1.50–3.54) and who knew that bloody diarrhea is more dangerous than other forms of diarrhea (aOR = 1.68, CI = 1.20–2.35) were associated with the caretaker reporting that their child had diarrhea in the 2 weeks preceding the survey (Table 3). The latter findings may indicate that mothers who understand how serious diarrhea can be may be more alert for it in their children and thus, more likely to report it during a survey.

Predictors of seeking healthcare outside the home for any diarrheal illness. On weighted multivariate analysis, seeking healthcare outside the home for diarrheal illness was less common for infants than children ages 24–59 months (aOR = 0.33, CI = 0.12–0.87) (Table 4). Caretakers who said lack of transportation was the main factor preventing them from reaching the health facility of their first choice were more likely to seek care outside the home for any diarrhea compared with caretakers who did not answer in this way (90.5% versus 78.9%; aOR = 3.18, CI = 1.13–8.89). This result may indicate that caretakers who have an expressed preference for certain health facilities may be more willing to seek care, perhaps because they are generally more informed. Caretakers of children who had sunken eyes during their diarrheal illness compared with caretakers of children who did not have sunken eyes (92.2% versus 64.9%) sought care more frequently outside the home (aOR = 4.76, CI = 2.12–10.70) (Table 4).

Predictors of seeking healthcare from a health facility among caretakers who sought care outside the home for any diarrheal illness. On weighted multivariate analysis, seeking care from a licensed health facility (versus a non-licensed health facility) among those caretakers who sought care outside the home for any diarrheal illness was significantly more common for infants versus older children (aOR = 5.06, CI = 1.88–13.61),

TABLE 2
Description of the population surveyed in the HUAS study population in western Kenya in 2007 (unweighted analysis; $N = 1,043$)

Characteristic	Interviewed caretakers ($N = 1,043$)		Interviewed caretakers of children with diarrhea in preceding 2 weeks ($N = 275$)	
	n/*N*	Percent	*n*/*N*	Percent
Child's age stratum (months)				
0–11	366	35	112	41
12–23	340	33	108	39
24–59	337	32	55	20
Child's sex: female	501	48	118	43
Primary caretaker of the child interviewed was a parent	987	95	266	97
Child's mother lives in household	1,016	97	271	99
Child's father lives in household	731	70	194	71
Child's primary caretaker completed primary school or above	549	53	131	48
Median no. (IQR) of people living in house for past 6 months	5 (4–7)		5 (4–7)	
Median no. (IQR) of rooms in house for sleeping	2 (1–2)		2 (1–2)	
Median no. (IQR) of children ages < 60 months living in house	2 (1–2)		2 (1–2)	

IQR = interquartile range.

when the caretaker had some formal education versus none (aOR = 3.32, CI = 1.56–7.07), when caretakers thought that bloody diarrhea could cause harm or death (aOR = 3.25, CI = 1.16–9.09), when caretakers did not report circumstances that make it difficult to reach their preferred health facility (aOR = 3.90, CI = 1.47–10.35), when the child was lethargic during the diarrheal episode (aOR = 5.73, CI = 1.79–18.42), when the child had been offered ORS at home (aOR = 6.99, CI = 3.01–16.22), and when the child was offered no special (i.e., alternative) remedies at home (aOR = 10.17, CI = 2.84–36.37). The latter may possibly be indicative of caretakers' higher education, which was also a predictor of seeking care at a health facility (aOR = 3.32, CI = 1.56–7.07). Caretakers who did not report looking for thirst as a sign of dehydration were less likely to seek care from a health facility for their child's diarrheal illness (aOR = 0.21, CI = 0.09–0.47) (Table 5).

Factors associated with ORS use among children with any diarrhea. Most (89.5%) caretakers indicated that ORSs works well to treat diarrhea. However, only 63 (22.9%) of 275 children with any diarrhea, regardless of severity, were offered ORS at home according to their caretakers. A higher proportion of children with MSD (46 of 182, 25.3%) compared with LSD (17 of 93, 18.3%) were offered ORS at home ($P > 0.05$).

We examined factors associated with the use of ORSs at home for the child's diarrheal illness (Table 6). In the multivariate weighted analysis, caretakers were less likely to use ORSs at home for infants versus older children (aOR = 0.35, CI = 0.14–0.89). They were more likely to use ORSs at home if the primary caretaker had some formal education versus none (aOR = 3.01, CI = 1.41–6.42), if the caretaker perceived that dehydration could result in harm or death (aOR = 5.54, CI = 2.23–13.73), if the child had vomiting three or more times per day during the diarrheal episode (aOR = 3.33, CI = 1.56–7.11), if the caretaker knew of a child who died of bloody diarrhea (aOR = 2.73, CI = 1.20–6.20), if the child was offered the usual amount to eat or less than usual during their diarrheal episode (aOR = 8.24, CI = 1.80–37.73), and if the caretaker believed that breastfeeding prevents diarrheal illness (aOR = 16.19, CI = 1.32–199.21).

Estimated care seeking for diarrhea in the HDSS from the HUAS and HUAS-lite. Our weighted analysis estimated that caretakers of 81.5% (CI = 76.5–86.4) of children in the HDSS with any diarrheal episode in the past 2 weeks sought care outside the home. In general, care was sought from licensed

TABLE 3
Independent predictors of any diarrheal illness among children < 5 years old in the HUAS in western Kenya in 2007 (weighted analysis; $N = 1,043$)

Variable*	Any diarrhea		Unadjusted OR (95% CI)	aOR† (95% CI)
	n/*N*	Weighted (%)		
Child's age group (months)				
0–11	112/366	30.5	2.27 (1.57–3.27)	2.19 (1.50–3.21)
12–23	108/340	31.4	2.37 (1.63–3.46)	2.24 (1.53–3.30)
24–59	55/337	16.2	Reference	Reference
Child's sex				
Male	157/542	24.7	1.32 (0.96–1.83)	1.24 (0.88–1.75)
Female	118/501	19.8		
Caretaker knows a child who died of bloody diarrhea				
Yes	63/185	33.0	1.99 (1.34–2.97)	2.30 (1.50–3.54)
No	207/843	19.8		
Caretaker thinks bloody diarrhea is more dangerous than simple loose watery and cholera-like diarrhea				
Yes	159/526	26.7	1.67 (1.21–2.31)	1.68 (1.20–2.35)
No	114/514	17.9		
Caretaker knows ways to prevent bloody diarrhea				
Yes	102/458	17.6	0.60 (0.43–0.83)	0.57 (0.41–0.81)
No	173/585	26.4		

*Based on the inclusion criteria, 22 variables were initially included in the model; results are shown for the significant variables controlling for age and sex.
†aORs, where all ORs control for other factors in the model.

TABLE 4

Independent predictors of seeking care outside the home for children < 5 years old with any diarrhea in the HUAS in western Kenya in 2007 (weighted analysis; $N = 275$)

Variable*	Sought care outside home for any diarrhea		Unadjusted OR (95% CI)	aOR† (95% CI)
	n/N	Weighted (%)		
Child's age group (months)				
0–11	76/112	67.7	0.31 (0.13–0.76)	0.33 (0.12–0.87)
12–23	90/108	84.3	0.80 (0.31–2.07)	0.72 (0.26–1.97)
24–59	48/55	87.1	Reference	Reference
Child's sex				
Male	123/157	81.9	1.06 (0.54–2.09)	1.27 (0.57–2.81)
Female	91/118	80.9		
Lack of transportation makes it difficult for caretakers to reach their health center of first choice				
Yes	51/59	90.5	2.55 (1.09–5.99)	3.18 (1.13–8.89)
No	163/216	78.9		
Sunken eyes as a symptom that the child presented with during the diarrheal illness				
Yes	145/162	92.2	6.38 (3.10–13.16)	4.76 (2.12–10.70)
No	69/113	64.9		
Antibiotic offered to the child at home during diarrheal illness				
Yes	38/43	93.3	3.65 (1.34–9.97)	3.41 (1.07–10.82)
No	176/232	79.2		
Feeding practices at home during diarrheal illness				
Offered less than usual to eat	189/223	86.5	4.57 (2.06–10.13)	3.42 (1.37–8.53)
Offered usual or more than usual to eat	23/46	58.3		
Caretaker thinks that medication is the best way to prevent any diarrheal illness				
Yes	41/48	90.5	2.44 (0.99–6.00)	3.51 (1.27–9.72)
No	173/227	79.6		

*Based on the inclusion criteria, 16 variables were initially included in the model; results are shown for the significant variables controlling for age and sex.
†aORs, where all ORs control for other factors in the model.

providers (57.6%, CI = 49.9–65.5), unlicensed providers (12.5%, CI = 7.2–17.7), and pharmacies (29.9%, CI = 22.5–37.3).

Among children with reported diarrhea specifically in the HUAS-lite, 82.0% of those children with MSD (95% CI = 80.6–83.4) received care outside the home versus 67.3% (95% CI = 65.4–69.2) of children with LSD (when averaged over the five surveys) (Table 1).

Care seeking for moderate-to-severe diarrhea in the HDSS from the HUAS-lite. Among those caretakers seeking care for MSD in the HUAS-lite, 61.9% (95% CI = 59.9–63.9) sought care from a health facility; 35.4% (95% CI = 32.8–37.9) of MSD cases seeking care at a health facility specifically visited one of the GEMS case-control study sentinel healthcare facilities (Table 1). Of note, there were no significant differences in the proportions of caretakers who sought care at GEMS case-control study sentinel health facilities for MSD (586/1657, 35.4%) or LSD (293/929, 31.5%) over the course of the five rounds ($P = 0.496$ for MSD; $P = 0.369$ for LSD).

DISCUSSION

Our study found that the 2-week period prevalence of diarrhea was 26% at the baseline HUAS and decreased over the five HUAS-lite surveys of caretakers of all children in the HDSS from 11% to 4% between 2009 and 2010. The key findings of our surveys were that less than one-half of children with diarrheal disease receive care at a licensed healthcare facility and that substantial proportions of children with diarrhea are given less food and drink than normal and are not offered ORS. Health use surveys can be helpful in extrapolating burden data from surveillance studies, like GEMS, which use sentinel hospitals to capture patients. Because GEMS calculates population-based incidence of diarrheal disease and its specific attributed etiologies, having reliable estimates on the proportion of children with diarrheal disease who are seen at the sentinel study clinics provides a basis for using a multiplier to adjust incidence rates to account for what was missed because of the surveillance methodology.[9]

These surveys also provide guides to direct interventions to reduce the public health impact of diarrheal disease. For example, our survey documents that ORSs are underused in Kenya,[20–23] similar to other locations in Africa.[21,24] Findings from this study and others[20–24] can provide an impetus for raising community and clinician awareness and parental demand for ORSs, an inexpensive remedy that has been estimated to save over 1.5 million children's lives per year.[3,25] Community education is also needed to ensure that parents continue to feed and provide increased drink to children, particularly infants, with diarrhea. Failure to do so may hasten severe dehydration and death from diarrheal disease.

In developing countries, diarrhea is often inadequately managed at home,[24] and delays in seeking care for moderate to severe pediatric diarrheal illness are common in Kenya, leading to poor outcomes.[26] Strategies, policies, and interventions to reduce childhood diarrheal disease should take into consideration that the caretakers in Kenya (and possibly, in similar settings) are not familiar with the critical importance of appropriate home management of diarrhea, especially for infants who may be at highest risk of poor outcomes. A concerning observation from the HUAS is that 85.5% of caretakers of children with diarrhea, regardless of severity, knew that ORSs work well to treat diarrhea but only

TABLE 5

Independent predictors of seeking care from a health facility among children < 5 years old with any diarrhea in the HUAS in western Kenya in 2007 (weighted analysis; $N = 214$)

Variable*	Sought care for any diarrhea at a health facility		Unadjusted OR (95% CI)	aOR† (95% CI)
	n/*N*	Weighted (%)		
Child's age group (months)				
0–11	53/76	69.7	2.30 (1.08–4.93)	5.06 (1.88–13.61)
12–23	46/90	51.8	1.08 (0.52–2.22)	1.35 (0.57–3.21)
24–59	24/48	49.98	Reference	Reference
Child's sex				
Male	77/123	54.7	1.03 (0.59–1.80)	0.65 (0.32–1.34)
Female	46/91	54.5		
Caretaker's education				
More than primary school (some formal education)	67/104	65.1	2.35 (1.25–4.44)	3.32 (1.56–7.07)
Less than primary school (no formal education)	56/110	44.2		
Caretaker looks to see if the child is thirsty to assess dehydration				
Yes	34/65	43.3	0.52 (0.27–1.03)	0.21 (0.09–0.47)
No	89/149	59.4		
Caretaker perceives that blood in stool can cause harm or death to the child				
Yes	112/186	57.9	2.95 (1.15–7.60)	3.25 (1.16–9.09)
No	11/28	31.8		
Caretaker never endures circumstances that make it difficult to reach the health facility of choice				
Yes	32/42	69.7	2.25 (0.93–5.44)	3.90 (1.47–10.35)
No	91/172	50.6		
Lethargy as a symptom during diarrheal illness				
Yes	112/185	57.6	2.41 (0.92–6.30)	5.73 (1.79–18.42)
No	11/29	36.1		
Child was offered ORSs at home for diarrheal illness				
Yes	43/56	75.5	3.50 (1.57–7.84)	6.99 (3.01–16.22)
No	80/158	46.8		
Child was offered no special remedies at home for diarrheal illness				
Yes	22/27	79.1	3.73 (1.17–11.86)	10.17 (2.84–36.37)
No	101/187	50.4		

*Based on the inclusion criteria, 14 variables were initially included in the model; results are shown for the significant variables controlling for age and sex.
†aORs, where all ORs control for other factors in the model.

22.9% of caretakers in practice offered their child ORSs at home during an episode. This finding, coupled with the finding that caretakers in the study population substantially decrease both fluid and food intake for their children during diarrheal illness, is worrisome and contrary to World Health Organization recommendations.[3] Such findings have also been reported recently in a number of studies in rural and urban Kenya, and they are consistent with global trends in reductions in ORS use and the practice of decreasing the amount of fluid given to children during their diarrheal illness.[21,24] Such inappropriate home management may have been a factor in the finding that caretakers were less likely to seek healthcare outside the home for infants with diarrhea, but among those caretakers who did seek healthcare, the location was most commonly a health facility. Furthermore, the finding that caretakers were significantly more likely to seek care when their ill child had lethargy, may represent inadequate home management of diarrheal illness as lethargy may have been a proxy for late presentation of infants to health facilities in a critical life threatening condition. Early home management may have avoided such situations.

Almost three-quarters of caretakers said that they usually walk the health facility of choice, and 74% of caretakers reported that it takes less than 1 hour to get to their health facility of choice. Moreover, the main reason that caretakers gave for not seeking care outside the home was that children did not seem to need care, which corroborates poor recognition of disease severity in children. Overprescription of antibiotics by clinicians and inappropriate use of antibiotics at home before seeking care have previously been reported in the study area and are responsible for the emergence of antimicrobial-resistant strains of enteric bacteria.[26–28] In the HUAS, we found that 14% of children who reached a health facility had already been offered unprescribed antibiotics administered by the caretaker, which is consistent with previous observations.[27] In recent qualitative studies in the area, caretakers reported a preference to using Western antimicrobial and antimotility drugs over fluid-based medicines, which are not as effective in stopping diarrhea.[20] Empowering caregivers to be comfortable giving ORSs and know to continue feeding by educational messages and campaigns and increasing community ORS availability are essential to improving diarrhea management.[22] Caretakers' knowledge of a child who had died of bloody diarrhea and their awareness that bloody diarrhea may be more dangerous than other forms of diarrhea were associated with the caretaker reporting that the child had diarrhea in the 2 weeks preceding the HUAS survey. This result could suggest that caretakers who are better informed on the potentially serious nature of diarrhea may be more astute in recognizing an episode of diarrhea among their young children. Caretakers were more likely to seek care in the HUAS if they reported that they never endure circumstances that make it difficult to reach their health facility of choice. This result may suggest that these particular

TABLE 6

Independent factors associated with use of ORSs at home among children < 5 years old with any diarrhea in the HUAS in western Kenya in 2007 (weighted analysis; $N = 275$)

Variable*	Reported ORS use at home for child's diarrheal illness		Unadjusted OR (95% CI)	aOR† (95% CI)
	n/*N*	Weighted (%)		
Child's age group (months)				
0–11	20/112	17.7	0.53 (0.25–1.14)	0.35 (0.14–0.89)
12–23	27/108	23.7	0.77 (0.37–1.61)	0.85 (0.35–2.06)
24–59	16/55	28.9	Reference	Reference
Child's sex				
Male	41/157	29.0	1.78 (0.90–3.53)	1.64 (0.78–3.48)
Female	22/118	18.7		
Caretaker's education				
More than primary school (some formal education)	36/131	30.6	1.92 (0.99–3.70)	3.01 (1.41–6.42)
Less than primary school (no formal education)	27/144	18.7		
Caretaker perceives that diarrhea with vomiting can result in harm to or death of child				
Yes	48/218	21.8	0.48 (0.22–1.01)	0.10 (0.03–0.32)
No	15/57	36.9		
Caretaker perceives that presence of dehydration can result in harm to or death of child				
Yes	43/160	29.0	1.86 (0.94–3.71)	5.54 (2.23–13.73)
No	20/115	18.0		
Child has vomiting three or more times per day during diarrheal episode				
Yes	32/89	35.2	2.19 (1.12–4.32)	3.33 (1.56–7.11)
No	31/183	19.9		
Caretaker knows a child who died of bloody diarrhea				
Yes	21/63	32.6	1.86 (0.89–3.88)	2.73 (1.20–6.20)
No	40/207	20.7		
Feeding practices at home during diarrheal illness				
Offered usual/less than usual to eat	59/223	28.1	5.10 (1.70–15.31)‡	8.24 (1.80–37.73)
Offered more than usual to eat	4/46	7.1		
Caretaker believes that breastfeeding prevents childhood diarrheal illness				
Yes	3/5	69.6	7.38§	16.19 (1.32–199.21)
No	60/270	23.7		

*Based on the inclusion criteria, 17 variables were initially included in the model; results are shown for the significant variables controlling for age and sex.
†aORs, where all ORs control for other factors in the model.
‡Exact Pearson χ^2 P value is 0.0076.
§Exact Pearson χ^2 P value is 0.081. CI for OR is not presented because of small cell sizes.

caretakers have little or no circumstantial barriers (such as cost, flooding, or lack of transportation) to seeking care for their child's diarrhea.

Our study is subject to biases, because we depended on caretakers' recall of the occurrence of the child's diarrheal episode over the previous 2 weeks; also, we assumed that caretakers were familiar with signs and symptoms of diarrhea, such as sunken eyes, wrinkled skin, and dehydration, to classify diarrhea as MSD or LSD. Qualitative behavioral research among caretakers of young children coupled with the HUAS and HUAS-lite surveys would have aided in interpretation of the reasons for the lack of appropriate home management and beliefs related to seeking care. Although diarrhea among young children occurred frequently, it seemed to differ in this community at the time of the one-time cross-sectional HUAS survey (26%) compared with the five HUAS-lite surveys (4–11%). Data were collected from a sample of 1,425 children in the HDSS population in 2007 and the entire population of approximately 21,000 children during five census rounds from May of 2009 to December of 2010; thus, the HUAS-lite estimates are likely more precise estimates of diarrhea prevalence, because we captured the whole HDSS population and not just a random sample as in the HUAS cross-sectional survey. The difference in prevalence between the baseline and census rounds may also be a consequence of the differences in methods used between the baseline HUAS and the subsequent five surveys. The baseline survey was a cross-sectional survey conducted at a single point in time (during a rainy season) among a randomly selected subset of children in the HDSS; in contrast, in the HUAS-lite, which was conducted in the entire HDSS population, we approached all children in the HDSS for interview over a much longer period for each of the five surveys. In addition, there may have been differences in caregivers recall between the two surveys or interviewer bias, because different teams administered the HUAS and HUAS-lite. However, declines in diarrhea have also been noted in HDSS surveillance over the last few years (KEMRI/CDC, unpublished data) as coincident with hygiene and in-home water treatment promotion, increased use of ORSs, and seeking treatment of diarrhea at a health facility among HDSS residents.[29] The proportion of childhood diarrhea episodes classified as MSD remained consistently between 50% and 60% when captured over the course of the five rounds of the HUAS-lite surveys. Given the findings from the HUAS-lite surveys that were carried out to assess seasonal trends in diarrhea prevalence and healthcare seeking, it is important that future studies calculating diarrheal incidence account for seasonality. The data collected on MSD prevalence and healthcare seeking from GEMS sentinel health facilities in the five HUAS-lite surveys will be used to extrapolate incidence

rates from GEMS surveillance for MSD in Kenya, which was conducted during the same time period in sentinel health facilities within the same geographic area.

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Authors' addresses: Richard Omore, John Williamson, Fenny Moke, Vincent Were, David Obor, Frank Odhiambo, and Kayla F. Laserson, Kenya Medical Research Institute/Centers for Disease Control and Prevention Research and Public Health Collaboration, Kisian Campus, Kisumu, Kenya, E-mails: romore@kemricdc.org, jwilliamson@ke.cdc.gov, fmoke@kemricdc.org, vwere@kemricdc.org, dobor@kemricdc.org, fodhiambo@ke.cdc.gov, and Klaserson@ke.cdc.gov. Ciara E. O'Reilly and Eric D. Mintz, Division of Foodborne, Waterborne, and Environmental Diseases, Centers for Disease Control and Prevention, Atlanta, GA, E-mails: bwf1@cdc.gov and edm1@cdc.gov. Tamer H. Farag, Karen L. Kotloff, and Myron M. Levine, Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, MD, E-mails: tfarag@medicine.umaryland.edu, Kkotloff@medicine.umaryland.edu, and mlevine@medicine.umaryland.edu. Anna Maria van Eijk, Liverpool School of Tropical Medicine, Liverpool, Merseyside, United Kingdom, E-mail: amvaneijk@yahoo.com. John Vulule, Centre for Global Health Research, Kenya Medical Research Institute, Kisumu, Kenya, E-mail: jvulule@kisian.mimcom.net. Robert F. Breiman, Emory Global Health Institute, Emory University, Atlanta, GA, E-mail: rfbreiman@emory.edu.

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PUBLICATION II

Rates of hospitalization and death for all-cause and rotavirus acute gastroenteritis before rotavirus vaccine introduction in Kenya, 2010-2013

Omore R, Khagayi S, Onkoba R, Ochieng JB, Juma J, Munga S, Kibet S, Nuorti JP, Odhiambo F, Mwenda J, Breiman RF, Parashar DU and Tate EJ

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RESEARCH ARTICLE Open Access

Rates of hospitalization and death for all-cause and rotavirus acute gastroenteritis before rotavirus vaccine introduction in Kenya, 2010–2013

Richard Omore[1,2*], Sammy Khagayi[1], Billy Ogwel[1], Reuben Onkoba[1], John B. Ochieng[1], Jane Juma[1], Stephen Munga[1], Collins Tabu[3], Sergon Kibet[4], J. Pekka Nuorti[2], Frank Odhiambo[1], Jason M. Mwenda[5], Robert F. Breiman[7], Umesh D. Parashar[6] and Jacqueline E. Tate[6]

Abstract

Background: Rotavirus vaccine was introduced in Kenya immunization program in July 2014. Pre-vaccine disease burden estimates are important for assessing vaccine impact.

Methods: Children with acute gastroenteritis (AGE) (≥3 loose stools and/or ≥ 1 episode of unexplained vomiting followed by loose stool within a 24-h period), hospitalized in Siaya County Referral Hospital (SCRH) from January 2010 through December 2013 were enrolled. Stool specimens were tested for rotavirus (RV) using an enzyme immunoassay (EIA). Hospitalization rates were calculated using person-years of observation (PYO) from the Health Demographic Surveillance System (HDSS) as a denominator, while adjusting for healthcare utilization at household level and proportion of stool specimen collected from patients who met the case definition at the surveillance hospital. Mortality rates were calculated using PYO as the denominator and number of deaths estimated using total deaths in the HDSS, proportion of deaths attributed to diarrhoea by verbal autopsy (VA) and percent positive for rotavirus AGE (RVAGE) hospitalizations.

Results: Of 7760 all-cause hospitalizations among children < 5 years of age, 3793 (49%) were included in the analysis. Of these, 21% (805) had AGE; RV was detected in 143 (26%) of 541 stools tested. Among children < 5 years, the estimated hospitalization rates per 100,000 PYO for AGE and RVAGE were 2413 and 429, respectively. Mortality rate associated with AGE and RVAGE were 176 and 45 per 100,000 PYO, respectively.

Conclusion: AGE and RVAGE caused substantial health care burden (hospitalizations and deaths) before rotavirus vaccine introduction in Kenya.

Keywords: Rotavirus, Morbidity, Mortality, Children, Kenyan

Background

Rotavirus is the most common cause of vaccine-preventable severe acute gastroenteritis (AGE) among infants and young children worldwide [1, 2]. In 2013, RVAGE was estimated to cause 215,000 global deaths among children < 5 years of whom 2% (~ 4000) were from Kenya [3] alone. In Kenya, RVAGE accounts for 19% (~ 9000) of annual hospitalizations among children < 5 years [4]. Two RV vaccines Rotarix® (GlaxoSmithKline), and RotaTeq® (Merck & Co.), are approved and recommended by the World Health Organization (WHO) for global use [5]. Efficacy and effectiveness studies of these vaccines have shown significant reduction in AGE and RVAGE associated hospitalizations and deaths among children < 5 years in both clinical trials and in settings where they have been incorporated into the national immunization programs [1, 6–10]. Consistent with data

* Correspondence: Omorerichard@gmail.com
[1]Kenya Medical Research Institute, Center for Global Health Research (KEMRI-CGHR), Kisumu, Kenya
[2]Health Sciences Unit, Faculty of Social Sciences, University of Tampere, Tampere, Finland
Full list of author information is available at the end of the article

from Mexico [6] and Brazil [7, 11], African countries that were early introducers of RV vaccines including Malawi [10], Ghana [12], and Rwanda [13], have shown remarkable declines in childhood morbidity and mortality associated with AGE and RVAGE. Furthermore, the cost benefit of these vaccines has equally been demonstrated [4, 7, 14] .RV vaccine (Rotarix®) was introduced into the Kenya national immunization program in July 2014. Recent population-based data on pre-vaccine disease rates are not available in Kenya. However, such data are needed to evaluate the impact of vaccination program and may help county and national level governments, regional and global decision makers with evidence needed to support investment in these vaccines.

We examined baseline rates of AGE and RVAGE specific hospitalizations and deaths among children < 5 years in rural western Kenya from January 1, 2010 to December 31, 2013 before RV vaccine introduction in Kenya.

Methods

Study site

Rotavirus surveillance and the Health Demographic Surveillance System (HDSS) platform in our study setting has been detailed elsewhere [15, 16]. In brief, the HDSS site is located in Siaya County in rural western Kenya. The HDSS is a longitudinal study that monitors births, deaths, out and in-migrations and other demographics of a defined population [16]. Our study was conducted in Karemo HDSS area within Siaya county referral hospital (SCRH) — the main regional referral hospital in this setting.

Rotavirus surveillance and laboratory methods

As part of the African-based, World Health Organization (WHO) coordinated RV rotavirus disease surveillance network [17], we conducted hospital-based prospective surveillance for RVAGE within the Kenya Medical Research Institute (KEMRI) operated HDSS area in Karemo [15]. Children aged 0–59 months residents of Karemo HDSS, hospitalized at the in-patient department of SCRH with AGE; defined as ≥3 looser than normal stools and/or ≥ 1 episode of unexplained vomiting followed by loose stool within a 24-h period beginning within the 7 days before seeking healthcare from January 1, 2010 to December 31, 2013 were eligible for enrolment. Trained health facility recorders approached all eligible patient children, explained the study and administered a questionnaire on demographics to their caretakers after obtaining informed consent. A study clinician then examined these patients and administered the standardized questionnaire to their parent/caretaker to gather information about symptoms, medical history, laboratory investigations, diagnosis, treatment and outcome of hospitalization. A whole stool specimen was collected from each participant in a plastic diaper from which at least 2 ml of stool was scooped into a specimen container using a sterile spatula within 48 h of admission, transported on the same day to the enteric laboratory based at the KEMRI-CGHR, and finally tested for rotavirus using a commercial enzyme immunoassay (EIA) (Rotaclone Kit, Meridian Bioscience). A case of RVAGE was defined as an AGE patient with a RV positive stool specimen.

Data management

Details of the enrolment, testing and data management have been described previously [15]. In brief, we linked clinic data to laboratory results and to the longitudinal data including cause of death from verbal autopsy (VA) from the HDSS. During data collection, built-in software in the electronic questionnaire with built-in checks and controls ensured quality control. The linked data were then uploaded and managed using a Microsoft SQL Server 2008 database. Data were analysed using SAS version 9.4 (SAS Institute, Inc. Cary, North Carolina, USA).

Statistical analysis

Descriptive analysis for AGE and RVAGE

Proportion of admissions due to AGE was calculated by dividing the number of AGE cases by the number of all-cause admissions at SCRH who were residents of Karemo HDSS during the study period. The proportion of admissions that were associated with RVAGE was calculated by dividing the number of RV positive stool samples with the total samples collected and tested. Positivity rates by month and patient characteristics (age, gender, clinical features and illness outcome) were calculated. These proportions were plotted by month to show seasonality.

Analysis of RVAGE, disease severity and risk factors

The severity of RVAGE was assessed by using the 20-point Vesikari score [18].A score of less than 11 was categorized as mild while a score of 11 or more was classified as severe. Bivariate comparison of the laboratory-confirmed RV positivity and patient characteristics and treatment outcomes were evaluated using chi-square tests.

Incidence rates of hospitalization and mortality due to AGE and RVAGE

We used person-years of observation (PYO) contributed by all children aged less than 5 years residents of Karemo region during the study period as the denominator. As described previously [15], we calculated PYO by totaling person-time for all children aged 0–59 months who met HDSS residency requirement during the 4-year study period from 1st January 2010 or date of enrolment (if after) until they exited or lost their HDSS residency status through out-migration or death.

The crude hospitalization rates were calculated by dividing the total number of AGE and RVAGE hospitalizations by the PYO contributed by children aged 0–59 months for the period that they met residency criteria for the HDSS.

We used two adjustments for the hospitalization rates. First, to account for possible missed AGE cases, we divided the crude rate of AGE and RVAGE by the proportion of all in-patients who met the stool collection criteria, whether a sample was collected or not.

The second adjustment accounted for children with AGE or possibly RVAGE who did not reach or attend a sentinel health care facility as reported from a population-based, healthcare utilization and attitude surveys (HUAS) for diarrhoea—a separate household survey conducted within the HDSS during the current RVAGE surveillance period [19].The HUAS revealed that the frequencies of seeking care for moderate-to-severe diarrhoea (MSD) from a hospital were 69, 70, 67, 57 and 64% for children aged 0–5, 6–11, 12–23, 24–59 and 0–59 months, respectively (GEMS--Kenya unpublished data). The 95% confidence intervals (CI) were calculated around crude rates by using the PEPI method [20]. Crude rates were then adjusted using Delta method [21, 22]. The adjusted hospitalization rates were finally stratified and reported by age groups that included; 0–5, 6–11, 12–23, 24–59, 0–11 and 0–59 months.

AGE and RVAGE mortality rates

Deaths were recorded at household level through regular interviews of HDSS residents. Diarrhoea as a cause of death was derived from Verbal autopsy (VA). The VA methodologies, coding and interpretation are described elsewhere [23, 24]. Upon the death of an HDSS resident, a trained village-based reporter sent a notification to HDSS data team. After a mourning period of at least 3 weeks, the interviewer from the HDSS approached the most appropriate interviewee who was closest to the deceased to administer a detailed questionnaire focusing on the signs, symptoms and medical history of the deceased. The VA data were collected electronically, validated and processed using an InterVA program, which is a probabilistic computer-based expert opinion algorithm that determines the most probable cause of death as described elsewhere [24]. We calculated the number of deaths attributed to RV by multiplying the total under-five deaths among HDSS residents in the study area by the proportion of deaths attributable to diarrhoea by VA, and the proportion of hospitalized AGE episodes attributable to RV in each of the various age groups as described below.

Mortality rates associated with rotavirus gastroenteritis were obtained by dividing the number of deaths attributed to rotavirus by the total PYO in each of the specific age groups as described above.

Results

Enrolment profile and patient characteristics

During the study period, a total of 7760 all-cause hospitalizations among children < 5 years of age were recorded at the SCRH paediatric ward, out of which 3793 were Karemo HDSS resident population. Among the 3793 Karemo HDSS resident children, 805 (21, 95%CI: 20–23) children were hospitalized due to AGE (Fig. 1). RV-positivity among hospitalized children from Karemo with AGE was more pronounced in infants (< 12 months of age), then toddlers (12–23 months of age), and was least in school-age children (24–59 months of age) (Table 1). Characteristics of patients who had stool specimens collected and those who did not have specimens collected are shown in Table 2.

Of the 541 stool samples collected, 204 (38%) were from infants aged 6–11 months. There was no difference in stool collection by gender. Furthermore, we did not observe any statistical difference in rotavirus positivity in male versus female patients among infants aged < 12 months ((69/211 [32.7%]) vs. (42/165 [25.4%]), OR = 1.42, $p = 0.13$),toddlers aged 12–23 months ((9/61 [14.7%]) vs. (12/46 [26.1%]), OR = 0.49, $p = 0.15$), or in children aged 24–59 months ((9/37 [24.3%]) vs. (2/21 [9.5%]), OR = 3.05, $p = 0.18$), respectively.

The overall annual proportion of rotavirus detection ranged from 43/147 (29.3%) in 2010 to 21/95 (22.1%) in 2013 and the annual proportion of samples detected with rotavirus did not differ significantly over the 4-year study period. Rotavirus hospitalizations were seen throughout the year over the surveillance period, but peaked from January through March and around August–September each year during study period (Fig. 2).

Compared with non-RVAGE cases, RVAGE cases were younger ((median age = 8 Interquartile range [IQR] 5–12) vs. 9 [IQR: 6–15] months; $p < 0.032$)), more likely to present with vomiting ((126/143 (88.1%) vs. 297/397 (74.8%)), and more likely to be classified as severe by Vesikari score (88/143 (61.5%) vs. 179/398 (44.9%), p-value = 0.0007).(Table 3).The length of hospitalization was similar for RVAGE compared to non-RVAGE (number of hospitalization days 4 [IQR] 3–6 vs. 4 [IQR] 3–6, p-value = 0.564).

$$\begin{aligned} \textit{No of deaths attributable to RV} = {} & (\textit{Total under-five deaths among HDSS residents in study area}) \\ & * (\textit{proportion of deaths attributable to diarrhea}) \\ & * (\textit{proportion of hospitalized AGE episodes attributable to RV}) \end{aligned}$$

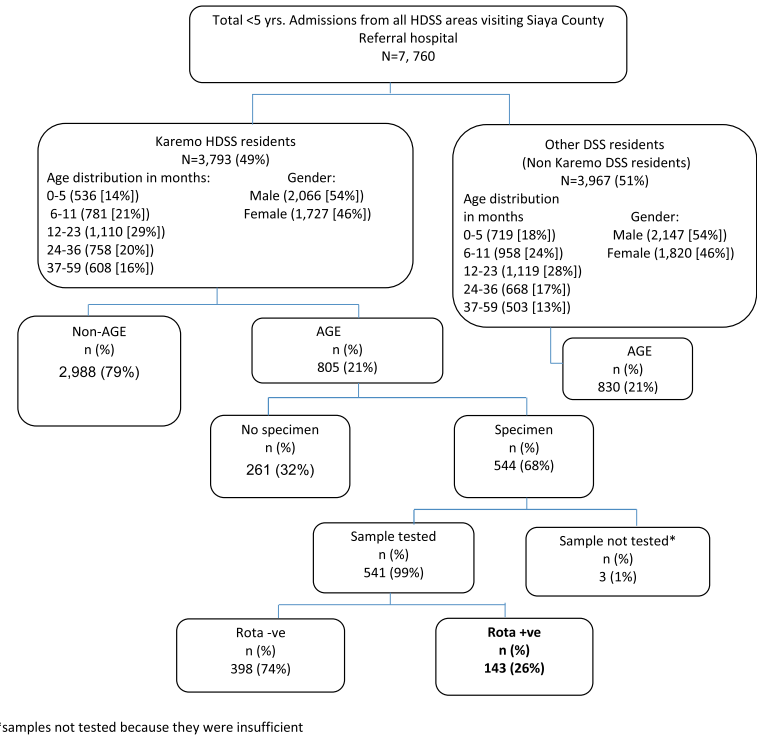

Fig. 1 Flow diagram of Karemo DSS residents < 5 yrs. who were hospitalized and enrolled in the study from Siaya county referral hospital, western Kenya 2010–2013

Table 1 Characteristics of children< 5 years hospitalized at SCRH with all cause morbidity, AGE and RVAGE, 2010—2013

Characteristics	All Cause Hospitalizations from Karemo DSS ($N = 3793$)	AGE Hospitalizations ($N = 805$)	AGE specimen collected and tested for RV ✗ ($N = 541$)	Proportion tested RV Positive ($N = 143$)
	n	n (row %)	n (row %)	n (row %)
Sex				
Male	2066	461 (22%)	309 (67%)	87 (28%)
Female	3793	344 (20%)	232 (67%)	56 (24%)
Year				
2010	920	224 (24%)	147 (66%)	43 (29%)
2011	1335	313 (23%)	206 (66%)	53 (26%)
2012	822	147 (18%)	93 (63%)	26 (28%)
2013	716	121 (17%)	95 (79%)	21 (22%)
Age (Months)				
0–5	536	205 (38%)	141 (69%)	45 (32%)
6–11	781	285 (36%)	204(72%)	57 (28%)
12–23	1110	205 (18%)	138 (67%)	30 (22%)
24–36	687	70 (10%)	40 (57%)	9 (23%)
37–59	679	40 (6%)	18 (45%)	2 (11%)

✗ 3 samples collected were not tested

Table 2 Characteristics of Karemo resident children < 5 years hospitalized with AGE who had stool collected and those without stool collected, Siaya County Referral Hospital, Western Kenya, 2010–2013

Characteristic	Stool Sample Collected (*N* = 544)	Stool Sample Not collected (*N* = 261)	*P*-value
	n (%)	n (%)	
Age			
0–5 months	143 (26)	62 (24)	0.0034
6–11 months	204 (38)	81 (31)	
12–23 months	139 (26)	66 (25)	
24–59 months	58 (11)	52 (20)	
Gender			
Male	312 (57)	149 (57)	0.9
Female	232 (43)	112 (43)	
Vesikari Score			
Severe	268 (49)	93 (36)	< 0.0001
Mild	276 (51)	168 (64)	

Hospitalization attributed to AGE in Karemo HDSS

The highest annual hospitalization rate (per 100,000 PYO) associated with AGE was observed in 2011 followed by 2010, 2012 and 2013 in descending order. The annual incidence (per 100,000) of hospitalizations due to all cause AGE was highest among infants and children aged 6–11 months remained most affected.

Hospitalization attributed to RVAGE among children < 5 years from Karemo HDSS

Incidence rates of RVAGE associated hospitalization was highest among infants, particularly among those aged 6–11 months. We observed the highest RVAGE hospitalization rate in 2011 followed by 2010, 2012 and 2013 in decreasing order. Hospitalization rates for AGE and RVAGE are shown in Table 4.

Mortality attributed to AGE and RVAGE

Discharge information was available for 531 (98%) of the hospitalizations due to AGE of whom 33 (6.2%) died during hospitalization. The case-fatality proportion among RVAGE ((4.2%), [6/142]) compared to that observed from non-RVAGE ((6.9%), [27/389]) cases was similar, $p = 0.26$.

The highest mortality rates of AGE and RVAGE were observed among infants (< 12 months of age), and remained most elevated among infants aged 6–11 months. Annual mortality rates associated with RVAGE were stable between 2010 and 2011, but increased before

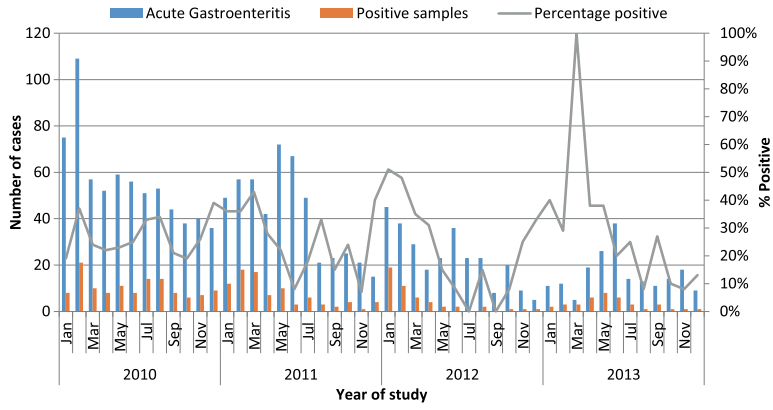

Fig. 2 Rotavirus infection trends among hospitalized children < 5 years from Karemo DSS resident population seeking Care from Siaya County Referral Hospital, western Kenya 2010–2013

Table 3 The Vesikari scores for severity of illness among RVAGE and non- RVAGE hospitalized children <5 yrs. in Siaya County Referral Hospital, western Kenya, 2010–2013

Variable	Points assigned	Rotavirus-positive	Rotavirus-negative	*P*-value
		N = 143	*N* = 398	
Duration of diarrhea (days)				
1–4	1	119 (83)	281 (70%)	0.0089
5	2	4 (3%)	31 (8%)	
> =6	3	20 (14%)	86 (22%)	
Max no. diarrhea/24 h				
1–3	1	41 (29%)	153 (38%)	0.1091
4–5	2	75 (52%)	177 (45%)	
> =6	3	27 (19)	68 (17%)	
Duration of vomiting (days)		*N* = 126	*N* = 296	
1	1	22 (15.4)	77 (19.4)	0.165
2	2	27 (18.9)	57 (14.4)	
> =3	3	77 (53.8)	162 (40.9)	
Max no. vomiting/24 h				
1	1	8 (7%)	39 (13%)	0.1003
2–4	2	95 (75%)	214 (72%)	
> =5	3	23 (18%)	43 (15%)	
Fever				
< 37.0	0	74 (52%)	196 (49%)	0.0435
37.1–38.4	1	58 (40%)	157 (40%)	
38.5–38.9	2	8 (6%)	12 (3%)	
> =39	3	3 (2%)	33 (8%)	
Dehydration		*N* = 55	*N* = 139	
1–5%	2	48 (87%)	117 (84%)	0.5852
> =6%	3	7 (13%)	22 (16%)	
Treatment*	2	143 (100%)	398 (100%)	–

*All cases were treated in the ward

RV vaccine introduction, especially among children aged 6–11 months. Mortality rates attributed to AGE and RVAGE are shown in Table 5.

Discussion

This study documents comprehensive, age-stratified population-based hospitalization and mortality rates associated with AGE and RVAGE before introduction of RV vaccines among Kenyan children < 5 years in a rural community whose demographic and healthcare seeking characteristics are well described [16, 19]. Unlike other WHO rotavirus surveillance study sites in Africa, our hospital-based surveillance site for rotavirus is unique for a few reasons. First, it is supported by an ongoing HDSS which monitors population denominators and conducts verbal autopsy [16]. Second, our surveillance hospital is the only regional public referral hospital for the local HDSS and the only in-patient facility within the HDSS, making our surveillance data representative of the population as shown from our current data and as previously observed [15]. Furthermore, the advantages of a population-based incidence rate are two-fold. First, they provide an opportunity to estimate number of people affected by a disease. Second, they can help to project the number of illness episodes that can be prevented with effectively known interventions such as vaccines [25].

Our 4-year study's most important findings are that before RV vaccine introduction in Kenya; approximately 90 and 60% of RVAGE hospitalized children were aged < 2 years and < 1 year, respectively, and that hospitalizations and mortality associated with AGE and RVAGE were highest among infants. Furthermore our data suggests that children bearing the greatest burden of morbidity and mortality associated with AGE and RVAGE were infants aged 6–11 months. This finding is similar to observations from neighboring Sudan where pre-RV vaccine data indicates that 91 and 61% of rotavirus hospitalizations occurred before 2 years and 1 year respectively [26].

Table 4 Adjusted† rates and 95% Confidence Intervals of hospitalization attributed to AGE and rotavirus per 100,000 Person-Years among in-patients aged 0–59 months residents of Karemo HDSS in Rural Western Kenya, 2010–2013

Year	Adjusted Rates† of Hospitalization attributed to AGE						Adjusted Rates† of Hospitalization attributed to RVAGE					
	0–5 months	6–11 months	12–23 months	24–59 months	0–11 months	0–59 months	0–5 months	6–11 months	12–23 months	24–59 months	0–11 months	0–59 months
2010	8612 (7854–9370)	8468(7717–9220)	7622(6909–8335)	619(416–822)	8478(7726–9230)	2718(2292–3144)	2153(2017–2289)	1540(1425–1654)	640(566–714)	44(25–64)	1804(1680–1928)	522(455–589)
2011	9428(8601–10,256)	12,317(11371–13,263)	12,900(11932–13,868)	927(667–1186)	10,913(10023–11,803)	3782(3258–4306)	1751(1627–1875)	2648(2495–2800)	664(588–741)	129(96–163)	2220(2080–2360)	640(565–716)
2012	5744(4918–6569)	5418(4617–6220)	4815(4599–5570)	365(157–573)	5526(4716–6335)	1745(1290–2200)	1336(1222–1449)	834(744–923)	352(148–410)	43(23–63)	1047(946–1148)	309(254–363)
2013	3604(2912–4296)	5335(4493–6178)	2916(2294–3539)	476(225–728)	4512(3737–5286)	1437(1000–1874)	772(703–841)	1307(1217–1396)	114(87–140)	22(10–33)	1055(974–1135)	249(210–289)
2010–2013	6806(6045–7568)	7798(6983–8614)	7010(6236–7783)	597(371–822)	7302(6513–8091)	2413(1959–2866)	1494(1383–1606)	1560(1446–1673)	439(379–499)	60(37–82)	1520(1408–1632)	429(369–488)

†Adjusted by applying the proportion of samples collected out of all the acute gastroenteritis admission in the hospital and health seeking behavior in the HDSS for children with reported diarrhoea at home

Table 5 Rates and 95% Confidence Interval of deaths attributed to AGE and rotavirus per 100,000 Person-Years among in-patients aged 0–59 month's residents of Karemo HDSS in Rural Western Kenya, 2010–2013

Mortality rates attributed to AGE per 100,000 Person-Years							Mortality rates attributed to Rotavirus per 100,000 Person-Years					
Year	0–5 months	6–11 months	12–23 months	24–59 months	0–11 months	0–59 months	0–5 months	6–11 months	12–23 months	24–59 months	0–11 months	0–59 months
2010	434(393–474)	475(432–517)	238(140–117)	100(80–120)	450(409–492)	172(146–198)	165(140–190)	119(97–140)	42(29–55)	33(22–44)	144(121–168)	46(33–59)
2011	342(306–378)	558(512–604)	353(316–389)	90(72–109)	452(411–494)	214(185–242)	99(80–119)	156(132–181)	63(48–79)	18(10–26)	131(109–154)	50(36–64)
2012	444(403–486)	314(280–349)	117(96–138)	43(30–56)	369(331–407)	118(97–140)	138(115–161)	91(72–110)	30(20–41)	3(0–6)	111(90–131)	56(41–70)
2013	368(331–406)	928(869–988)	225(195–254)	68(52–84)	649(599–699)	207(178–235)	92(73–111)	297(263–331)	25(15–34)	13(7–20)	188(161–215)	33(22–44)
2010–2013	401(362–441)	558(511–604)	210(181–238)	75(58–92)	479(436–521)	176(150–202)	124(103–146)	156(132–181)	46(33–59)	14(7–22)	144(120–167)	45(32–59)

Furthermore, our finding is consistent with observations from the first 2 years of the current study [15], a study conducted at the coastal region of Kenya [27], Global Enteric Multicenter Study (GEMS) [2] and other studies conducted in Europe [28] before introduction of RV vaccines. Our observation that 21% of hospitalizations among children < 5 years in the HDSS were due to AGE is similar to 23% reported previously from mid-term analysis of our current study [15], 22% reported from Kilifi HDSS in coastal region of Kenya [27], 21% from neighboring Mwanza region in Tanzania [29], and 21% from Ethiopia [30]. In addition, our finding that 26% of hospitalized AGE case patients were infected with RV remains similar to the rate of 27% reported from mid-term analysis of our current surveillance data [15] and to 29% from Kilifi HDSS at the Kenyan coast [27]. These observations suggest that AGE and RVAGE burden in our setting is comparable to those from other settings in Kenya and neighboring countries before RV vaccine introduction. Our observation that rates of hospitalization due AGE and RVAGE declined over the study period before vaccine introduction may be associated with unknown non-RV vaccine intervention factors. However, the proportion of all deaths that were associated with AGE and RVAGE did not follow the same pattern. Thus, these observed trends are difficult to explain, though in part may reflect the effects of other interventions. Although widespread distribution and use of zinc and ORS as part of devolved government development efforts in Kenya has been described [31] and may be a contributing factor to the observed decline in diarrhea burden in this setting, such argument remains speculative and prompts further investigation. This trend however is consistent with other observations from a recent community-based survey conducted in this setting [19], and is not dissimilar to the global trend of diarrhoea and rotavirus disease [3, 32].

Our data show that rotavirus was more commonly detected among infants. Moreover, RVAGE presented with more severe episodes than non-RVAGE as characterized by severe dehydration, vomiting and low grade fever —an observation similar to other previous studies [30, 33–35]. Rotavirus is the most common cause of severe dehydrating diarrhoea and is the leading pathogen associated with moderate-to-severe diarrhoea (MSD) [35], as further reaffirmed by GEMS — the largest diarrhoea etiology case-control study ever conducted in countries representing the highest disease burden regions located in Africa and Asia [2]. Severe dehydration caused by diarrhoea in children is a major cause of preventable morbidity and mortality in Kenya [31]. As commonly observed in our setting and consistent with the caretakers healthcare seeking trends in Kenya [19, 31], delay in seeking care for childhood diarrhoea and reducing amount of fluid and food intake during childhood AGE illness can lead to severe disease. Our current study found that case-fatality among RVAGE was not significantly different from non-RVAGE cases, suggesting that rotavirus may not be associated with mortality in hospital based studies as shown from other studies [33, 36]. This finding supports the assumption that seeking care for RVAGE from a health care facility enables access to appropriate rehydration, which would then reduce the risk of death from the disease.

Understanding seasonality of rotavirus can help formulate hypothesis for assessing potential factors influencing transmission and guide policy makers in deciding on appropriate interventions and approaches that can work in local settings for improving case management during peak seasons [37]. For example, in settings such as USA, rotavirus seasons have been observed to be delayed, shortened, and diminished [4, 38] after vaccine introduction. In our current analysis, rotavirus detection peaked in months which are locally known to be usually warm and dry. Our current findings are consistent with recent observations from Kenya [15, 33], and remains similar to findings from other studies conducted in Burkina Faso [37], Peru and Bangladesh [39] before rotavirus vaccine introduction in those settings. Although there is no unifying rotavirus seasonality pattern globally [40], it's spread by the faecal-oral route remains agreeable [35], and even airborne or droplet transmission has been postulated [41]. The later attribute potentially makes the virus transmission route also to resemble that of other non-enteric respiratory infectious diseases such as measles [42].These observations suggests that a drop in humidity and rainfall combined with dry soil could potentially increase additional chance for transmission through aerial contaminated faecal materials since survival of rotavirus may still be favored in such conditions as described elsewhere [41, 43].

Treating RVAGE is expensive. In Kenya, it has been estimated that rotavirus disease cost the national healthcare system $10.8 million each year, and that a 2-dose rotavirus vaccine (RVV) series can avert ~ 2500 deaths, ~ 6000 hospitalizations and ~ 860,000 clinic visits with a cost saving of $2.1 million annually [4].RV vaccines have been shown to be effective in reducing the hospitalizations and death due to diarrhoea in children and the protective effect potentially lasts through 2nd year of life [1, 44].While the benefit of these vaccines has been documented in other African countries where they were introduced ahead of Kenya, such as in South Africa [45], Rwanda [3], Ghana [12],and Togo [46], population-level benefits of RVV are yet to be demonstrated from Kenya.

A possible limitation of our current study is that many rotavirus-associated fatalities are likely associated with delay in healthcare seeking [5]. Furthermore, VA relies on signs, symptoms and circumstances prior to death to

assign cause of death which is subject to misclassification error, and therefore the method as applied in our current study may lead to over or under-estimation of mortality [36]. Our methodology for estimating diarrhoea deaths attributable to rotavirus was based on the following 3 assumptions: (i) that in the absence of treatment, the hospitalized severe cases would not have survived; (ii) the treatment effect on survival of severe diarrhoea is equal for rotavirus and non-rotavirus diarrhoea; and that (iii) the rotavirus attributable fraction of severe diarrhoea observed in the sentinel hospital are generalizable to the source population within each age stratum as already described elsewhere [36]. Maintaining caution when interpreting these estimates is important since we recognize that such assumptions may affect the validity and generalizability of the estimates to the general population. However, since there are currently no reliable data for the direct measurement of the proportion of diarrhoea deaths that are attributable to rotavirus [22, 36] especially in the high disease burden regions located mostly in low-and middle income countries such as in our setting [3], we believe our methodology remains more reasonable, robust and applicable as recommended by WHO [22, 36]. Moreover, our current hospital surveillance data suggests agreeable representation of the source population consistent with previous observations [15].

Conclusions

This study shows that AGE and RVAGE associated hospitalization and deaths are high in this setting with children aged 6–11 months bearing the greatest burden. These findings support the introduction of a vaccine that would potentially provide protection to young children before the disease peaks at 6–11 months of age in this setting. While improvements in drinking water, sanitation and hygiene can effectively prevent other forms of diarrhoea, such interventions do not adequately prevent the spread of rotavirus, thus leaving vaccines as the best alternative in preventing AGE and RVAGE in settings such as ours [5]. Continued surveillance will be important for measuring the impact of rotavirus vaccine introduction in Kenya.

Abbreviations

AGE: Acute gastroenteritis; CDC: US Centers for Disease Control and Prevention; CGHR: Center for Global Health Research; EIA: Enzyme immunoassay; GEMS: Global Enteric Multi-Center Study; HDSS: Health Demographic Surveillance System; KEMRI: Kenya Medical Research Institute; MoH: Ministry of Health; PYO: Person-years of observation; RVAGE: Rotavirus AGE; SAS: Statistical Analysis Software; SCRH: Siaya county referral hospital; VA: Verbal autopsy; WHO: World Health Organization

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Availability of data and materials

Data were obtained with permission of the KEMRI and CDC HDSS Steering committee. Any data requests may be sent to the above steering committee, through the corresponding author.

Disclaimer

The findings and conclusions in this report are the findings and conclusions of the authors and do not necessarily represent the official position of the Kenya Medical Research Institute or the US Centers for Disease Control and Prevention.

Authors' contributions

Conceived and designed the study: RO1, SK1, RO2, JPN, RFB, JMW, UDP, JT. Performed the study: RO1, SK1, BO, RO2, JBO, JJ, SM, CT, SK2, FO, RFB, UDP, JT. Analyzed the data: RO1, SK1, BO, RO2, JBO, JT. Contributed reagents, materials/analysis tools: ALL. Wrote the paper: RO1, SK1, JT. Reviewed the manuscript: All authors. Interpretation of data and critical revision of the manuscript for important intellectual content: RO1, SK1, JPN, RFB, UDP, JT. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Written informed consent was obtained from all the guardians or caretakers of the children before enrolment into the study. This study was approved as part of the HDSS by both the Ethical Review Committee of the Kenya Medical Research Institute and CDC-Atlanta.

Consent for publication

Not applicable.

Competing interests

None declared.

Publisher's Note

Author details

[1]Kenya Medical Research Institute, Center for Global Health Research (KEMRI-CGHR), Kisumu, Kenya. [2]Health Sciences Unit, Faculty of Social Sciences, University of Tampere, Tampere, Finland. [3]Division of Disease Surveillance and Response, Ministry of Public Health and Sanitation, Nairobi, Kenya. [4]WHO Country Office for Kenya, Nairobi, Kenya. [5]WHO Regional Office for Africa (WHO/AFRO), Brazzaville, Congo. [6]Division of Viral Diseases, US Centers for Disease Control and Prevention, Atlanta, GA, USA. [7]Global Health Institute, Emory University, Atlanta, GA, USA.

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PUBLICATION III

Epidemiology, Seasonality and Factors Associated with Rotavirus Infection among Children with Moderate-to-Severe Diarrhea in Rural Western Kenya, 2008-2012: The Global Enteric Multicenter Study (GEMS)

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RESEARCH ARTICLE

Epidemiology, Seasonality and Factors Associated with Rotavirus Infection among Children with Moderate-to-Severe Diarrhea in Rural Western Kenya, 2008–2012: The Global Enteric Multicenter Study (GEMS)

Richard Omore[1,9]*, Jacqueline E. Tate[2], Ciara E. O'Reilly[3], Tracy Ayers[3], John Williamson[4], Feny Moke[1], Katie A. Schilling[3], Alex O. Awuor[1], Peter Jaron[1], John B. Ochieng[1], Joseph Oundo[5], Umesh D. Parashar[2], Michele B. Parsons[3], Cheryl C. Bopp[3], Dilruba Nasrin[6], Tamer H. Farag[6], Karen L. Kotloff[6], James P. Nataro[6,7], Sandra Panchalingam[6], Myron M. Levine[6], Kayla F. Laserson[4,8], J. Pekka Nuorti[9], Eric D. Mintz[3], Robert F. Breiman[5,10]

1 Centre for Global Health Research, Kenya Medical Research Institute, Kisumu, Kenya, **2** Division of Viral Diseases, US Centers for Disease Control and Prevention, Atlanta, GA, United States of America, **3** Division of Foodborne, Waterborne and Environmental Diseases, US Centers for Disease Control and Prevention, Atlanta, GA, United States of America, **4** US Centers for Disease Control and Prevention, Kisumu, Kenya, **5** Global Disease Detection Division, Kenya Office of the US Centers for Disease Control and Prevention, Nairobi, Kenya, **6** University of Maryland, School of Medicine, Center for Vaccine Development, Baltimore, MD, United States of America, **7** Department of Pediatrics, University of Virginia School of Medicine, Charlottesville, VA, United States of America, **8** CDC India, Delhi, India, **9** University of Tampere School of Health Sciences, Tampere, Finland, **10** Emory Global Health Institute, Emory University, Atlanta Georgia, United States of America

* omorerichard@gmail.com

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Abstract

Objective

To evaluate factors associated with rotavirus diarrhea and to describe severity of illness among children <5 years old with non-dysenteric, moderate-to-severe diarrhea (MSD) in rural western Kenya.

Methods

We analyzed data from children <5 years old with non-dysenteric MSD enrolled as cases in the Global Enteric Multicenter Study (GEMS) in Kenya. A non-dysenteric MSD case was defined as a child with ≥3 loose stools in 24 hrs. and one or more of the following: sunken eyes, skin tenting, intravenous rehydration, or hospitalization, who sought care at a sentinel health center within 7 days of illness onset. Rotavirus antigens in stool samples were detected by ELISA. Demographic and clinical information was collected at enrollment and during a single follow-up home visit at approximately 60 days. We analyzed diarrhea

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severity using a GEMS 17 point numerical scoring system adapted from the Vesikari score. We used logistic regression to evaluate factors associated with rotavirus infection.

Results

From January 31, 2008 to September 30, 2012, among 1,637 (92%) non-dysenteric MSD cases, rotavirus was detected in stools of 245 (15.0%). Rotavirus-positive compared with negative cases were: younger (median age, 8 vs. 13 months; $p<0.0001$), had more severe illness (median severity score, 9 vs 8; $p<0.0001$) and had to be hospitalized more frequently (37/245 [15.1%] vs. 134/1,392 [9.6%]), $p<0.013$). Independent factors associated with rotavirus infection included age 0–11 months old (aOR = 5.29, 95% CI 3.14–8.89) and presenting with vomiting ≥3 times/24hrs (aOR = 2.58, 95% CI [1.91–3.48]). Rotavirus was detected more commonly in warm and dry months than in the cool and rainy months (142/691 [20%] vs 70/673 [10%]) $p<0.0001$).

Conclusions

Diarrhea caused by rotavirus is associated with severe symptoms leading to hospitalization. Consistent with other settings, infants had the greatest burden of disease.

Introduction

Diarrhea continues to be the second leading cause of death among children under 5 years worldwide and was responsible for approximately 800,000 (~10.5%) of global deaths in this age group in 2015 [1]. Of the 7.6 million global deaths reported among children <5 years in 2010, 9.9% were attributed to diarrheal diseases [2]. This was a remarkable decrease from the 8.9 million reported deaths in 2008 when diarrheal diseases accounted for 15% of deaths [3]. Despite these reductions rotavirus has remained as the most commonest cause of severe gastroenteritis [4] and the estimated decrease in deaths associated with the disease has been reported to range from ~500,000 deaths in 2008 among children <5 years of age, accounting for 5% of total global deaths [5] to ~200,000 in 2015 among the same age group [6], consistent with the WHO Child Health Epidemiology Reference Group (CHERG) estimates [1]. Approximately two-thirds or more of these deaths continue to occur in South Asia and sub-Saharan Africa [1, 2, 4]. In Kenya, rotavirus diarrhea is estimated to cause over 19% (~9,000) of diarrhea hospitalizations, 16% (~1.5 million) of clinic visits for diarrhea and more than 4,000 deaths among children <5 years of age annually [5, 7, 8]. More severe diarrhea and vomiting leading to severe dehydration are common classical symptoms associated with rotavirus disease [9–11].

Currently available rotavirus vaccines have been shown to be effective in reducing the disease burden [12–16]. In July 2014, Kenya introduced rotavirus vaccine as part of the National Immunization Program. Understanding the epidemiology of rotavirus infections in the local setting therefore remains essential for documenting the basis for rotavirus immunization. Furthermore such information is useful in guiding implementation of other concurrent interventions that are effective in the prevention and treatment of diarrhea such as oral rehydration therapy (ORT) inclusive of continued and ideally increased fluid intake and feeding during diarrheal episodes, zinc treatment, and improvements in water and sanitation [17]. In this study, we describe the epidemiology, seasonality, clinical features and factors associated with rotavirus infection among children <5 years of age with non-dysenteric MSD in rural western Kenya prior to rotavirus vaccine introduction.

Materials and Methods

Study design

We evaluated data collected from cases enrolled in the Global Enteric Multicenter Study (GEMS), a 4-year; prospective, age-stratified, health center-based matched case-control study of MSD among children aged 0–59 months old residing within a defined and enumerated population [18–20].

Study setting

The study was conducted in the Asembo, Gem and Karemo communities in Siaya County, (formerly Nyanza province) in rural western Kenya. The Kenya Medical Research Institute (KEMRI) in collaboration with the U.S. Centers for Disease Control and Prevention (CDC) has been operating a health and demographic surveillance system (HDSS) in these communities since 2001, see Fig 1. The study setting has been described further elsewhere [19, 20].

Study case definition, recruitment and laboratory methods

A non-dysenteric MSD case was defined as a child with ≥3 loose stools in 24 hrs. and one or more of the following: sunken eyes, skin tenting, requiring intravenous rehydration, or hospitalization, who sought care from outpatient or in-patient department of a study sentinel health center (SHC) within 7 days of illness onset. In this analysis, MSD cases with dysentery were excluded.

Caretaker's maximum education was classified as formal education (completed primary, secondary or post-secondary) or non-formal (incomplete primary, religious education or no education). We classified dehydration as either mild or moderate to severe as follows: a child was considered mildly dehydrated if 2 or more of the following were present: restless or

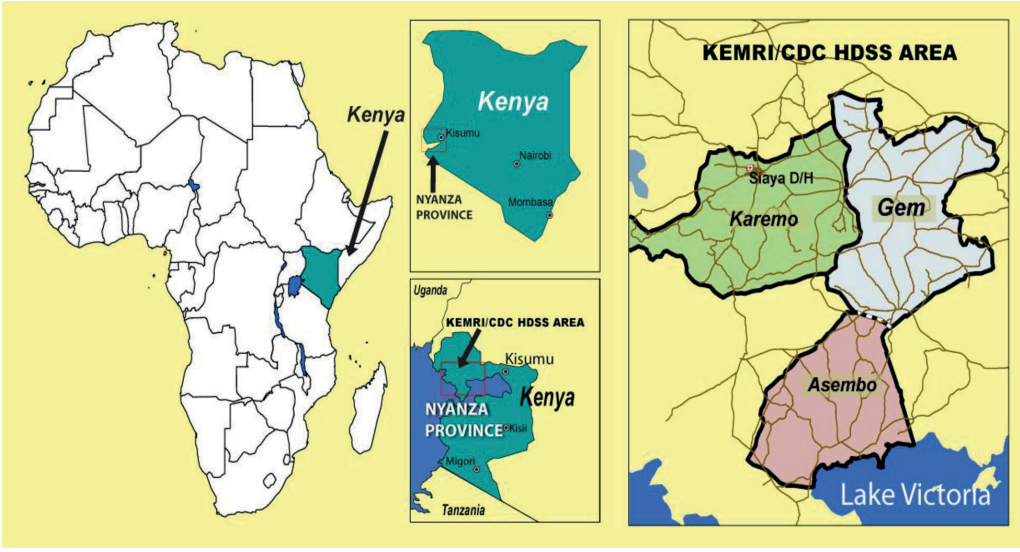

Fig 1. KEMRI/CDC HDSS study area (Asembo, Gem and Karemo) where GEMS Kenya Study was conducted.

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irritable on arrival or at admission to the SHC, sunken eyes, thirsty, drank eagerly; skin pinch goes back slowly (1–2 seconds). A child was considered moderately to severely dehydrated if 2 or more of the following were present: lethargic or unconscious on arrival or at admission to the SHC, sunken eyes, drank poorly or unable to drink, skin pinch goes back very slowly (>2 seconds). Fever was defined by the presence of an axillary body temperature greater than or equal to 38°C or parental perception.

At enrollment, demographic, clinical, epidemiological information and stool samples were collected. Rotavirus VP6 antigen was detected in the whole stool specimen by a well-validated commercial enzyme-linked immunosorbent assay (ELISA) (ProSpecT rotavirus kit, Oxford, Basingstoke, UK). Detailed laboratory methods are described elsewhere [21]. A single home visit ~ 60 days (targeted range 50–90 days) following enrollment was carried out to assess each child's health outcome from the acute diarrheal illness [8, 18]. Mortality that occurred at any time point between initial enrollment from the SHC and the follow-up visit was recorded.

Statistical analysis

Data collection and management procedures for GEMS have been described previously [22]. Data were analyzed using SAS version 9.4 (SAS Institute, Inc. Cary, North Carolina, USA).

To compare non-dysenteric MSD cases who tested positive vs. negative for rotavirus, we report proportions and chi square p-values for categorical variables, including mortality recorded at ~60 days follow-up. Medians for continuous variables were compared with Wilcoxon rank sum test. We initially explored the association between each factor and rotavirus positivity among non-dysentery MSD cases one at a time using univariable logistic regression models. Since many of the factors of interest might be highly correlated, we assessed correlation across variables and when present, only the variable with the strongest association with rotavirus positivity was considered for the multivariable model. We then tested for two-way interactions between each of the variables and age because risk factors are likely to be different for infants. We conducted manual backwards stepwise elimination; the final multivariable model included all variables and aimed to include interactions which retained statistical significance at $p<0.05$. We report adjusted odds ratios (aOR) and 95% confidence intervals (CI) from the final model as variables significantly associated with rotavirus. Collinearity was assessed in the final model using condition index as described elsewhere [23, 24].

To assess bias, sensitivity analysis was performed by constructing additional models with various subsets of the data. Children were eligible for re-enrollment as an MSD case after 90 days post enrollment. Therefore, it was possible for some children to be enrolled for more than one episode of MSD. We constructed additional models excluding all observations for the 33 cases who were enrolled more than once, to ensure consistency of results and assess any potential bias. In addition, at enrollment, case stools were tested for a panel of enteric pathogens and thus could have had more than one pathogen identified. We assessed models limited to the 86 cases who had rotavirus as a single pathogen and 159 cases who had rotavirus with other enteric co-infections separately.

Additionally, to further evaluate clinical features' associated with rotavirus, we applied a 17 point scoring system, referred to in this analysis as "GEMS modified Vesikari score system" which was adapted from the 20 point scale developed by Ruuska and Vesikari [25] to assess severity of rotavirus diarrhea in a separate subgroup analysis which was different with the above models. The score was calculated based on symptoms of diarrheal illness and the child's characteristics at enrollment. To compare clinical features and modified Vesikari scores we used chi square tests.

Assessment of seasonal patterns was limited to the first three years (36 months) of the study where we had un-interrupted continuous and consistent monthly study enrollments that could

support a seasonality analysis. We classified months for this period into cool and rainy (April, May, June, September, October and November) and warm and dry (January, February, March, July, August and December) based on the seasonal patterns in the study area. We compared proportions of rotavirus positivity by season type and computed prevalence odds ratios and confidence intervals using bivariate logistic regression. We further explored seasonality pattern (probability of monthly stool samples testing positive for rotavirus) in a separate logistic regression model for the first three years of data where there was continuity using sine and cosine functions of time [26].

Verbal cause of death (VA)

VA data collection and analysis methods used in this study has been described elsewhere in detail [19, 27]. In brief, VA interviews were conducted by trained field workers using VA questionnaires. They interviewed the main caregiver of the deceased child on signs and symptoms leading to the death and care seeking behavior during the illness. Information from these questionnaires were processed into Inter- VA -4 (version 4.02) program to obtain most probable/underlying cause of death as further described elsewhere [28].

Ethics Statement

This evaluation is covered by the GEMS Kenya protocol which was approved by the scientific and ethical review committees of KEMRI (KEMRI protocol # 1155) and the Institution Review Board (IRB) of the University of Maryland, School of Medicine, Baltimore, MD USA (UMB Protocol # H-28327). The IRB for the Centers for Disease Control and Prevention, Atlanta, GA, USA formally deferred its review to the University of Maryland IRB (CDC Protocol # 5038). Written informed consent was obtained in the local dialect (i.e. Dholuo) from all participating caretakers before recruitment of their children into the study. Data were fully anonymized at collection.

Results

Enrollment Profile

From January 31, 2008 to September 30, 2012, 1,778 MSD cases were enrolled in GEMS at the Kenya site; 253 were positive for rotavirus. During the first three years of the study when we had consistent enrollments without interruption, 1,476 MSD cases were enrolled. When stratified by in-patient and out-patient type, children <12 months of age compared to children 23 to 59 months of age were at increased risk of rotavirus infection and the risk of infection reduced by increasing child age regardless of patient type. During the three years period, dysentery was significantly less commonly observed among any rotavirus positive (5/217 [2.3%])) compared to negative (106/1,258 [8.4%]) MSD cases, odds ratio = 0.26; 95% confidence interval (CI), 0.10–0.64, p = 0.003. Furthermore the pattern remained similar with dysentery being observed to be less common among rotavirus-positive compared to negative MSD cases when we stratified our analysis by in-patient and out-patient MSD cases. Among both in-patient and out-patient MSD cases, the highest rotavirus isolation occurred in the first year of the study with a decrease among in-patient but a stable rate of isolation among out-patient MSD cases in the second and third years respectively (Table 1).

All dysentery cases from the four year study period were excluded from further analysis including 8 (3.2%) rotavirus MSD cases, 132 (8.7%) rotavirus negative MSD cases and 1 rotavirus-negative MSD case with unknown dysentery status (Fig 2). A total of 1,637 non-dysenteric

Table 1. Proportion of all rotavirus-positive vs negative stool samples from all GEMS children enrolled with MSD episodes within in-patient and out-patient departments during the first 3 years of non-interrupted enrollment, western Kenya, Jan 2008-Feb 2011.

	In-Patient MSD cases						Out-Patient MSD cases					
Characteristic	Rotavirus positive		Rotavirus negative			P-value	Rotavirus positive		Rotavirus negative			P-value
	(N = 34)		(N = 125)				(N = 183)		(N = 1,134)			
	n	%	n	%	OR95%CI		n	%	n	%	OR95%CI	
Child's age stratum (in months)												
0–11	23	67.6	54	43.2	†	0.01	114	62.3	482	42.5	5.41 [3.10–9.43]	<0.0001
12–23	10	29.4	37	29.6		0.04	54	29.5	309	27.2	3.99 [2.21–7.23]	<0.0001
24–59	1	2.9	34	27.2		Ref	15	8.2	343	30.2	Ref.	
Median age in months	9 [IQR 6–13]		13 [IQR 8–24]		N/A	0.002	8 [IQR 5–15]		14 [IQR 8–27]			<0.001
Dysentery												
Yes	1	2.9	13	10.5	0.26 [0.03–2.05]	0.201	4	2.2	1041	91.8	0.25 [0.09–0.69]	0.007
No	33	97.1	111	89.5	Ref.		179	97.8	93	8.2	Ref.	
Year of study												
Year 1	15	44.1	65	52	Ref.		70	38.3	486	42.9	Ref.	Ref
Year 2	10	29.4	37	29.6	1.17 [0.48–2.87]	0.755	56	30.6	390	34.4	0.99 [0.68–1.45]	0.987
Year 3	9	26.5	23	18.4	1.69 [0.65–4.40]	0.292	57	31.1	258	22.8	1.53 [1.05–2.24]	0.028

† Fisher`s exact test method used

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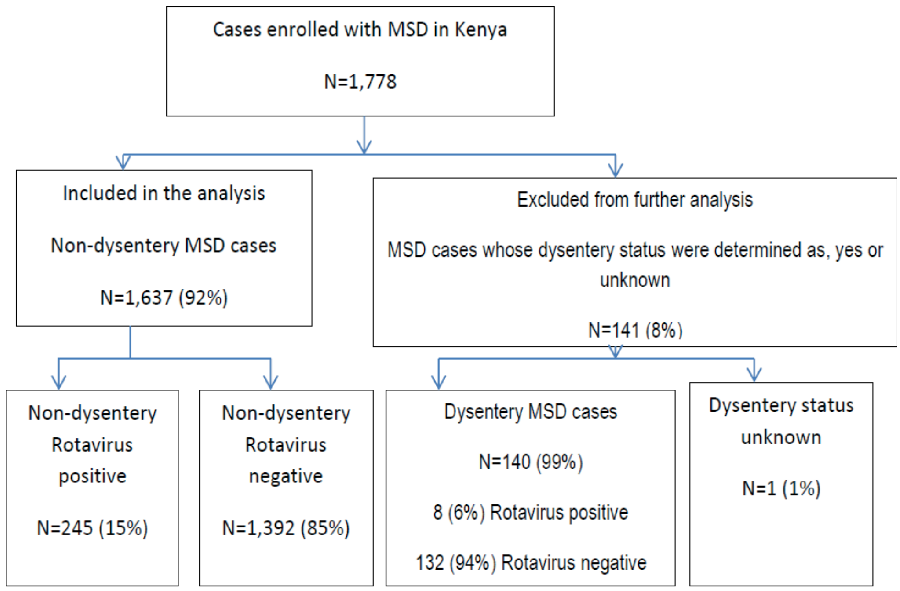
MSD cases of whom 245 (15%) were rotavirus-positive and 1,392 rotavirus-negative were included in further analyses as shown in Fig 2.

Breast feeding information presented in the current analysis was only available for the first three years of the study and was available for 1,364 of the 1,476 MSD cases enrolled in that period. In general 441 (32.3%) of the cases had stopped breastfeeding, 867 (63.6%) were partially breastfed and 56 (4.1%) were exclusively breastfed. When we limited our analysis further among 235 cases who at enrollment were aged <6 months and who were ideally expected to be on exclusive breastfeeding, only 50 (21.3%) were exclusively breastfeeding, 180 (76.6%) were partially breastfeeding and 5 (2.1%) had stopped breastfeeding. Exclusive breastfeeding was less frequently reported among caretakers of rotavirus positive (8/59 [13.6%])) compared to negative (42/176 [23.9%]) MSD cases, p = 0.095.

Factors associated with rotavirus infection

Compared with rotavirus-negative cases, rotavirus-positive cases were significantly younger (median age; 8 vs 13 months $p<0.0001$). The majority (64%) of rotavirus-positive cases were aged 0–11 months as shown in Table 2 and in Fig 3. Further patient demographics, clinical characteristics and laboratory findings are listed in Table 2.

From birth prevalence increased to 20% at age 1 month and remained at more or less at the same level through age 8 months, with a sharp drop-off in month 9, 10 and 11, see Fig 3. Although some of the SHC did not have full in-patient facilities, patients in this study who required more time for rehydration at the facility were retained in an improvised in-patient unit sometimes called "ORS corner" for a few hours while undergoing further observation while being rehydrated either through IV fluid or ORS. However in situations when further complications or such patients required full hospitalization then they were referred appropriately to the next level or superior health centers or hospitals with full in-patient services.



MSD: Moderate-to-Severe Diarrhea

Rotavirus antigen detected by ELISA

Fig 2. Flow diagram of enrollment of MSD cases in GEMS-Kenya, and the number of non-dysenteric MSD rotavirus-positive and negative cases used for analysis, western Kenya 2008–2012.

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Hospitalization was more commonly observed among MSD patients <1 year of age who were rotavirus-positive versus negative (67.6% [25/37] vs. 46.3% [62/134], $p<0.035$) and among all rotavirus-positive vs negative MSD cases regardless of age (15.1% [37/245] vs. 9.6% [134/1,392], $p<0.013$). However, the overall length of stay in hospital was generally similar (median = 2 days) for hospitalized rotavirus-positive and negative MSD cases. Other factors that were associated with rotavirus MSD in univariable analysis include; vomiting ≥3 times in 24 hours, ≥7 loose stools in 24 hours, unable to drink, sunken eyes, irritability/restlessness, lethargy, abnormal mental status and IV fluids given (Table 2).

Univariable and multivariable analysis

In univariable analysis, compared with rotavirus-negative cases, rotavirus-positive cases were significantly more likely to present with sunken eyes (238/245 (97.1%) vs. 1,307/1,392 (93.9%), OR = 2.21, 95%Confidence interval (CI): 1.01–4.84, p = 0.047); to be restless (179/245 (73.1%) vs. 856/1,392 (61.5%), OR = 1.7,95%CI: 1.25–3.0, p = 0.0006); to have abnormal mental status (186/245 (75.9%) vs. 874/1,392 (62.8%), OR = 1.87,95%CI:1.37–2.55, p<0.0001) and to be unable to drink (16/245 (6.5%) vs. 44/1,392 (3.2%), OR = 2.14,95%CI:1.19–3.86, p = 0.011) and to be hospitalized upon seeking care (37/245 (15.1%) vs. 134/1,392 (9.6%), OR = 1.67, 95% CI:1.13–2.47,p = 0.01. Other factors associated with rotavirus infection included age, vomiting,

Table 2. Bivariate analysis of baseline characteristics of children with rotavirus-positive and rotavirus negative non-dysenteric MSD (n = 1637), western Kenya, 2008–2012.

	Rotavirus-positive		Rotavirus-negative		*P*-value
	N = 245		N = 1,392		
Characteristic	**n**	**%**	**n**	**%**	
Child's age stratum (in months)					
0–11	156	63.7	626	45.0	<0.001
12–23	72	29.4	379	27.2	<0.001
24–59	17	6.9	387	27.8	
Median age in months	8 [IQR 5–14]		13 [IQR 7–25]		<0.001*
Gender					
Female	120	49.0	591	42.5	0.058
Caretakers Education∫∫					
Formal education	125	51.0	606	43.6	0.118
Non-formal education	120	49.0	784	56.4	
Clinical symptoms in the child at enrollment (% yes)					
Vomiting ≥3 times/24hrs	171	69.8	627	45.0	<0.001
Maximum no. of loose stools/24hrs					
≥ 7/24hrs	78	31.8	333	23.9	0.009
≤ 6/24hrs	167	68.2	1059	76.1	
Unable to drink	16	6.5	44	3.2	0.011
Sunken eyes	238	97.1	1307	93.9	0.047
Irritable/restlessness	179	73.1	856	61.5	<0.001
Lethargy	35	14.3	127	9.1	0.013
Child's mental status abnormal§§	186	75.9	874	62.8	<0.001
History of Fever (as observed by caretaker)	173	70.6	1076	77.3	0.024
Dehydration§					
Moderate-to-severe‡ ‡	55/241	22.8	250/1333	18.8	0.14
Mild ‡	186/241	77.2	1083/1333	81.2	
Child was admitted to hospital	37	15.1	134	9.6	0.01
IV fluid given	43	17.6	155	11.1	<0.005

*p value based on Wilcoxon Rank Sums test

∫∫ = denominator = 1,635;

§§ = A child's mental status was considered abnormal if restlessness or irritable or lethargy or unconsciousness was present or observed by clinician at enrollment

§ A child was considered dehydrated if either mild or moderate to severe dehydration symptoms were present as described by the following classifications

‡ ‡ A child was considered moderately to severely dehydrated if 2 or more of the following were present: lethargic or unconscious on arrival/admission; sunken eyes; drank poorly or unable to drink; skin pinch—goes back very slowly (>2 seconds)

‡ A child was considered mildly dehydrated if 2 or more of the following were present: Restless/irritable on arrival/admission; sunken eyes; thirsty, drank eagerly; skin pinch—goes back slowly (1–2 seconds); ¶ = denominator is 1,574

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number of loose stools, hospitalization and administration of IV fluids upon seeking care (Table 2). Number of loose stools during the diarrheal illness were significantly correlated with age, while intravenous fluid was correlated with fever, dehydration and admission. Receipt of IV fluids and hospitalization were highly correlated and could not be included in the model together. Only receipt of IV fluids was retained for model selection. In multivariable analysis, younger age and vomiting ≥3 times per day remained significantly associated with rotavirus infection (Table 3). We found no statistically significant interactions between any of the variables that qualified for the multivariable model. In addition, sensitivity analysis of models

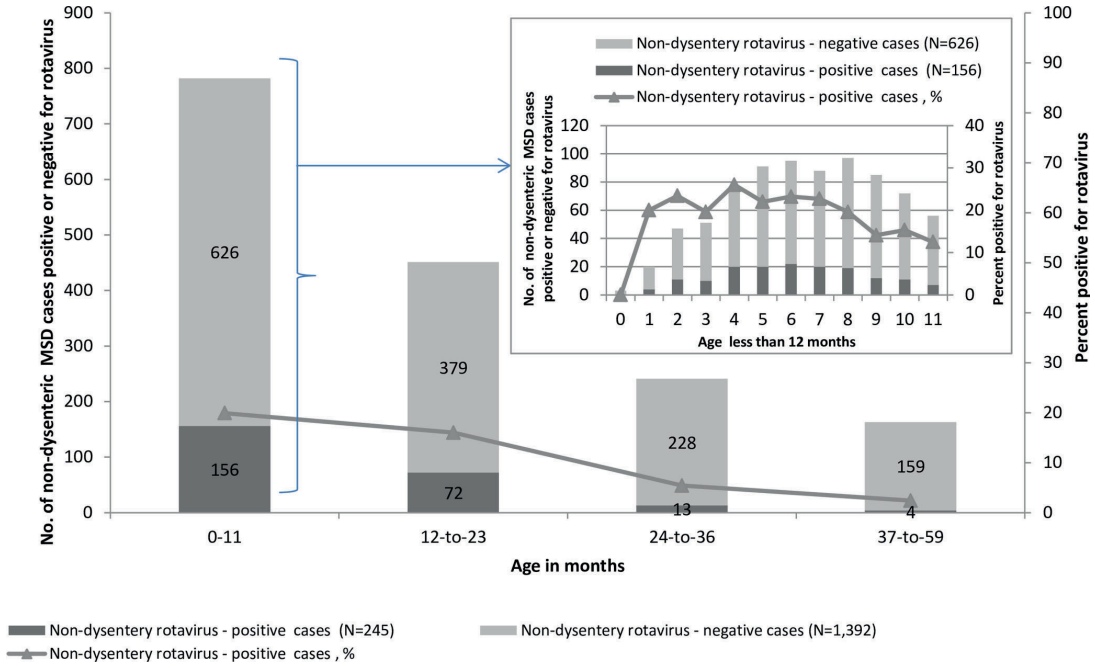

Fig 3. Rotavirus positivity among non-dysenteric MSD cases by age group, western Kenya 2008–2012.

doi:10.1371/journal.pone.0160060.g003

excluding repeat enrollments and subsets of single and multiple pathogen positivity yielded the same conclusions presented for the overall analysis, thus, data are not shown.

Finally using the GEMS modified Vesikari score at enrollment, we found that rotavirus-positive compared to negative cases were more likely to have a higher median Vesikari score (9 vs. 8), $P<0.01$ and were commonly observed to present with more severe disease symptoms. (Table 4).

Mortality at sixty-day follow-up

Overall 1,580 (96.5%) of the 1,637 enrolled cases had their caretakers successfully interviewed at 60-day follow-up. A higher proportion of rotavirus-positive (11/242 [4.5%]) compared to negative (51/1,476 [3.5%]) cases died before the home visit follow-up interview, although the differential in case fatality was not statistically significant ($P = 0.36$). VA cause of death information was available for 60 MSD cases that including rotavirus-positive (10 [17%]) and negative (50 [83%]) cases that had died before follow-up. The causes of death among the 10 rotavirus-positive cases included: diarrhea 5 (50%), HIV 2 (20%), malaria 1 (10%), TB 1 (10%) and parasitic disease 1 (10%). The causes of death among the 50 rotavirus-negative cases included; diarrhea 13 (26%), HIV 13 (26%), malaria 13 (26%), malnutrition 5 (10%), pneumonia 3(6%), TB 2 (4%) and measles 1 (2%). The median time from discharge to death was 12 (IQR) 7–18 days for rotavirus-positive MSD cases and 14 (IQR) 7–33 days for rotavirus-negative MSD cases P = 0.56

Table 3. Crude and adjusted odds ratios of factors associated with rotavirus among children <5 years of age with non-dysenteric MSD, western Kenya, 2008–2012.

Characteristic†	Odds ratio (OR) for being ELISA positive for rotavirus diarrhea [95% confidence interval (CI)]	
Child's age stratum (in months)	**Unadjusted Odds Ratio (OR) 95% CI**	**Adjusted Odds Ratio (aOR) 95% CI**
0–11	5.67 (3.38–9.51)	5.29 (3.14–8.89)
12–23	4.32 (2.50–7.47)	4.08 (2.35–7.07)
24–59	Ref ††	Ref
Gender		
Female	1.3 (0.99–1.71)	
Male	Ref	Ref
Clinical symptoms in the child at enrollment		
Vomiting ≥3 times/24hrs		
Yes	2.82 (2.10–3.78)	2.66 (1.98–3.57)
No	Ref	Ref
Maximum no. of loose stools/24hrs		
≥ 7/24hrs	1.49 (1.10–2.00)	
≤ 6/24hrs	Ref	Ref
Dehydration		
Moderate-to-severe	1.28 (0.92–1.78)	
Mild	Ref	Ref
IV fluid given		
Yes	1.7 (1.17–2.46)	
No	Ref	Ref

† 6 variables initially entered into the model out of which 2 (above) were associated with rotavirus positivity. Variables dropped were 4 namely; Child offered IV fluid, dehydration, Maximum stool in 24hrs and gender

††Ref denotes the referent group

doi:10.1371/journal.pone.0160060.t003

Seasonality of rotavirus

For the first 3 years of the study, prevalence of non-dysenteric rotavirus-positive MSD cases by year of study ranged from 14.2% (85/598) in the first year to 13.8% (63/457) in the second year and finally to 20.7% (64/309) in the third year. Stool samples collected during usually warm and dry months compared with usually cool and rainy months were twice as likely to be rotavirus-positive, (142/691 [20.5%] vs 70/673 [10.4%]; OR = 2.16, 95%CI, 1.58–2.96). Although we found that the proportion of cases positive for rotavirus was highest in August, December, January and February as shown in Fig 4, when we tested seasonality in a model using sine and cosine functions of time, it revealed that the pattern of seasonality (probability that a stool sample would test positive for rotavirus) was significantly inconsistent across the 3 years of the study period (*P*-value = <0.0001).

Discussion

In this study, we describe the epidemiology and factors associated with rotavirus infection among patients <5 years of age in rural western Kenya, using comprehensive baseline and 60-day follow-up data. Our study finding that the risk of rotavirus infection was highest among infants—an age group that accounted for more than 60% of rotavirus infections in our study is consistent with other observations already made from other sub-Saharan African and Asian countries [8, 29]. However, we did not detect any rotavirus cases in neonates but few neonates with MSD were enrolled in our study.

Table 4. Numerical (GEMS modified) scoring system for severity of diarrhea among rotavirus-positive and negative children with non-dysenteric MSD, western Kenya, January 31, 2008-September 30, 2012.

Child characteristics	Points assigned	Rotavirus-positive		Rotavirus-negative		p-value
	(N = 17)	N = 245		N = 1,392		
		N	%	n	%	
Duration of diarrhea (days)						
1–4	1	221	90.2	1,247	89.6	0.954
5	2	14	5.7	85	6.1	
≥6	3	10	4.1	60	4.3	
Max no. diarrhea/24 hrs.						
3–6	2	167	68.2	1,059	76.1	0.010
≥7	3	78	31.8	333	23.9	
Vomited 3+ times/24 hrs.						
Yes	3	171	69.8	627	45.0	<0.001
No	0	74	30.2	765	55.0	
Fever †						
<37.0	0	82	33.5	550	39.5	<0.001
37.1–38.4	1	128	52.2	534	38.4	
38.5–38.9	2	17	6.9	112	8.1	
> = 39	3	18	7.4	195	14.0	
Dehydration††						
Moderate/Severe‡‡	3	55	22.8	250	18.8	0.156
Mild‡	2	186	77.2	1,083	81.2	
Treatment						
Out-patient without IV fluid	0	198	80.8	1,215	87.3	0.023
Out-patient with IV fluid	1	10	4.1	43	3.1	
Hospitalization with or without IV fluid	2	37	15.1	134	9.6	0.013
Median Score †††	N/A	9 [IQR] 8–10		8 [IQR] 6–10		<0.001

† Denominator = 1,636

†† Denominator = 1,574

††† Median calculated for children not missing information (rotavirus-positive = 241 and rotavirus negative = 1,332)

‡ A child was considered mildly dehydrated if 2 or more of the following were present: Restless/irritable on arrival/admission; sunken eyes; thirsty, drank eagerly; skin pinch—goes back slowly (1–2 seconds)

‡‡ A child was considered moderately to severely dehydrated if 2 or more of the following were present: lethargic or unconscious on arrival/admission; sunken eyes; drank poorly or unable to drink; skin pinch—goes back very slowly (>2 seconds)

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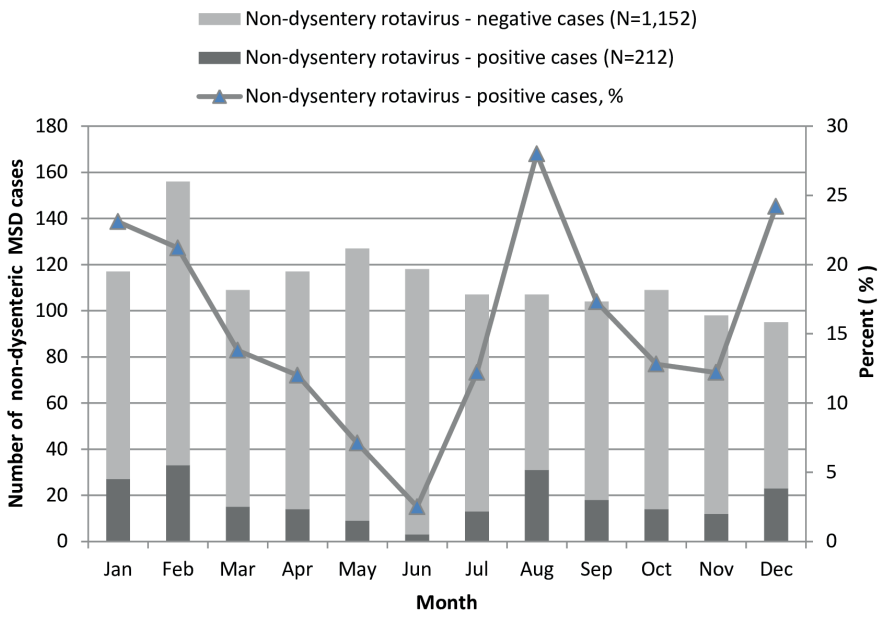
Clinical assessment, treatment and decision for admission of diarrhea patients to a hospital can be influenced by differences in socio-economic factors, or by clinician's attitudes. In the current study, rotavirus cases among children <1 year also had an increased likelihood of hospitalization compared to rotavirus-negative infants, an observation we argue may have not been biased by test results, since stool testing is batched and results are not available to clinicians who decide on hospitalization and treatment until later in the clinical course. Our current study demonstrates that the proportion of infants infected with rotavirus among out-patients was higher compared to children 24–59 months of age. Furthermore among in-patient study population, infants were at the greatest risk of hospitalization, followed by children 12–23 months of age compared to children 24–59 months of age. Consistent with other studies, rotavirus diarrhea has been shown to be a major cause of hospitalization mostly in infants [30].



††Assessment of seasonal patterns was limited to the first three years (36 months) of the study where we had un-interrupted continuous and consistent monthly study enrollments that could support a seasonality analysis.

Fig 4. The seasonal distribution of rotavirus-positive compared with negative cases among children with non-dysenteric moderate-to-severe diarrhea (MSD) in western Kenya, January, 2008- February, 2011.

doi:10.1371/journal.pone.0160060.g004

In our current study as seen elsewhere [11], clinically diagnosed fever by our study clinicians was associated with rotavirus diarrhea. However, when we asked caretakers separately whether they had observed history or presence of fever during their child's diarrheal episode, the caretakers reported fever was seen to be more common among rotavirus-negative compared to positive MSD cases suggesting that caretakers may have not been either keenly observant of fever or may have not recognized fever to be related to the diarrheal illness. Our previous healthcare utilization and attitude survey, conducted before hospital-based surveillance began, revealed that fever was not among the factors that prompted caretakers to seek care for their child`s diarrheal illness[20]. This observation may in part explain the lack of appreciation by caretakers in this community that fever and diarrhea may be related.

Our modified GEMS clinical scoring system adapted from the Vesikari score system [25] enabled us to assess the severity of rotavirus compared to non-rotavirus MSD. As shown in our study and consistent with findings across many settings, in young children, rotavirus disease is characterized by diarrhea, vomiting, and severe dehydration [31]. The overall median severity score was significantly higher among rotavirus positive than negative cases and similar observations have been made in other studies elsewhere [32, 33]. We also observed that diarrhea severe enough to lead to hospitalization was prevalent among the infants and young children diagnosed with rotavirus disease—a finding that is consistent with observations previously made elsewhere[33] and also by the World Health Organization [31]. Overall our current

study shows that there was generally very little exclusive breastfeeding, with almost 80% of MSD cases aged <6 months either partially breastfeed or had stopped breastfeeding. Furthermore, although not statistically significant, exclusive breastfeeding was less frequently reported among caretakers of rotavirus positive (13.6%) compared to negative cases (23.9%)—an observation which is not dissimilar to that made in other settings[33]. These findings may suggest that maternal antibodies could be insufficient to protect against severe rotavirus illness. Second, the age-associated differences observed in rotavirus prevalence, including the less common rotavirus occurrence among breastfed children aged <6 months and those aged <4 months as observed in our study is worth noting. Infants receive passive protection from trans-placental and breastmilk antibodies for the first 6 months of life. Infants who continue to exclusively breastfeed are less likely to be exposed to pathogens than infants on mixed feedings during the six months of age [34]. The child's first exposure to a rotavirus infection during the first six months of life often results in severe disease due to lack of antibodies to fight the infection and is more likely to lead to hospitalization as our current findings suggest since passive immunity wanes and natural immunity acquired from such exposure builds up; subsequent infections tend to produce milder illness which may be characterized by less severe disease and admission to hospital as suggested by our data. Therefore as we have observed in this study and as shown from other settings, the rate of illness declines as the child's age increases and probably as children acquire immunity increasingly from subsequent rotavirus infections[35].

Active, sentinel surveillance of rotavirus diarrhea could provide useful data that can guide the interpretation of diarrheal disease trends following rotavirus vaccine introduction in settings such as Kenya. During the first 3 years of year surveillance, we found rotavirus prevalence rate of 14.2% in year 1 and which remained stable in year two (13.8%) but increased to 20.7% in year 3 among children seeking care at a hospital or health center for non-dysenteric MSD. Our prevalence rate of rotavirus among MSD patients <5 years in year one and two of the surveillance is slightly higher but remains comparable to a prevalence of 12% reported from a population-based surveillance study conducted in both urban slums in Nairobi and rural western Kenya [36] and to 13.5% from a similar study conducted in Nigeria [37]. Furthermore, our observed prevalence especially in year 3 is similar to that observed in other hospital-based studies conducted in the neighboring countries like Tanzania (21%) [10]and Ethiopia (21%) [38]. However, our reported prevalence of rotavirus is relatively lower than other observations from other studies conducted in Africa; for example 33% in Burkina Faso[9] and 45% in Uganda [32]. The differences observed across these studies may be explained by differences in study methodologies including variations in seasonality, study periods, study populations and possibly laboratory techniques. However the observed variations in rotavirus rates further highlights the need and importance of national and regional standardization of rotavirus surveillance using different approaches and techniques that can support comparison and monitoring of rotavirus trends post-vaccine implementation and to perform vaccine impact assessment and cost-effective analyses.

Studies from other countries within and outside Africa have shown that rotavirus vaccines are safe, effective and cost-effective interventions against severe rotavirus disease [29]. Following implementation of rotavirus vaccination, remarkable declines in overall diarrhea occurrence and hospitalization associated with rotavirus diarrhea have occurred in a number of both developed and a few developing countries [39–41]. Vaccination is currently the best way to prevent severe rotavirus illness, particularly in settings such as our study area where access to medical care is limited or sometimes unavailable [31] and ORT use is low[20, 39]. Furthermore in countries with poor immunization programs, as in many African countries, administration of vaccine doses may be delayed. The cost-effectiveness of the rotavirus vaccine declines rapidly with a delayed administration of the first rotavirus vaccine dose which highlights the need for

strong immunization programs. With support from GAVI, in July 2014, Kenya implemented routine rotavirus vaccination under the country's national infant immunization program. To realize its full life-saving potential, rotavirus vaccination must reach all vaccine-eligible children.

Although it has been estimated that rotavirus vaccine introduction in Kenya could prevent more than 5,000 hospitalizations and over 800,000 clinic visits among children <5 years annually [42], results would be optimized when complementary interventions such as increasing use of oral rehydration salts (ORS) and exclusive breastfeeding among children < 6 months and those with diarrhea are also strengthened. Dehydration can be reversed through oral rehydration therapy (ORT) (that is continued feeding and fluids including breastfeeding and ORS use at home) or, if more serious, through hospitalization and IV fluids. Furthermore ORT is important in management of rotavirus diarrhea as antibiotics or other drugs have no known benefit on treating such an illness or acute watery diarrhea due to cholera, cryptosporidiosis, and many other similar illnesses. Our finding that there was no difference between all-cause deaths among children with rotavirus compared to non-rotavirus MSD at sixty day follow-up is an important observation that could possibly highlight that mortality is not associated with rotavirus in hospital based studies. This is possible because detection of rotavirus generally requires a visit to clinic, which presumably would lead to rehydration, but non-detected rotavirus cases that did not make it to a clinic would be less likely to access rehydration and may die in the community without seeking care. When examining the verbal autopsy data, we were not powered to compare diarrhea deaths between rotavirus and non-rotavirus MSD cases at the 60-day follow-up visits. However our VA data presented in this analysis has shown that deaths from rotavirus-positive compared to those from negative MSD cases occurred a few days after enrollment which further suggests that children who reach a healthcare facility with acute rotavirus diarrhea may recover sooner than non-rotavirus MSD cases. Our findings further suggests that diarrhea was the leading cause of death among children with moderate-to-severe diarrhea in our study population—an observation that may suggest that diarrhea continues to be a leading cause of morbidity and mortality in this setting.

Our study is subject to biases and limitations. Data from this study may not be generalized to all children <5 years in Kenya as it was conducted in a single rural site in western Kenya. Also, our modified Vesikari score needs to be interpreted with caution. In our study, information on the duration of vomiting and the maximum number of episodes of vomiting over a 24-hour period was not collected because the caretakers were interviewed only at study enrollment. The incomplete capture of information on vomiting in our study did not allow us to calculate the full 20-point Vesikari score. We resolved this by modifying the Vesikari score based on GEMS data and we were able to construct a 17-point scoring system instead.

As rotavirus vaccine is introduced into the Kenya national immunization program, monitoring its impact on diarrheal disease burden, clinical presentation, and seasonality will be important.

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Crump, Elizabeth Blanton, and Benjamin Nygren, Centers for Disease Control and Prevention, Atlanta, GA, USA; GEMS Data Coordinating Center, Perry Point Veterans Administration Medical Center, Perry Point, MD; University of Maryland, School of Medicine, Center for Vaccine Development, Baltimore, MD, USA. We are grateful to the caretakers in the Asembo, Gem and Karemo community who participated in this work. This manuscript is published with the approval of the Director, KEMRI. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention.

Author Contributions

Conceived and designed the experiments: RO JET CEO JW TA MML EDM KLK THF DN JP. Nataro KFL RFB.

Performed the experiments: RO JET CEO JW TA JO JBO CCB MBP FM JP. Nataro KAS AOA PJ.

Analyzed the data: RO JET CEO TA JW JP. Nuorti EDM RFB.

Contributed reagents/materials/analysis tools: RO JET CEO TA JW FM KAS AOA PJ JBO JO UDP MBP CCB DN THF KLK JP. Nataro SP MML KFL JP. Nuorti EDM RFB.

Wrote the paper: RO JET CEO TA JW JP. Nuorti UDP KFL KLK EDM RFB.

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PUBLICATION IV

Intussusception Cases Among Children Admitted to Referral Hospitals in Kenya, 2002-2013: Implications for Monitoring Postlicensure Safety of Rotavirus Vaccines in Africa

Omore R, Osawa F, Musia J, Rha B, Ismail A, Kiulia NM, Moke F, Vulule J, Wainaina AM, Tole J, Machoki SM, Nuorti JP, Breiman RF, Parashar UD, Montgomery JM, Tate JE.

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Brief Report

Intussusception Cases Among Children Admitted to Referral Hospitals in Kenya, 2002–2013: Implications for Monitoring Postlicensure Safety of Rotavirus Vaccines in Africa

Richard Omore,[1,2] Francis Osawa,[3] Janet Musia,[4] Brian Rha,[5] Amina Ismail,[6] Nicholas Mukaria Kiulia,[7] Fenny Moke,[1] John Vulule,[1] Anthony Mungai Wainaina,[8] John Tole,[9] Stanley Mugambi Machoki,[9] J. Pekka Nuorti,[2] Robert F. Breiman,[10,11] Umesh D. Parashar,[5] Joel M. Montgomery,[11] and Jacqueline E. Tate[5]

[1]Kenya Medical Research Institute, Centre for Global Health Research, Kisumu, Kenya; [2]Department of Epidemiology, School of Health Sciences, University of Tampere, Finland; Departments of [3]Surgery, [4]Pediatrics and Child Health, School of Medicine, University of Nairobi, Kenya; [5]Division of Viral Diseases, US Centers for Disease Control and Prevention, Atlanta, Georgia; [6]Division of Disease Surveillance and Response, Ministry of Public Health and Sanitation, Nairobi, Kenya; [7]Enteric Viruses Research Group, Institute of Primate Research, Nairobi, Kenya; [8]Kenyatta National Hospital, Nairobi, Kenya; [9]Aga Khan University Hospital, Nairobi, Kenya; [10]Global Health Institute, Emory University, Atlanta, Georgia; and [11]Global Disease Detection Division, Kenya Office of the US Centers for Disease Control and Prevention, Nairobi, Kenya

Corresponding Author: Richard Omore, MSc. CHD, Kenya Medical Research Institute, Center for Global Health Research, PO Box 1578-40100, Kisumu, Kenya. E-mail: romore@kemricdc.org.

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To describe the epidemiology of intussusception before introduction of the rotavirus vaccine, we reviewed the records of 280 patients younger than 5 years who were hospitalized in Kenya between 2002 and 2013. The patients who died (18 [6.4%]) had sought care later after symptom onset than the patients who survived (median, 5 vs 3 days, respectively; $P = .04$). Seeking prompt care may improve therapeutic outcomes.

Key words. childhood mortality; intussusception; Kenya; risk factors.

Intussusception is a rare, life-threatening, acute intestinal obstruction with which a segment of the bowel prolapses into a more distal segment. Its causes are usually unknown, and the disease has no clear seasonality [1, 2]. Intussusception is the most common abdominal complication in infants and children younger than 2 years [3].

Both internationally recommended rotavirus vaccines have been associated with a low risk of intussusception, but the benefits of vaccination, including decreases in mortality and hospitalization rates, outweigh the risk [4]. The World Health Organization therefore recommends the global use of rotavirus vaccine [5]. As rotavirus vaccines are introduced in low- and middle-income countries, we urgently need to understand the prevaccine epidemiology and clinical characteristics of intussusception and establish surveillance to monitor the rates of intussusception prospectively [5–7].

Kenya introduced rotavirus (Rotarix; GlaxoSmithKline Biologicals) vaccine in the routine immunization program in July 2014. However, background data on intussusception in Kenya and the sub-saharan African region are limited. Here, we describe the pre–rotavirus vaccine epidemiology and risk factors for intussusception-related mortality among Kenyan children younger than 5 years who were hospitalized between 2002 and 2013.

METHODS

Study Design and Setting

We retrospectively reviewed medical records to identify pediatric patients hospitalized with intussusception at 12 geographically dispersed referral hospitals in Kenya from January 2002 to November 2013. The exact review period varied by hospital depending on the availability of patient records.

Data Collection

In each study hospital, pediatric surgeons systematically reviewed hospital logbooks and treatment and discharge records to identify all pediatric patients clinically diagnosed

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with intussusception and confirmed the diagnosis by using Brighton Collaboration level 1 criteria [3] during the time period in which records were available at the hospital.

Demographic and clinical characteristics, type of surgery, and outcome information were abstracted by using standard case-report forms.

Statistical Analysis

Fisher's exact test was used to compare characteristics of the patients who died and those of the patients who survived. Medians were compared by using the Wilcoxon rank-sum test. For all statistical tests, a 2-sided *P* value of <.05 was considered statistically significant. Data were entered into a Microsoft Access database and analyzed by using SAS version 9.4 (SAS Institute, Inc, Cary, NC). The study protocol was reviewed and approved by the Kenyatta National Hospital (KNH) Ethics Review Committee (protocol number P514/09/2012). Approval from the US Centers for Disease Control and Prevention Institutional Review Board (protocol number 6513) relied on KNH approval.

RESULTS

Of the 305 records for children treated for intussusception at the 12 referral hospitals during the study period, 25 (8.2%) were excluded from further analysis because of missing age (n = 12), because the age was >60 months (n = 12), or because the episode occurred before 2002 (n = 1); thus, 280 (91.8%) patients were included. The majority of these patients were <1 year of age (192 [68.6%]), male (186 [66.4%]), and referred from another district-level hospital (165 [58.9%]). None of the referrals were from any of the 12 participating hospitals to another. Intussusception cases were diagnosed throughout the year in October to December (81 [28.9%]), July to September (75 [26.8%]), January to March (65 [23.2%]), or April to June (59 [21.1%]), and no seasonal pattern was detected. During the time period when all hospitals had records available (2010–2013), 31 to 48 cases were identified annually.

Vomiting (88.2%), blood detected in stool or gross rectal bleeding (81.1%), abdominal distension (75%), and diarrhea (74.6%) were the most common clinical symptoms (Table 1). The overall median time to seeking care was 3 days (interquartile range, 2–6 days) after illness onset. Overall, 97 (35%) of the patients underwent abdominal radiography only, 36 (13%) underwent ultrasonography only, and 55 (20%) underwent both ultrasonography and abdominal radiography, whereas 92 (33%) underwent neither ultrasonography nor abdominal radiography. Overall, surgery was the most common treatment (73.2%); nonoperative reduction was uncommon (only 5 [1.8%] patients were treated with contrast-fluid enema). For 26.1% of the patients, the type of treatment was unknown.

Eighteen (6.4%) patients died during hospitalization while undergoing treatment. Compared with the patients who survived, those who died were more likely to be younger (7.0 vs 5.5 months, respectively; $P = .04$), to have sought care late after symptom onset (median, 3 vs 5 days, respectively; $P = .04$), to have had fever on admission ($P = .004$), and to have been treated by bowel resection ($P = .003$) (Table 1).

DISCUSSION

We describe here characteristics of patients with intussusception who presented for care at Kenya's main referral hospitals before the national rotavirus vaccine introduction. Compared with patients who survived, those who died were younger and were more likely to have sought care late after symptom onset (as characterized by the presence of fever at admission) and to have undergone bowel resection. However, these observations need to be interpreted with caution, because the study was not designed to assess prognosis, and the results may simply reflect differences in age, gender, or severity at presentation among those who sought care. In Kenya, most district- or lower-level hospitals do not have specialized pediatric care for diagnosing or treating intussusception. More than half of the cases were referrals to provincial or higher-level hospitals from district-level hospitals, which is comparable with findings from another study conducted at Moi Teaching and Referral Hospital in Kenya [8].

Consistent with results from previous studies in Africa [7], surgery was the most common treatment of intussusception in our study. However, nonoperative treatment of intussusception by using ultrasound-guided reduction causes no radiation exposure and has been shown to result in better success rates than surgery. Furthermore, nonsurgical treatment methods are safe, painless, and quicker than surgery and have not been associated with complications or recurrence of intussusception [9, 10].

However, in our study, late care seeking may have been associated with the use of surgery because patients may have had progressive disease, as evidenced by the presence of fever, a classical sign of severe disease. Our finding that patients who died were more likely to have been treated through bowel resection than manual reduction may also have been a consequence of late presentation to a facility where intussusception could be managed. Although referral was appropriate, it may have led to further delays in appropriate management, potentially leading to fatal outcomes. Prompt care seeking by the patient and early

Table 1. Comparing Characteristics of Children Aged 0 to 59 Months Who Died Versus Those Who Survived After Treatment for Intussusception at Referral Hospitals in Kenya, 2002—2013

Background Characteristic	All (N = 280)	Died (n = 18)	Survived (n = 262)	P^a
Demographic characteristics (n [%])				
Child age				
0–5 mo	81 (28.9)	9 (50)	72 (27.4)	.195
6–11 mo	11 (39.3)	6 (33.3)	105 (40.1)	
12–23 mo	43 (15.4)	2 (11.1)	41 (15.7)	
24–59 mo	45 (16.1)	1 (5.6)	44 (16.8)	
Median (IQR) age of patients (mo)	7.0 (5–14)	5.5 (4.0–9.0)	7.0 (5.0–14.0)	**.04**
Gender (n [%])[b]				
Male	186 (66.4)	11 (61.1)	175 (67)	.611
Female	93 (33.2)	7 (38.9)	86 (33)	
Days before seeking care (median [IQR])	3 (2–6)	5 (3–9)	3 (2–5)	**.04**
Days to death/discharge upon recovery after admission (median [IQR])	5 (3–8)	2 (1–6)	6 (4–8)	**.01**
Clinical features (n [%])				
Fever	177 (63.2)	17 (94.4)	160 (61.4)	**<.01**
Temperature[c]				
<37.0	38 (17)	1 (6.2)	37 (17.9)	**.01**
37.0–38.4	125 (56.1)	5 (31.2)	120 (58)	
38.5–38.9	21 (9.4)	3 (18.8)	18 (8.7)	
≥39.0	39 (17.5)	7 (43.8)	32 (15.4)	
Vomiting	247 (88.2)	17 (94.4)	230 (87.8)	.71
Diarrhea	209 (74.6)	13 (72.2)	196 (74.8)	.78
Blood in stool	227 (81.1)	13 (72.2)	214 (81.7)	.35
Abdominal pain	178 (63.6)	10 (55.6)	168 (64.1)	.46
Abdominal distension	210 (75)	16 (88.9)	194 (74)	.26
Abdominal mass	111 (39.6)	5 (27.8)	106 (40.5)	.33
Rectal mass	80 (28.6)	4 (22.2)	76 (29)	.79
Type of intussusception (n [%])				
Ileocolic	132 (47.1)	10 (55.6)	122 (46.6)	.76
Colocolic	40 (14.3)	5 (27.8)	35 (13.4)	
Ileoileal	22 (7.9)	2 (11.1)	20 (7.6)	
Diagnosis method (n [%])[d]				
Ultrasound	91 (32.5)	10 (55.6)	81 (30.9)	**.04**
Abdominal radiograph	152 (54.3)	14 (77.8)	138 (52.7)	**<.05**
Treatment method (n [%])[e]				
Operative				
Bowel resection	91 (32.5)	12 (66.7)	79 (30.2)	**<.01**
Manual reduction	128 (45.7)	4 (22.2)	124 (47.3)	**<.05**
Ileostomy	5 (1.8)	1 (5.6)	4 (1.5)	.28
Nonoperative				
Air reduction	0 (0)	0 (0)	0 (0)	NA
Contrast-fluid enema	5 (1.8)	0 (0)	5 (1.9)	>.1
Unknown	73 (26.1)	1 (5.6)	72 (27.5)	.049

Abbreviations: IQR, interquartile range; NA, not applicable.
[a]Significant *P* values are indicated with bold type.
[b]Gender information was missing for 1 child.
[c]The total number was 223. Died was 16. Survived was 207.
[d]Multiple diagnosis methods were possible.
[e]Multiple treatment methods possible.

detection and treatment of intussusception at a primary- or secondary-level facility could lead to better outcomes, as observed elsewhere [11, 12]. Children with symptoms lasting >1 day before seeking care have been shown to be at increased risk for requiring surgery [11]. Creating awareness among parents and healthcare workers to recognize the signs and symptoms associated with intussusception could help to improve early care seeking, diagnosis, and treatment [13].

The case-fatality rate in our study was low compared with 14% reported from other regions in Kenya [8], 28% in Rwanda [14], and ~13% reported from other African countries [7]. Although the in-hospital case-fatality rate in our study was similar to that (4.2%) reported from a multicountry surveillance study in Egypt, Kenya, India, and Brazil [15], the difference in this rate may be a result of methodological differences, because we were not able to ascertain disease outcomes after discharge and records of the children who died may have been less accessible.

Our findings are comparable with those of other studies in which intussusception was reported to be more common among patients aged 0 to 11 months [7] and among boys [14]. The incidence of naturally occurring intussusception is normally low in the first 3 months of life, as observed in

other countries such as Bangladesh [16]. Intussusception among Kenyan children peaked at 4 to 6 months of age. The higher occurrence of intussusception among children 4 to 6 months of age is important when interpreting trends in intussusception after the introduction of rotavirus vaccine. The lack of information about the epidemiology of intussusception in young children could lead some to suggest a link to vaccination rather than a natural increase in cases coinciding with the time period when vaccine is typically given.

This study had limitations. First, given that intussusception is rare and the availability of records varied over the almost 11 years of our retrospective study period, we were unable to systematically monitor trends in intussusception over time. Furthermore, we may have underestimated the number of intussusception cases, particularly in the early years of the study when record keeping may not have been as complete as in later years. Second, our study methodology did not allow an observation window beyond hospital discharge, possibly leading to an underestimation of the case-fatality rate. Third, we did not have baseline population data for the catchment area of participating hospitals given the large number of patient referrals, which made the calculation of population-based baseline incidence rates for intussusception impossible. Finally, the method of treatment was not recorded in approximately one quarter of the cases. Although surgeons reported that these cases met the Brighton Collaboration criteria for confirmed intussusception, we were not able to verify this confirmation, which may have led to an overestimate of the number of cases that met the level 1 criteria for intussusception.

Despite these limitations, we made key observations in this study that are important for setting up prospective surveillance of intussusception in Kenya. First, we were able to identify the hospitals with the highest numbers of intussusception cases to be targeted as sentinel sites for postlicensure monitoring of rotavirus vaccine effects. Second, understanding where and how intussusception cases present and referral patterns will help us to identify cases more efficiently.

Continued monitoring of intussusception in Kenyan children and scaling up efforts targeted at reducing delays in seeking care for intussusception may contribute to early diagnosis and appropriate treatment for better outcomes in this setting.

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