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Intra-Household Transmission of *Shigella* in an Urban Slum in Nairobi, Kenya

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Bachelor of Arts

Vanderbilt University

2011

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Abstract

Intra-Household Transmission of *Shigella* in an Urban Slum in Nairobi, Kenya

By Carmen Hazim

Background: Worldwide, secondary attack rates of shigellosis in households have been found to be as high as 40%. While shigellosis incidence has been studied in urban informal settlements in Kenya, data on the transmission of *Shigella* within families and households are limited. Using population-based surveillance in an urban slum in Kenya, we performed a descriptive analysis of the frequency and possible transmission of shigellosis within households and calculated the incidence of diarrhea among shigellosis cases and their household contacts.

Methods: Population-based data were collected from periodic household interviews and stool specimens were collected for laboratory testing. We calculated the number of laboratory diagnosed shigellosis cases that belonged to common households (households with multiple cases) and the incidence of diarrhea in those households during the month before and after diagnosis. Households that saw one or more cases were stratified by time between cases and by number of household inhabitants.

Results: *Shigella* species were isolated from 508 (18%) of 2855 specimens tested. Approximately 18.5% of cases were from common households. Overall, 9% of households with one case of shigellosis had a second case. Households with ≥5 inhabitants were twice as likely to have a subsequent case diagnosed at any time during the study period. Among all household inhabitants, diarrhea incidence was higher in the month before the diagnosis of a shigellosis case in that household, than in the month after the diagnosis.

Conclusion: Confirmed shigellosis cases were frequently identified from common households. Larger households were at greatest risk for subsequent cases. Promotion of improved water, sanitation, and hygiene practices among household members is essential to prevent household transmission of *Shigella* in crowded settings. Interventions in informal settlements must consider targeting larger households and households with inhabitants in the age groups most at risk.

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Chapter 1: Introduction

Worldwide, *Shigella* is responsible for over one million deaths and approximately 160 million infections annually. *Shigella* disproportionately affects developing countries, where 99% of all shigellosis infections take place (Kotloff et al., 1999). Informal settlements, or urban slums are often found in developing nations, and are home to approximately 31% of the world's urban population (Moreno & Global Urban Observatory., 2003). As they are characterized by widespread poverty, high population density, poor sanitation, and a scarcity of safe drinking water and health services, slums present the ideal conditions for the rapid spread of infectious diseases. *Shigella*'s low infectious dose and ability to be transmitted from person-to-person or through ingestion of contaminated food or water, places those living in such conditions at an increased risk for infection (Mintz & Chaignat, 2008).

Located in Nairobi, Kenya, Kibera is one of the largest informal settlements in Africa. In late 2006, the International Emerging Infections Program (IEIP) of KEMRI/CDC, a co-operation between the U.S. Centers for Disease Control and Prevention (CDC) and the Kenya Medical Research Institute (KEMRI), began conducting population-based infectious disease surveillance (PBIDS) in 2 of the 13 villages of Kibera. PBIDS' objectives include determining the burden of major disease syndromes (diarrheal disease, febrile illness, tuberculosis, pneumonia, and jaundice), characterizing the epidemiology of those syndromes, identifying emerging pathogens, and discerning priority diseases for prevention (Breiman et al., 2011). As a neglected disease with increasing antimicrobial drug resistance, shigellosis has the potential to re-emerge with heightened virulence and thus it is one of the diarrheal diseases under surveillance in Kibera (Sansonetti, 2006).

Within Kibera, the IEIP PBIDS study area is approximately 0.38 km^2 with a population density of approximately 77,000 persons per km^2 (Feikin et al., 2011). Identifying the need to understand the epidemiology of *Shigella* within Kibera, a recent study was conducted using PBIDS data and estimated that more than 1 in every 200 persons living in Kibera experiences shigellosis annually (Njuguna et al., 2013). While the study looked at incidence among individuals, it did not investigate the potential for transmission of *Shigella* within families and households. Worldwide, secondary attack rates within households have been found to be as high as 40%, placing those living in close contact with an infected individual at higher risk (Mintz & Chaignat, 2008). Annually, there are approximately 28,500 individuals from around 7,400 households enrolled and actively participating in the PBIDS system in Kibera (Njuguna et al., 2013). The overall objective of the current study was to analyze PBIDS data collected prospectively in order to understand the intra-household transmission of *Shigella* in Kibera.

The specific study objectives were: (1) to describe the frequency of shigellosis within households, (2) to describe the incidence of diarrhea in those households during the month before and after each diagnosis of shigellosis, and (3) to describe the demographic and clinical characteristics of both shigellosis cases and their household contacts. We hypothesized that the incidence of diarrhea in households with at least one case of shigellosis would be higher in the month before and after diagnosis when compared to the overall diarrhea incidence across Kibera, as suggested in previous literature (Feikin et al., 2011).

Procedures taken to prevent the transmission of *Shigella* vary by country, and current initiatives

for the prevention and treatment of *Shigella* are insufficient (Bovee, Whelan, Sonder, van Dam, & van den Hoek, 2012; Kotloff et al., 1999). While several analyses have revealed the need for more specific interventions targeting transmission occurring within families, many of these studies took place in developed countries where the water, sanitation, and hygiene practices are far superior to those in Kibera (Bovee et al., 2012; De Schrijver, Bertrand, Gutierrez Garitano, Van den Branden, & Van Schaeren, 2011; Ethelberg, Olsen, Gerner-Smidt, & Molbak, 2004; Leder, Sinclair, Forbes, & Wain, 2009). The descriptive analysis of *Shigella*, as it affects intra-household transmission and the frequency of diarrhea within households in Kibera, can inform more robust strategies and innovative prevention measures that might be more relevant to developing countries and informal settlements in particular.

Chapter 2: Literature Review

Shigella Characteristics and Clinical Features

Discovered in 1897 by internationally renowned microbiologist, Dr. Kiyoshi Shiga, *Shigella* is a toxin-producing, Gram-negative bacteria, with an infectious dose as low as 10 organisms (Bovee et al., 2012; DuPont, Levine, Hornick, & Formal, 1989; Trofa, Ueno-Olsen, Oiwa, & Yoshikawa, 1999). Shigellosis is an acute intestinal infection caused by inflammation, mucosal ulceration, and bleeding, due to the multiplication of the *Shigella* bacteria in the epithelial cells of the colon and distal small intestine (Mintz & Chaignat, 2008; Rolfo et al., 2012). Four species or serogroups of *Shigella* exist: *S. dysenteriae*, *S. flexneri*, *S. boydii*, and *S. sonnei* (Mintz & Chaignat, 2008). While the first three serogroups contain multiple serotypes, *S. sonnei* only has one (von Seidlein et al., 2006). Communities usually contain more than one serotype and co-infection with other enteric pathogens is possible.

Shigellosis is characterized by fever, nausea, vomiting, or cramps, in the presence of loose and sometimes bloody stools. Symptoms can also include mucus in stools, watery diarrhea, toxemia, and tenesmus. Mild and asymptomatic infections can also occur. Complications can include sepsis, encephalopathy, metabolic abnormalities, toxic megacolon, and intestinal perforation (WHO, 2005). Convulsions are a complication of shigellosis in young children (Mintz & Chaignat, 2008). Sequelae can differ by serogroup and serotype. In general, *S. flexneri* and *S. dysenteriae* cause more severe illness than *S. sonnei* and *S. boydii*, and often present bloody stools (Ram, Crump, Gupta, Miller, & Mintz, 2008). A late complication of *S. flexneri* infection in individuals with the genetic marker HLA-B27 can be post-infection arthritis, or Reiter syndrome ("Shigellosis: Technical Information," 2009). *S. dysenteriae* type 1 is known for

producing Shiga toxin. In presence of this cytotoxin, which can be produced by other enteric pathogens such as *Escherichia coli*, shigellosis cases can have more severe and prolonged symptoms, and are at risk for life threatening complications such as seizures, coma, and hemolytic-uremic syndrome (HUS) (S. K. Gupta et al., 2007). Severity of illness and risk of death is highest for *S. dysenteriae* type1, and lowest for *S. sonnei* infections (WHO, 2005).

The incubation period of shigellosis is typically 1 – 3 days but can be up to 1 week for infections with *S. dysenteriae* type 1. While symptoms often last 4 – 7 days, the period of communicability can continue for another 4 weeks. In rare cases, asymptomatic carriers can transmit infection for months. Proper treatment with antimicrobials can shorten this communicable period (Mintz & Chaignat, 2008). Once infected with a particular serogroup, an individual will have immunity to that serogroup that can last for several years. However, infection can still occur with other *Shigella* species ("Shigellosis: Technical Information," 2009).

Transmission of *Shigella* and Risk Factors for Severe Disease and Death

Shigella can be transmitted from person-to-person or through ingestion of contaminated food or water (Mintz & Chaignat, 2008). The bacteria can be transmitted from one infected person to the next through the fecal-oral route or sexual activity. Flies can also transmit the pathogen as they can breed in infected feces and later contaminate food ("Shigellosis: Technical Information," 2009). Humans are the only natural hosts, but some other primates such as chimpanzees may also be infected (Sansonetti, 2006). In industrialized countries, groups at risk for transmission and outbreaks include children in day-care centers, persons in custodial institutions, men who

have sex with men, deployed military personnel, and international travelers and their household contacts. In developing countries, *Shigella* infection is a problem among both children and caretakers of young children, displaced and crowded populations, and individuals in institutional care (A. Gupta, Polyak, Bishop, Sobel, & Mintz, 2004; Kotloff et al., 1999; Rolfo et al., 2012).

The risk of severe or fatal illness varies by host characteristics such as age, nutritional status, and immune response (Mintz & Chaignat, 2008). The most severe cases of shigellosis are often seen in children, the elderly, and immunocompromised persons (Bovee et al., 2012). While 69% of all episodes worldwide occur in children < 5 years old, it is unusual to see shigellosis in infants < 6 months of age (Kotloff et al., 1999; Mintz & Chaignat, 2008). Many studies have focused on shigellosis in young children as children have the highest case-fatality rates (Kotloff et al., 1999). However, a significant number of cases also occur in adults over 40 years of age, and disregarding these age groups in analyses can miss important trends transmission (Sansonetti, 2006; von Seidlein et al., 2006).

Children who are not breastfed are at higher risk for severe infection as breastfeeding can confer immunity to infants and young children and reduce their exposure to potentially contaminated food and water. Individuals with immunodeficiency due to recent infection, malnourishment, or the human immunodeficiency virus (HIV) are at increased risk for *Shigella* infection and severe illness. HIV infected individuals may endure persistent or recurrent shigellosis even with adequate antibiotic treatment (Kotloff et al., 1999; WHO, 2005). Mortality associated with shigellosis is lower among individuals with better nutritional status, higher socioeconomic status, better access to primary care, and more extensive use of antibiotics (Sansonetti, 2006)

Diagnosis, Treatment, and Prevention

Multiple methods exist for the diagnosis of *Shigella,* which can be isolated from whole stool samples or rectal swabs. Stool culture using routine microbiology is the most basic means of detecting *Shigella* (Brooks et al., 2006; WHO, 2005). The use of appropriate culture media (differential, low selectivity, MacConkey agar, together with high selectivity XLD or S/S agar) increase the likelihood of *Shigella* isolation (Mintz & Chaignat, 2008). Sensitive molecular techniques such as polymerase chain reaction (PCR) are conducted in equipped laboratories (Brooks et al., 2006; WHO, 2005). Various serotyping methods include the use of commercial antisera, pulsed-field gel electrophoresis (PFGE), ribotyping, rapid amplification of polymorphic DNA (RAPD), plasmid profiling, PCR, and genome sequencing (Khan et al., 2006; Lefebvre et al., 1995). Antimicrobial susceptibility is generally determined the Kirby-Bauer disk diffusion method (Brooks et al., 2006; Iwalokun et al., 2001).

Antimicrobial drugs are known to effectively treat *Shigella* infection and shorten the duration of illness and bacterial shedding (Brooks et al., 2006; Guerrant et al., 2001). Resistance to commonly used antibiotics such as ampicillin, co-trimoxazole and nalidixic acid is widespread and thus ciprofloxacin, formerly used as a back-up drug to treat shigellosis, is now the drug of choice for all patients with bloody diarrhea, irrespective of their age. Aside from ciprofloxacin and some other fluoroquinolones, pivmecillinam and ceftriaxone are currently the only antimicrobials that are usually effective for the treatment of multi-resistant strains of *Shigella* in all age groups. The World Health Organization (WHO) recommends that, in addition to antimicrobial treatment, zinc supplementation, rehydration, through products such as oral

rehydration solution (ORS), and continued feeding be used. Symptoms such fever or pain should also be addressed with anti-pyretic drugs and analgesics. Severe cases or patients in critical condition should be taken to a hospital for specialized treatment (WHO, 2005).

No WHO-recommended vaccines exist for the prevention of *Shigella* infection. While several vaccines are under development, especially for *S. flexneri*, none have been licensed. It is recommended that children be immunized against measles to reduce the possibility of con-infection and thus reduce the incidence and severity of all diarrheal diseases, including shigellosis. Measures to prevent the transmission of *Shigella* include hand washing with soap, safe disposal of human waste and diapers, breastfeeding infants and young children, proper sanitization of soiled clothing and other fomites, control of flies, safe handling and processing of food, and ensuring access and use of safe drinking water (WHO, 2005).

Household Transmission and Secondary Cases

Worldwide, secondary attack rates within households have been found to be as high as 40% (Mintz & Chaignat, 2008). Several studies have been conducted on the intra-household or intra-familial transmission of *Shigella* and other bacterial gastrointestinal diseases. Many of the studies in industrialized countries have revealed the need for more specific interventions targeting transmission occurring within families (Bovee et al., 2012; De Schrijver et al., 2011; Ethelberg et al., 2004; Leder et al., 2009). However, limited literature exists on household or family transmission in developing countries, where the sanitation systems and hygiene practices are sub-optimal and in need of improvement (Khan et al., 2006).

A 2006 study in Bangladesh used PFGE to study the intra-familial transmission of *Shigella* infection. The study found that the risk of diarrhea among children with intra-familial transmission of *Shigella* was nine times the risk among children without intra-familial transmission. In addition, the attributable risk for *Shigella*-associated diarrhea due to intra-familial transmission was 50% (Khan et al., 2006). Another study, conducted in the Netherlands, assessed risk factors for secondary transmission in households. The study found that many *Shigella* infections brought into households had been acquired during travel to developing nations. Households most at risk for secondary transmission contained more than six inhabitants. Children <6 years old were most at risk for acquiring a secondary infection and 20% of secondary infections were asymptomatic (Bovee et al., 2012).

Several studies have looked at outbreaks in communities and within households (De Schrijver et al., 2011; Ethelberg et al., 2004; Leder et al., 2009). In 2008, a descriptive household cohort study was used to investigate an outbreak of *S. sonnei* infection among the Orthodox Jewish community of Antwerp, Belgium. The authors aimed to described the extent of the outbreak and identify risk factors for secondary transmission. Risk factors evaluated were the number of children in a household, the age of the children, handwashing practices, the number of toilets, and whether the index case was admitted to hospital or received antimicrobial treatment. Significant risk factors for secondary transmission included households with ≥3 children, children <5 years old, and children <12 years old who helped bathe and look after younger siblings. The secondary attack rate was found to be 8.5%, however the study assumed secondary

cases aquired their infections at home when it is possible they were acquired elsewhere (De Schrijver et al., 2011).

Within a household, multiple modes of transmission are possible. Transmission can occur from a common source of exposure, such as contaminated food or water, or due to secondary spread of infection from transmission through the oral fecal route (Leder et al., 2009). Asymptomatic carriers also can place a household at increased risk for secondary transmission (Bovee et al., 2012). Through many studies using various methods, it is clear that the presence of *Shigella* or another enteric pathogen in a household places those in contact or in close proximity with the infected individual at risk of acquiring that same infection.

Global Burden of Shigellosis

Worldwide, *Shigella* is responsible for over one million deaths and approximately 160 million infections. *Shigella* disproportionately affects developing countries, where 99% of all shigellosis infections take place annually. In 1999, it was estimated that 1.1 million (0.7%) of episodes result in death (Kotloff et al., 1999). However, between 1990 and 2010 the estimated percentage of shigellosis related deaths decreased approximately 37% (Lozano et al., 2012). It is estimated that less than 1% of cases are treated in hospitals (WHO, 2005). Worldwide, 69% of all shigellosis episodes and 61% of all shigellosis-related deaths occur in children <5 years old (Kotloff et al., 1999). After rotavirus, which is the most common cause of severe diarrheal disease worldwide (Parashar, Hummelman, Bresee, Miller, & Glass, 2003), *Shigella* has been

credited as the most frequent cause of diarrhea in sub-Saharan Africa and very impoverished areas of Asia (Ram et al., 2008; von Seidlein et al., 2006).

Antibiotic resistance is increasing among several strains of *Shigella*, which have acquired plasmid-encoded resistance to several antimicrobial drugs (Kotloff et al., 1999). Outbreaks of multi-drug resistant *Shigella* have been seen in many countries in sub-Saharan Africa (Ries et al., 1994). Worldwide, shigellosis outbreaks have been seen in prisons, day-care centers, mental hospitals, and other crowded settings characterized by poor hygiene. Although shigellosis is endemic to both tropical and temperate climates, each *Shigella* serogroup has a different geographic distribution. *S. sonnei* is the most common species isolated in industrialized nations, and *S. flexneri*, *S. boydii*, and *S. dysenteriae* are the most typical of developing countries (Mintz & Chaignat, 2008). Outbreaks of *S. dysenteriae* 1 are most common in overcrowded, impoverished settings with poor sanitation and hygiene, and have occurred in Africa, South Asia, and Central America (WHO, 2005).

Shigellosis in Kenya

More than 60% of the population in Nairobi, Kenya lives in urban settlements characterized by widespread poverty, high population density, poor sanitation, and a scarcity of safe drinking water and health services ("Matrix Development Consutants," 2003). In Kibera, one of the largest contiguous informal settlements in Africa, the burden of disease is high (Feikin et al., 2011). A recent study conducted in Kibera between May 1, 2008 and December 31, 2010 used population-based infectious disease surveillance (PBIDS) data to describe the epidemiology and

drug susceptibility patterns of shigellosis in the urban settlement. The study found that 24% of the 1,096 stool samples collected from the PBIDS study area in Kibera, contained *Shigella*. The overall crude incidence of 287/100,000 person years observed (PYO) revealed a high burden of shigellosis in Kibera. The authors used the incidence rates to project the burden of shigellosis among individuals living in all of Kibera and across all Kenyan informal settlements. They estimated that, annually "more than 1 in every 200 persons" living in Kibera are infected with *Shigella* and over 17,000 cases of shigellosis occur in Kenyan urban slums (Njuguna et al., 2013).

In Kibera, infants and adults ≥50 years old had the lowest adjusted incidence rates. The low incidence of shigellosis in people ≥50 years old was believed to be due to protective immunity, safer food preparation, and better hygiene. Females aged 35 – 49 years old were more likely than males to have shigellosis, perhaps as they are at greater risk of being infected by young children. Despite the fact that worldwide, most shigellosis associated infections occur in children <5 years of age (Kotloff et al., 2013; Kotloff et al., 1999), in Kibera the highest rates were found among adults between the ages of 35 and 49 years old (Njuguna et al., 2013). In rural western Kenya, among hospitalized children <5 years old, those who died were more likely to have *Shigella* isolated from their stool than those who survived (O'Reilly et al., 2012).

Chapter 3: Manuscript

Intra-Household Transmission of *Shigella* in an Urban Slum in Nairobi, Kenya

By Carmen Hazim

Abstract

Background: Worldwide, secondary attack rates of shigellosis in households have been found to be as high as 40%. While shigellosis incidence has been studied in urban informal settlements in Kenya, data on the transmission of *Shigella* within families and households are limited. Using population-based surveillance in an urban slum in Kenya, we performed a descriptive analysis of the frequency and possible transmission of shigellosis within households and calculated the incidence of diarrhea among shigellosis cases and their household contacts.

Methods: Population-based data were collected from periodic household interviews and stool specimens were collected for laboratory testing. We calculated the number of laboratory diagnosed shigellosis cases that belonged to common households (households with multiple cases) and the incidence of diarrhea in those households during the month before and after diagnosis. Households that saw one or more cases were stratified by time between cases and by number of household inhabitants.

Results: *Shigella* species were isolated from 508 (18%) of 2855 specimens tested. Approximately 18.5% of cases were from common households. Overall, 9% of households with one case of shigellosis had a second case. Households with ≥5 inhabitants were twice as likely to have a subsequent case diagnosed at any time during the study period. Among all household inhabitants, diarrhea incidence was higher in the month before the diagnosis of a shigellosis case in that household, than in the month after the diagnosis.

Conclusion: Confirmed shigellosis cases were frequently identified from common households. Larger households were at greatest risk for subsequent cases. Promotion of improved water, sanitation, and hygiene practices among household members is essential to prevent household transmission of *Shigella* in crowded settings. Interventions in informal settlements must consider targeting larger households and households with inhabitants in the age groups most at risk.

Introduction

Worldwide, *Shigella* is responsible for over one million deaths and approximately 160 million infections annually (Kotloff et al., 1999). The toxin-producing, Gram-negative bacteria are responsible for the acute enteric disease shigellosis, which is characterized by fever, nausea, vomiting, or cramps, in the presence of loose and often bloody stools (Bovee et al., 2012; Mintz & Chaignat, 2008; Njuguna et al., 2013). *Shigella* disproportionately affects developing countries, where 99% of all shigellosis infections take place (Kotloff et al., 1999). Within informal settlements, or urban slums, poverty, high population density, poor sanitation, and a scarcity of safe drinking water and health services present ideal conditions for the rapid spread of many diseases. *Shigella*'s low infectious dose (10 – 100 organisms) and ability to be transmitted from person-to-person or through ingestion of contaminated food or water, places those living in slums at an especially increased risk for infection (Mintz & Chaignat, 2008).

In 2006, the International Emerging Infections Program (IEIP) of KEMRI/CDC, a co-operation between the Centers for Disease Control and Prevention (CDC) and the Kenya Medical Research Institute (KEMRI), began conducting population-based infectious disease surveillance (PBIDS) in 2 of the 13 villages of Kibera, an urban slum in Nairobi, Kenya. Using PBIDS data, a recent study in Kibera, estimated that "more than 1 in every 200 persons" in Kibera experiences shigellosis yearly (Njuguna et al., 2013). While the study looked at incidence among individuals, it did not investigate the transmission of *Shigella* within families and households. Worldwide, secondary attack rates in households have been found to be as high as 40% and thus those living in close contact with an infected individual are at particularly higher risk (Mintz & Chaignat, 2008). While several analyses have revealed the need for more specific interventions targeting

transmission occurring within families, many of these studies took place in industrialized settings where the sanitation systems and hygiene practices are far superior to those found in the urban slum in Kenya (Bovee et al., 2012; De Schrijver et al., 2011; Ethelberg et al., 2004; Leder et al., 2009).

To fill the knowledge gap and assess the intra-household transmission of *Shigella* in Kibera, PBIDS data were analyzed to describe the frequency of shigellosis within households, the incidence of diarrhea in those households in the month before and after the date of diagnosis, and the demographic and clinical characteristics of both shigellosis cases and their household contacts. We hypothesized that the incidence of diarrhea in households with at least one case of shigellosis would be higher in the month before and after diagnosis when compared to the overall diarrhea incidence across Kibera, as suggested in previous literature (Feikin et al., 2011). The descriptive analysis of *Shigella*, as it affects intra-household transmission and the frequency of diarrhea within households in Kibera, can inform more robust strategies and innovative prevention measures that would be perhaps more relevant to developing countries and informal settlements in particular.

Methodology

Study site

Located in the heart of Nairobi, Kibera is one of the largest contiguous informal settlements in Africa. Like most slums, Kibera has inadequate water and sanitation infrastructures; water is often obtained from unregulated and possibly contaminated sources (Gulis, Mulumba, Juma, &

Kakosova, 2004; Njuguna et al., 2013). The KEMRI/CDC IEIP PBIDS study area is located in Gatwikera and Soweto West villages in Kibera. The PBIDS surveillance area is divided into 10 geographic clusters, or zones based on pre-existing neighborhoods (Njuguna et al., 2013). The Ngong River, which runs along the southern border of Kibera, is highly polluted with human excrement and waste.

Surveillance and laboratory procedures

The data collection and laboratory procedures used in PBIDS surveillance have been described previously (Brooks et al., 2006; Feikin, Audi, et al., 2010; Feikin et al., 2011; Njuguna et al., 2013). Briefly, population-based surveillance is used to prospectively collect data on key syndromes of diarrheal disease, febrile illness, tuberculosis, pneumonia, and jaundice in the Gatwikera and Soweto West villages of Kibera. Community interviewers are secondary school graduates trained by KEMRI/CDC clinicians on data collection and physical examinations in accordance with the World Health Organization's (WHO) Integrated Management of Childhood Illness (IMCI) (WHO, 2008). Visiting enrolled households bi-weekly, community interviewers collect data on illnesses, vaccinations, and deaths since the previous visit. The exact days of occurrence of cough, fever, and diarrhea symptoms are recorded. If a study participant is not home or is under 13 years of age, a proxy with knowledge of that individual's health is interviewed on their behalf. From September 2009 to June 2011, in response to the H1N1 epidemic, household surveillance switched from bi-weekly to weekly visits, thus shortening the recall period from 14 to 7 days.

Participants in PBIDS have access to free medical services at Tabitha Clinic, a study clinic owned and operated by the non-governmental organization Carolina for Kibera. At the end of each household visit, community interviewers encourage study participants who reported any signs of illness to visit the study clinic. Individuals seen at the clinic who met one of the following criteria were asked to provide stool samples for testing:

1. Diarrhea: 3 or more loose stools in 24 hours in the absence of signs of dehydration or dysentery. Stool samples were only collected from the first diarrhea-presenting patient ≥5 years old and the first patient <5 years old, each day.
2. Diarrhea with dehydration: diarrhea with symptoms of dehydration, which included drinking eagerly, sunken eyes, irritability, lethargy, and slow skin pinch.
3. Dysentery: diarrhea with observed or reported blood in stool.
4. Asymptomatic: No symptoms of illness in the last 2 weeks. Stool samples were collected monthly from 35 asymptomatic patients for use as controls.

Stools samples were collected at the clinic unless an individual was unable to provide a sample at that time, in which case they would be sent home with an empty container to be filled and picked up by a sample collector within 4 hours of leaving the clinic. Before May 2009, stool specimens were processed at the KEMRI/CDC microbiology laboratory in Kisumu, thereafter they were processed at Tabitha Clinic Laboratory using standard microbiological procedures (Bergey, Holt, & Krieg). All stool specimens were cultured for *Shigella*, nontyphoidal *Salmonella*, *Vibrio* species, and *Campylobacter* species. Using the Kirby-Bauer disc diffusion method (Bauer, Kirby, Sherris, & Turck, 1966), isolates of *Shigella*, nontyphoidal *Salmonella*, and *Vibrio* species were tested for antimicrobial susceptibility to commonly used antimicrobials including ampicillin, amoxicillin/ clavulanic acid, ceftriaxone, chloramphenical, ciprofloxacin,

gentamycin, kanamycin, nalidixic acid, streptomycin, sulfisoxazole, tetracycline, and trimethoprim-sulfamethoxazole. The Clinical Laboratory Standards Institute (CLSI) guidelines were used in the interpretation of the results (CLSI, 2006).

Period of study

Laboratory data from January 1, 2009 to December 31, 2012 were selected on the basis of quality and completeness (Njuguna et al., 2013). Additionally, household visit data were selected from an extended time interval of December 1, 2008 to January 31, 2013 to allow for investigations of disease transmission in households during the month before and after each laboratory diagnosis.

Case definitions

A shigellosis case was defined as a person enrolled in the PBIDS study who had a positive stool culture for *Shigella* between January 1, 2009 and December 31, 2012. For analysis purposes, individuals were considered to be shigellosis cases for the month before and after their date of diagnosis, after which time, they were considered non-shigellosis confirmed household contacts. An individual diagnosed with two different strains of *Shigella* within 1 month was considered as two different cases. A household contact was defined as any study participant who was not a shigellosis case at that time but rather an individual or family member residing in the same household as a shigellosis case. A *Shigella* household was considered any household that (1) had a household identification number and was enrolled in PBIDS between December 1, 2008 and January 31, 2013, (2) contained at least one laboratory confirmed shigellosis case, and (3) was present to be interviewed and thus found in the household visit data during the month before and

after the date of diagnosis of that case. In combination, all individuals, both cases and household contacts, residing in a *Shigella* household will henceforth be referred to as household inhabitants.

Analysis

The intra-household transmission of *Shigella* in Kibera slum was assessed using descriptive epidemiology. Data were analyzed using SAS version 9.3 (Cary, NC). We identified laboratory confirmed cases of shigellosis and their serogroups from data collected between January 1, 2009 and December 31, 2012. Due to missing data on the date of diagnosis, we considered the diagnosis date of a shigellosis case to be the date that the *Shigella* positive stool specimen was collected. Cases missing key household identification numbers were excluded. Household identification numbers for the remaining cases were used to identify *Shigella* households and household contacts from the household visit data in the month before and after diagnosis, between December 1, 2008 and January 31, 2013. In the event that household surveillance data was missing for a shigellosis case in the month before and after diagnosis, the interview data collected from that case's household contacts was still used in analysis as those contacts were still at risk for transmission. We did not follow a non-shigellosis confirmed household contact if they migrated out of the household during the month before or after the diagnosis date of each shigellosis case, as they were no longer considered at risk. We did, however, follow shigellosis cases if they migrated from one household to another during the study period.

To describe the demographic characteristics of shigellosis within Kibera, the total number of shigellosis cases and cases per serogroup were characterized for each age group, gender, year, and geographic zone. As geographic zones differ in size and proximity to the Ngong River, a

possible reservoir for *Shigella*, we sought to understand if an individual living in a zone bordering the river was at increased risk of shigellosis infection. We calculated the relative risk that living in a particular zone, compared with all other zones, poses for shigellosis infection in general and by *Shigella* serogroups. We calculated the risk in the exposed group as shigellosis cases living a particular zone divided by number of enrolled PBIDs participants living in that zone. The risk in the unexposed was calculated as all cases from other zones over the number of enrolled participants living in all other zones. Risk ratios were also calculated for cases that were not connected with a particular geographic zone, and thus labeled "zone X," because they either could no longer be located within the study area for household interviews, had migrated out of the study area, or refused to participate in household surveillance. In order to assess seasonal trends, we averaged shigellosis cases by month for the years 2009-2012. Monthly averages were charted in comparison with average monthly rainfall data obtained from the National Oceanic and Atmospheric Administration (NOAA) website Dagoretti Corner data station.

To assess the frequency of shigellosis within households we calculated the number of cases that belonged to common households, or households with multiple cases. To understand if the number of household inhabitants is related to the number of cases seen in a household, we stratified the number of households with one or more cases identified in household surveillance by the maximum number of inhabitants present for interviews during the study period. In addition, using laboratory data, we calculated the number of households that saw one or more cases and stratified those households by the time intervals between cases. We compared *Shigella* serogroups and antibiotic susceptibility patterns among cases that belonged to the same household and occurred within 2 months of each other, in order to evaluate whether the cases

were due to infection with the same strain which would be compatible with transmission that had occurred within the household. The longer the time interval between cases, the less likely that both had acquired their infections from the same source, or that one was the source of infection for the other. Thus, given typical incubation and shedding periods of 3 days and 4 weeks respectively, a 2-month interval was chosen.

To further assess for possible transmission between shigellosis cases and household contacts, the diarrhea incidence rate among shigellosis cases, household contacts, and all *Shigella* household inhabitants was calculated for each age group in the month before and after each shigellosis diagnosis. As previously described (Breiman et al., 2012; Feikin, Jagero, et al., 2010; Feikin et al., 2011), diarrhea incidence rates were calculated as number of new episodes of diarrhea per person-year of observation (PYO). Only new episodes of diarrhea reported on the interview day or the 3 days prior (days 0 – 3) were used to calculate incidence rates among children <5 years old. For persons ≥5 years old, new episodes of diarrhea reported on the interview day or 4 days prior (days 0 – 4), were used. The number of days used in the calculation of rates was restricted in order to minimize recall bias. A previous analysis of the PBIDS study methods and data quality found that an individual's ability to accurately recall events decays which time (Feikin, Audi, et al., 2010). Diarrhea rates were calculated as occurring in the month before or in the month after each shigellosis diagnosis, based on when days 0-3 or 0-4 fell in respect to the diagnosis date. A symptom-free interval for diarrhea was considered to be 3 days (Feikin et al., 2011). The denominator of person-years observed included all days during which a new episode might have occurred (days 0 – 3 for <5 years; days 0 – 4 for ≥5 years). We excluded days from

the denominator where there was no information as to whether or not an individual had an episode of diarrhea (Feikin, Audi, et al., 2010).

In studying clinical characteristics, we examined the antibiotic susceptibility patterns of *Shigella* isolates and symptoms reported by household inhabitants during household interviews. We identified shigellosis cases and household contacts that reported having diarrhea in the month before and after each case's diagnosis date, and counted the number of symptoms typical to shigellosis that they reported. As interviews did not record each symptom's exact days of occurrence, we determined if a symptom occurred before or after diagnosis, based on when the majority of that interview's recall days (4 or 7 days depending on if the interviews were weekly or bi-weekly) occurred. For example, if the majority of the days leading up to an interview took place in the month before a shigellosis diagnosis, then the symptoms reported in that interview were considered to have occurred in the month before diagnosis. Data on antibiotic susceptibility was used to assess resistance of all *Shigella* isolates and isolates by serogroup.

Ethical considerations

This project's protocol, surveillance questionnaires, and consent forms were reviewed and approved by the Ethical Review Committee at the Kenya Medical Research Institute (No. 1899) and the Institutional Review Board of CDC-Atlanta (No. 4566). For the collection of data at the clinic and households, written informed consent was obtained from participating individuals and the parents or guardians of minors.

Results

A total of 2855 stool specimens were tested between January 1, 2009 and December 31, 2012. Initially 514 out of the 2855 specimens tested were found positive for *Shigella*. After excluding 6 cases due to incorrect or missing household identification information, 508 (18%) shigellosis cases remained for inclusion in this analysis (**Figure 1**). As re-infection can occur, 14 study participants were diagnosed more than once. Household surveillance data were missing for 18 laboratory confirmed shigellosis cases (16 study participants) in the month before and after diagnosis, despite data being available for some of their family contacts.

Demographics

Shigella isolates included 321 (63%) *S. flexneri*, 48 (9%) *S. dysenteriae*, 43 (9%) *S. sonnei*, and 38 (8%) *S. boydii*. The specific *Shigella* species could not be determined for 58 (11%) of the isolates, and further sub-typing has yet to be carried out. *S. flexneri* was the most common cause of shigellosis among all age groups, genders, and years. Descriptive statistics for the shigellosis cases can be seen in **Table 1**. The majority (59%) of shigellosis cases were female. Females also accounted for the majority of cases within each serogroup. Adults 18 – 34 years old made up the largest proportion (38%) of cases overall and across all serogroups, while infants <1 year of age accounted for the smallest proportion (1%) of cases. A higher proportion (32%) of cases were diagnosed in 2010 than in 2009 (23%), 2011 (23%), or 2012 (22%). There were more cases (40%) of *S. dysenteriae* in 2009, and more unspeciated cases (41%) in 2011, than in any other year within the study period.

The highest proportion (19%) of shigellosis cases were from zone 2 of the study area, followed by 17% in zone 1 (**Table 2**). Zone 2 also had the highest proportion of cases among all

serogroups with the exception of *S. boydii*, which was found in more isolates from zone 10. We found that study participants who live in zone 2 were 1.72 (95% CI: 1.38 – 2.14) times more likely to be diagnosed with shigellosis than those living in any other zone (**Figure 2**). Similarly, participants living in zone 2 were 2.53 (95% CI: 1.28 – 5.02) times more likely to have *S. sonnei* and 1.66 (95% CI: 1.25 – 2.20) times more likely to have *S. flexneri* isolated from their stool than those living in any other zone. A significant positive association was also seen between residents of zone 4 and *S. dysenteriae* infection (RR: 2.98, 95% CI: 1.18 – 7.50). Although they were seen at the study clinic and thus in laboratory surveillance, 3% of cases were not connected with a particular geographic zone (identified as zone X in Table 2) as they either could no longer be located within the study area, had migrated out of the study area, or refused to participate in household interviews. **Figure 3** illustrates the seasonal trends of *Shigella* infection and rainfall. From 2009 to 2012, the highest concentrations of cases were diagnosed in May and November, with averages of 18 and 14 cases, respectively. For the same years, average rainfall increased to 5.22 inches in April and 1.69 inches in October from the months before.

Shigellosis within households

The 508 cases of shigellosis originated from 455 households (**Figure 4**). Of the 508 cases, 94 (18.5%) were from common households. Household visit data was missing for 13 of the 455 households and thus household size, reported symptoms, and diarrhea incidence were only calculated for the 442 remaining households. Using the household surveillance data from December 1, 2008 to January 31, 2013, we found that households with ≥5 inhabitants were 2.04 (95% CI: 0.99 – 4.16) times as likely to see a second case than those with <5 inhabitants. As can be seen in **Table 3**, households that only saw one shigellosis case during the study period,

typically had 5 – 6 household inhabitants. The majority of households that saw four cases during the study period had seven or more inhabitants.

The laboratory surveillance data from January 1, 2009 to December 31, 2012 revealed that out of 455 households only 41 (9%) ever saw a subsequent case, and 32 of these households only ever saw two cases during the study period (**Table 4**). The table shows that the number of households with two cases increased steadily as the time separating infection dates increased. It is important to note that these time intervals are cumulative, thus the cases that were 1 week apart were also within 3 months of each other. While six households each saw three cases at any time during the study period and three households saw four cases at any time during the study period, there were no households that ever saw more than two cases fall within 3 months of each other.

Out of the 11 households that had two cases within at most 2 months of each other, only six households had both cases infected with the same serogroup. *S. flexneri* was the most common serogroup to be isolated from these households. Antimicrobial susceptibility data was available for both cases in three of the six households. For two of the three households, antimicrobial resistance either increased from the first case to the second case, or remained the same. In the third household, both cases had matching levels of susceptibility for all but two antibiotics, to which the first case showed resistance and the second case showed sensitivity.

Among all household inhabitants, the incidence rates of diarrhea were typically higher in the month before a diagnosis of shigellosis than in the month after (**Table 5**). In all three groups diarrhea incidence was highest among persons 12 – 23 months old. The 12 – 23 month old

shigellosis cases had 15.51 new diarrhea episodes per person year observed (PYO) in the month before diagnosis and 4.25 new diarrhea episodes per PYO in the month after diagnosis. In the month after diagnosis, the majority of household contacts had higher rates of diarrhea than shigellosis cases.

Clinical characteristics

Of the 490 shigellosis cases, for whom data from household interview were available, 30% reported diarrhea at any time in the month before diagnosis and 24% in the month after. Among household contacts, 5% reported having diarrhea at any time in the month before or after a shigellosis case was diagnosed in their household. A higher percentage of shigellosis cases with diarrhea reported having blood in their stools than household contacts. As shown in **Table 6**, higher proportions of shigellosis cases with diarrhea in the month before laboratory diagnosis reported symptoms than those with diarrhea in the month after. The majority of shigellosis cases with diarrhea reported having watery stools (75% in month before and after), abdominal pain (83% in month before, 97% in month after), fever (60% in month before, 68% in month after), and restlessness or irritability (50% in month before, 63% in month after). The majority of household contacts with diarrhea also reported these symptoms, with the exception of restlessness and irritability. In the month before diagnosis, a higher percentage of household contacts reported having water stools, vomiting, and being very thirsty.

Of the 508 *Shigella* isolates, only 379 (75%) had antimicrobial susceptibility testing completed (**Table 7**). The majority of shigellosis isolates were resistant to the following antibiotics: trimethoprim-sulfamethoxazole (91%), sulfisoxazole (77%), tetracycline (75%), streptomycin

(65%), and ampicillin (62%). Isolates from all serogroups showed resistance to trimethoprim – sulfamethoxazole, sulfisoxazole, tetracycline, and streptomycin. In addition, the majority of *S. flexneri* and *S. boydii* isolates were resistant to ampicillin. The greatest number of isolates showed sensitivity to ceftriaxone, ciprofloxacin, gentamycin, kanamycin, and nalidixic acid.

Discussion

Our study found that approximately 18% of all stool specimens tested between January 1, 2009 and December 31, 2012 were culture positive for *Shigella*. *S. flexneri* was the most common species isolated, a finding typical of many developing countries (Kotloff et al., 1999; Njuguna et al., 2013; Ram et al., 2008; von Seidlein et al., 2006). In addition, the greatest proportions of cases were among females and individuals 18 – 34 years of age. While laboratory-confirmed cases of shigellosis were diagnosed year round, higher concentrations of cases were seen in May and November. It is typical for diarrhea incidence to increase in a population following a period of rain (Carlton et al., 2014). The increase in rainfall in April and October, due to the rainy seasons in Kenya, corresponded accordingly with the higher number of cases in May and November. The highest proportion of cases was diagnosed in 2010, possibly an effect of the increased frequency of household interviews from bi-weekly to weekly. While there is not a significant risk of *Shigella* infection in any of the zones bordering the Ngong River, our calculations indicated that those living in zone 2 have a higher risk. However, as **Figure 2** illustrates, the location of the study clinic in zone 2 may have influenced the health seeking behaviors of the inhabitants living in that zone or in close proximity to the study clinic (Breiman et al., 2011).

A higher percentage of shigellosis cases reported diarrhea than household contacts. The majority of shigellosis cases and household contacts with diarrhea reported having watery stools, abdominal pain, fever, and restlessness or irritability. While it is possible that the typical shigellosis symptoms reported among household contacts with diarrhea were indicators of a *Shigella* infection, these symptoms could indicate infections caused by other pathogens. Household contacts with diarrhea who reported vomiting, nausea, and abdominal pain may have been infected with *Shigella*; however, infection with another enteric pathogen is also possible as testing was not carried out to determine etiology (O'Reilly et al., 2012).

Among shigellosis cases, there was a higher rate of diarrhea in the month before diagnosis compared with the month after. In the month after diagnosis, the rate of diarrhea was typically higher among household contacts than shigellosis cases. The higher rate of diarrhea in children <5 years old is consistent with the fact that, worldwide, children in general have higher rates of diarrhea (Kotloff et al., 2013; Lozano et al., 2012). As hypothesized, households with at least one shigellosis case had a higher incidence of diarrhea than was found among all PBIDS participants by a previous study (Feikin et al., 2011). Although the previous study calculated diarrhea incidence for a different time interval, the higher rate found in our study may indicate that the presence of a shigellosis case in a household can increase diarrhea incidence among both infected individuals and household contacts.

Approximately 18.5% of cases were from common households. The majority of households with one case of shigellosis never saw a second case during the study period. Additionally, very few households had two or more cases diagnosed within 2 months of each other. We hypothesize that out of the 11 households that had two cases within at most 2 months of each other, secondary transmission most likely occurred in the two households that had the same serogroup isolated and similar patterns of antimicrobial resistance. Our calculations did, however, show that households with ≥5 inhabitants were twice as likely to have a subsequent case diagnosed at any time during the study period. Although the number was not significant, it suggests that the number of household inhabitants may influence intra-household transmission. As most *Shigella* households had ≥5 inhabitants we would have expected to see even more cases than were identified through laboratory surveillance. In addition, we would have expected to see more cases from common households be diagnosed within 2 months of each other, as the high population density, over-crowded homes, poor sanitation and hygiene practices, and open channels of raw sewage present in Kibera can increase the likelihood of acquiring *Shigella*.

Many findings from our study were consistent with previous literature. The high proportion of shigellosis cases identified is consistent with earlier studies and indicates a high burden of shigellosis in Kenya (Brooks et al., 2006; Njuguna et al., 2013; Shapiro et al., 2001). While most studies have found the highest burden of shigellosis in children <5 years old (Kotloff et al., 1999; Rolfo et al., 2012; von Seidlein et al., 2006), the older age range (18–34 years olds) identified in our study was consistent with the recent study of shigellosis in Kibera (Njuguna et al., 2013). A previous study from Denmark found that 11.9% of all *S. sonnei* cases belonged to common households (Ethelberg et al., 2004). As Demark is more developed than Kenya, it is

understandable that our study found a higher percentage (18.5%) of cases from common households. Antibiotic susceptibility testing revealed that many *Shigella* isolates were resistant to commonly used antimicrobials, a trend seen by several previous studies (Brooks et al., 2006; Gaudreau et al., 2011; Iwalokun et al., 2001; Peirano, Souza, Rodrigues, & *Shigella* Study, 2006).

As the stool specimens were serotyped using more conventional methods, we were unable to assess the true extent of intra-familial transmission of *Shigella* in Kibera with the same degree of certainty that methods such as molecular fingerprinting could have provided (De Schrijver et al., 2011; Khan et al., 2006). The lack of complete data on *Shigella* serotypes, such as *S. dysenteriae* type 1, prevented us from distinguishing cases as primary or secondary and determining if infection had been acquired from another household inhabitant or an individual outside the home (Bovee et al., 2012; De Schrijver et al., 2011). It is also possible that multiple pathogens were present in some stool samples.

It is likely that some cases of shigellosis were missed by clinic and laboratory surveillance. Furthermore, some household contacts of shigellosis cases may have been among the missed cases. Among the variety of reasons cases could have been missed, PBIDS study participants may have (1) visited a clinic other than Tabitha Clinic, (2) not sought treatment, (3) been asymptomatic or unaware of his or her infection, or (4) self-medicated - many antibiotics are readily available without a prescription (Breiman et al., 2011; Njuguna et al., 2013; Taffa & Chepngeno, 2005).

Due to the long recall period, symptoms typical of shigellosis and days of diarrhea reported by study participants were subject to recall bias or even misclassification (Feikin, Audi, et al., 2010). In addition, misclassification may have occurred for symptoms reported by proxies with limited knowledge of the true symptoms experienced by a study participant. These limitations may have affected our calculation of diarrhea incidence rates as diarrhea incidence was calculated using days of diarrhea reported during household interviews. Another limitation is that we did not calculate the diarrhea incidence among persons in households without a laboratory diagnosis during the study period, and we only calculated diarrhea incidence in *Shigella* households in the month before and month after a case was diagnosed in that household. Thus we did not have baseline rates of diarrhea in households to compare with the rates we calculated when *Shigella* was present in a household inhabitant. Ideally we would want a comparison group to see if the rate of diarrhea in *Shigella* households is higher than in households without a laboratory diagnosis of any kind. This is an analysis that must be considered in the future.

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Tables and Figures

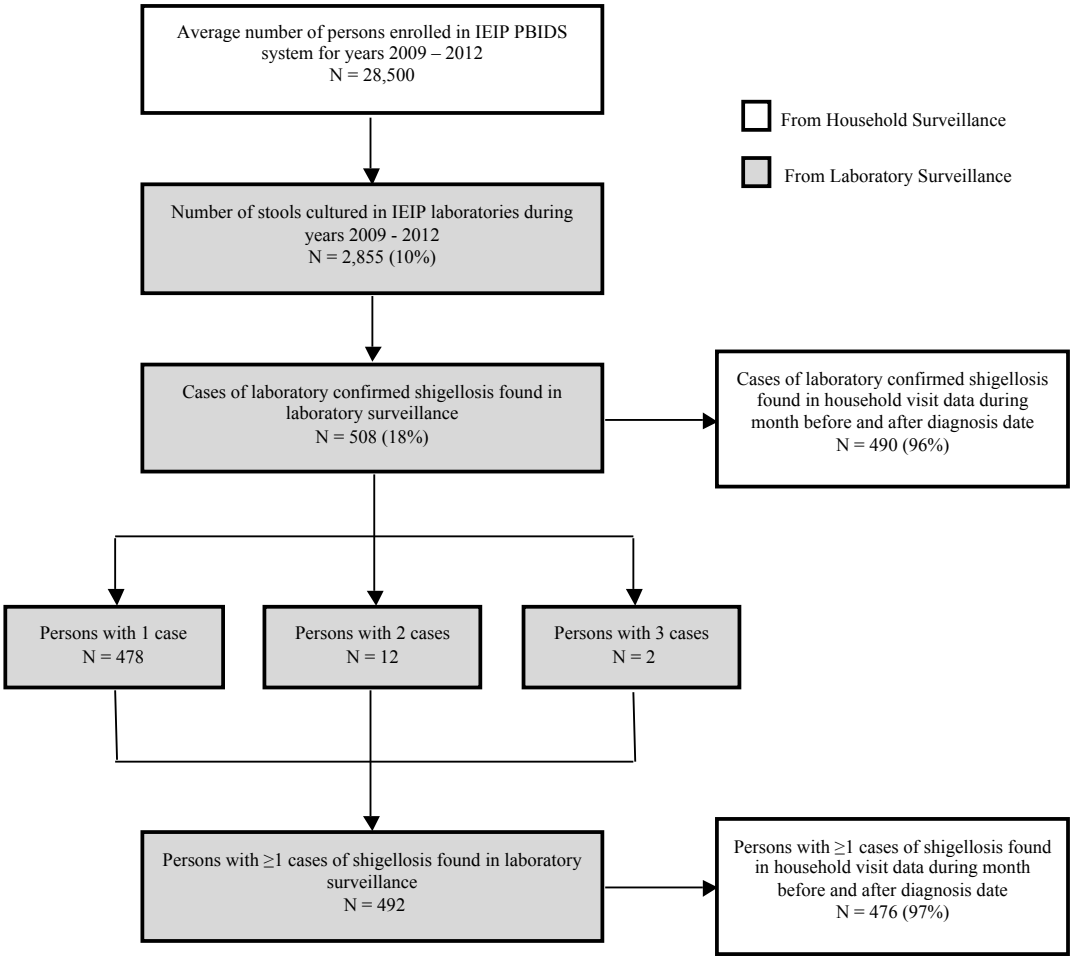


Figure 1: Flow chart illustrating the layout of shigellosis cases diagnosed in Kibera, Kenya over years 2009 – 2012.

Table 1: Demographic information of laboratory confirmed shigellosis cases, stratified by serogroups, in Kibera, Nairobi, Kenya, Jan 1, 2009 – Dec 31, 2012.

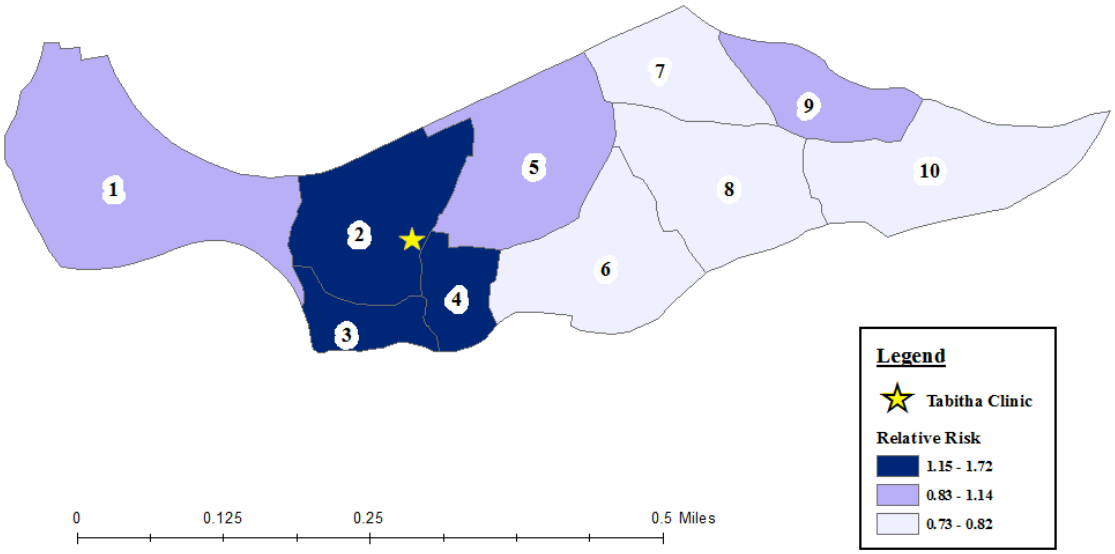
	Number of laboratory confirmed cases (%)					
	All *Shigella*	*S. boydii*	*S. dysenteriae*	*S. flexneri*	*S. sonnei*	Unspeciated
Gender						
Male	206 (41)	15 (39)	23 (48)	133 (41)	16 (37)	19 (33)
Female	302 (59)	23 (61)	25 (52)	188 (59)	27 (63)	39 (67)
Age						
<12 m	5 (1)	0 (0)	1 (2)	2 (1)	0 (0)	2 (3)
12 – 23 m	26 (5)	1 (3)	0 (0)	20 (6)	3 (7)	2 (3)
24 – 59 m	51 (10)	4 (11)	2 (4)	34 (11)	5 (12)	6 (10)
5 – 9 y	43 (8)	3 (8)	5 (10)	25 (8)	4 (9)	6 (10)
10 – 17 y	95 (19)	7 (18)	14 (29)	51 (16)	11 (26)	12 (21)
18 – 34 y	194 (38)	17 (45)	17 (35)	128 (40)	14 (33)	18 (31)
35 – 49 y	80 (16)	6 (16)	8 (17)	50 (16)	6 (14)	10 (17)
≥ 50 y	14 (3)	0 (0)	1 (2)	11 (3)	0 (0)	2 (3)
Year						
2009	115 (23)	4 (11)	19 (40)	69 (21)	13 (30)	10 (17)
2010	164 (32)	25 (66)	14 (29)	100 (31)	13 (30)	12 (21)
2011	116 (23)	3 (8)	11 (23)	66 (21)	12 (28)	24 (41)
2012	113 (22)	6 (16)	4 (8)	86 (27)	5 (12)	12 (21)
Overall	508 (100)	38 (100)	48 (100)	321 (100)	43 (100)	58 (100)

Table 2: Frequency of shigellosis cases for each geographic zone and relative risk of living in a zone compared to any other zone, stratified by serogroup in Kibera, Kenya 2009 - 201

Zone*	All *Shigella*		*S. boydii*		*S. dysenteriae*		*S. flexneri*		*S. sonnei*		Unspeciated	
	No. (%)	RR (95% CI)	No. (%)	RR (95% CI)	No. (%)	RR (95% CI)	No. (%)	RR (95% CI)	No. (%)	RR (95% CI)	No. (%)	RR (95% CI)
1	87 (17)	1.01 (0.80-1.27)	6 (16)	0.92 (0.38-2.19)	8 (17)	0.98 (0.46-2.09)	58 (18)	1.08 (0.81-1.43)	7 (16)	0.95 (0.42-2.14)	8 (14)	0.78 (0.37-1.65)
2	96 (19)	1.72 (1.38-2.14)	6 (16)	1.38 (0.58-3.30)	8 (17)	1.47 (0.69-3.15)	59 (18)	1.66 (1.25-2.20)	11 (26)	2.53 (1.28-5.02)	12 (21)	1.92 (1.02-3.63)
3	18 (4)	1.19 (0.75-1.89)	3 (8)	2.77 (0.85-9.00)	2 (4)	1.41 (0.34-5.79)	10 (3)	1.04 (0.56-1.95)	2 (5)	1.58 (0.38-6.52)	1 (2)	0.57 (0.08-4.09)
4	26 (5)	1.38 (0.93-2.04)	2 (5)	1.42 (0.34-5.90)	5 (10)	2.98 (1.18-7.50)	15 (5)	1.26 (0.75-2.10)	1 (2)	0.61 (0.08-4.42)	3 (5)	1.40 (0.44-4.46)
5	58 (11)	1.14 (0.87-1.50)	1 (3)	0.24 (0.03-1.75)	6 (13)	1.27 (0.54-2.98)	40 (12)	1.26 (0.91-1.75)	3 (7)	0.66 (0.21-2.15)	8 (14)	1.42 (0.67-2.99)
6	42 (8)	0.73 (0.54-1.00)	3 (8)	0.7 (0.21-2.27)	4 (8)	0.74 (0.27-2.06)	27 (8)	0.75 (0.50-1.11)	5 (12)	1.07 (0.42-2.72)	3 (5)	0.44 (0.14-1.42)
7	24 (5)	0.8 (0.53-1.20)	2 (5)	0.9 (0.22-3.72)	1 (2)	0.34 (0.05-2.49)	16 (5)	0.85 (0.51-1.40)	1 (2)	0.38 (0.5-2.79)	4 (7)	1.20 (0.43-3.30)
8	50 (10)	0.78 (0.58-1.04)	6 (16)	1.34 (0.56-3.21)	4 (8)	0.65 (0.23-1.81)	28 (9)	0.68 (0.46-1.01)	3 (7)	0.54 (0.17-1.73)	9 (16)	1.31 (0.65-2.67)
9	30 (6)	0.91 (0.63-1.31)	2 (5)	0.81 (0.19-3.35)	1 (2)	0.31 (0.04-2.24)	19 (6)	0.91 (0.58-1.45)	4 (9)	1.49 (0.53-4.16)	4 (7)	1.08 (0.39-2.96)
10	61 (12)	0.82 (0.63-1.07)	7 (18)	1.35 (0.59-3.07)	6 (13)	0.85 (0.36-2.01)	37 (12)	0.78 (0.55-1.10)	5 (12)	0.79 (0.31-1.99)	6 (10)	0.69 (0.30-1.61)
X	16 (3)	0.72 (0.44-1.17)	0 (0)	0.00 -	3 (6)	1.44 (0.46-4.52)	12 (4)	0.85 (0.48-1.51)	1 (2)	0.53 (0.07-3.78)	0 (0)	0.00 -
Total	508 (100)		38 (100)		48 (100)		321 (100)		43 (100)		58 (100)	

* Participants in zone X either could no longer be located within the study area for household interviews, had migrated out of the study area, or refused to participate in household surveillance.

Risk ratios were calculated using the number of enrolled partcipants living in a particular zone as persons at risk and shigellosis cases living in that zone as the exposed group that saw an shigellosis outcome. The unexposed group consisted of all participants living in other zones.



Data Source: KEMRI / CDC International Emerging Infections Program

Figure 2: Map of Risk Ratios of shigellosis diagnosis by geographic zone in Gatwikera and Soweto West villages of Kibera, Nairobi, Kenya.

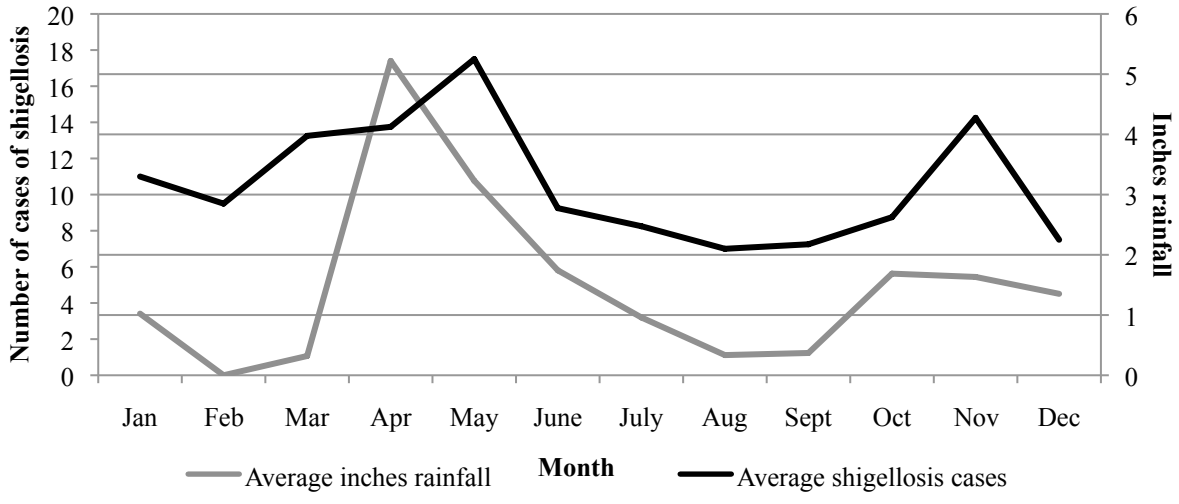


Figure 3: Average monthly shigellosis cases and average monthly rainfall in Kibera, Kenya over years 2009 – 2012.

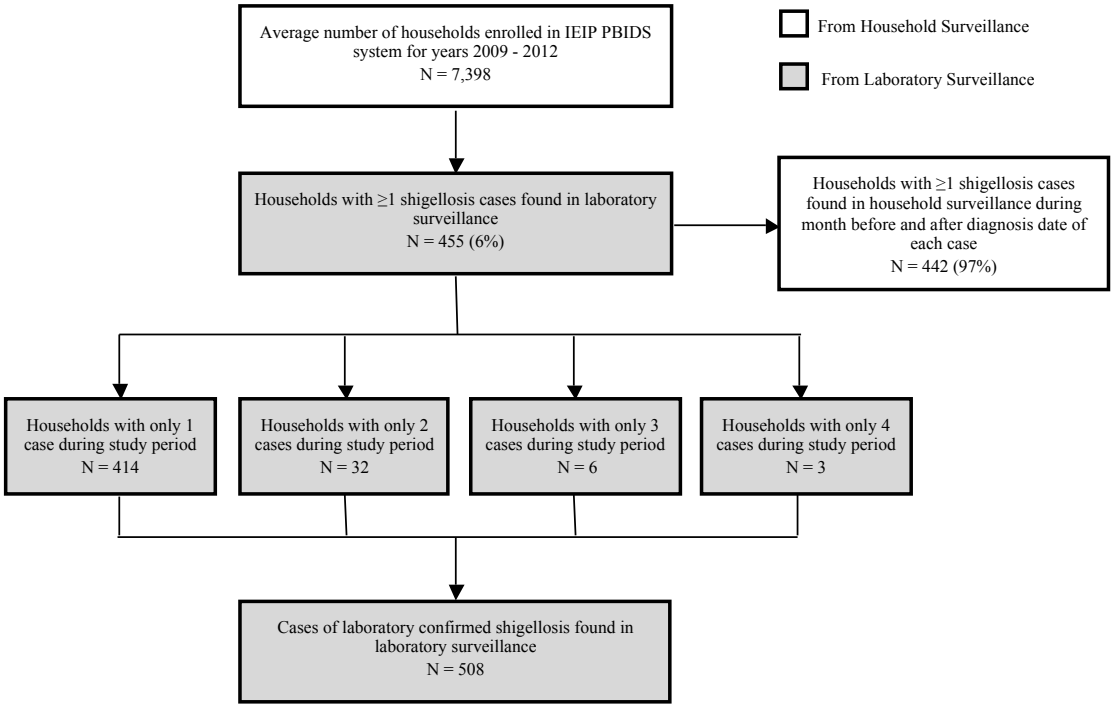


Figure 4: Flow chart illustrating the layout of households with one or more cases of shigellosis in Kibera, Kenya over years 2009 – 2012.

Table 3: Frequency of households with ≥1 shigellosis cases divided into the maximum number of household inhabitants, from household surveillance in Kibera, Kenya, Dec 1, 2008 – Jan 31, 2013.

No. of cases	No. of households* (%)	Number of Shigellosis households divided into the maximum number of household inhabitants (%) **			
		1 – 2 people	3 – 4 people	5 – 6 people	7+ people
1	401 (100)	44 (11)	108 (27)	131 (33)	118 (29)
2	32 (100)	0 (0)	6 (18)	13 (41)	13 (41)
3	6 (100)	1 (17)	1 (17)	0 (0)	4 (66)
4	3 (100)	0 (0)	1 (33)	0 (0)	2 (67)
Total	442 (100)	45 (10)	116 (26)	144 (33)	137 (31)

*Household visit data was missing for 13 households identified in laboratory surveillance.

**Household size includes all household inhabitants that were enrolled in PBIDS and present for interview one month before and after a case of shigellosis.

Table 4: Number of households with ≥1 cases of shigellosis divided into time intervals between diagnosis dates, from laboratory surveillance in Kibera, Kenya, Jan 1, 2009 – Dec 31, 2012.

Number of cases	Number of shigellosis households divided into time between diagnosis dates of cases in those households*					
	At any time**	Within 3 months	Within 2 months	Within 1 month	Within 2 weeks	Within 1 week
1	414	-	-	-	-	-
2	32	16	11	7	5	3
3	6	0	0	0	0	0
4	3	0	0	0	0	0
Total	455	16	11	7	5	3

*Time segments are cumulative. "Within 3 months" includes households seen within 2 and 1 months.

**Includes all households that saw at least one case of shigellosis identified in the laboratory surveillance.

Table 5: Rates of diarrhea incidence per person year observed (PYO) during month before and after each shigellosis diagnosis, from household surveillance in Kibera, Kenya, Dec 1, 2008 – Jan 31, 2013.

Age	Shigellosis Cases		Household Contacts		All Household Inhabitants	
	In month before	In month after	In month before	In month after	In month before	In month after
<12 m	14.05	0.00	4.22	4.10	4.72	3.93
12 – 23 m	15.51	4.25	7.83	4.27	9.50	4.27
24 – 59 m	3.36	1.58	1.77	1.79	1.99	1.76
5 – 9 y	4.52	0.00	0.46	0.66	0.84	0.60
10 – 17 y	5.00	0.29	0.57	0.36	1.33	0.35
18 – 34 y	5.98	1.01	0.14	0.31	1.40	0.46
35 – 49 y	6.00	0.38	0.33	0.61	1.58	0.56
50+ y	4.51	2.85	0.00	0.00	0.72	0.48

Table 6: Frequency of symptoms reported among shigellosis cases and household contacts that reported diarrhea in the month before and after each shigellosis diagnosis, from household surveillance in Kibera, Kenya, Dec 1, 2008 – Jan 31, 2013.

Symptoms	Among shigellosis cases that reported diarrhea (%)		Among household contacts that reported diarrhea (%)	
	In month before N=149	In month after N=117	In month before N=109	In month after N=108
Blood in stool	60 (40)	49 (42)	11 (10)	14 (13)
Watery stool	112 (75)	88 (75)	97 (89)	83 (77)
Nausea	49 (33)	38 (32)	29 (26)	31 (29)
Abdominal pain	124 (83)	97 (93)	60 (55)	73 (68)
Fever	89 (60)	80 (68)	61 (56)	59 (55)
Vomiting	39 (26)	36 (31)	37 (34)	32 (30)
Very Thirsty	64 (43)	64 (55)	66 (61)	46 (43)
Convulsions*	0 (0)	1 (1)	1 (1)	4 (4)
Restless or Irritable*	74 (50)	74 (63)	41 (38)	28 (26)

*Typical of children under 5 years of age

Table 7: Antibiotic resistance of *Shigella* isolated from stools, from laboratory surveillance in Kibera, Kenya, Jan 1, 2009 – Dec 31, 2012.

Antibiotic tested	Number of *Shigella* Resistant (%)					
	All *Shigella* N= 379*	*S. boydii* N=32	*S. dysenteriae* N=34	*S. flexneri* N=238	*S. sonnei* N=32	Unspeciated N=42
Amoxicillin/clavulanic acid	122 (32)	13 (41)	4 (12)	87 (37)	4 (13)	14 (33)
Ampicillin	235 (62)	21 (66)	16 (47)	166 (70)	6 (19)	26 (62)
Ceftriaxone	4 (1)	0 (0)	0 (0)	4 (2)	0 (0)	0 (0)
Chloramphenicol	89 (23)	3 (9)	3 (9)	68 (29)	2 (6)	13 (31)
Ciprofloxacin	5 (1)	0 (0)	0 (0)	4 (2)	0 (0)	1 (2)
Gentamycin	9 (2)	1 (3)	0 (0)	7 (3)	0 (0)	1 (2)
Kanamycin	11 (3)	1 (3)	1 (3)	7 (3)	1 (3)	1 (2)
Nalidixic acid	11 (3)	2 (6)	1 (3)	6 (3)	0 (0)	2 (5)
Streptomycin	248 (65)	25 (78)	27 (79)	140 (59)	25 (78)	31 (74)
Sulfisoxazole	290 (77)	26 (81)	30 (88)	177 (74)	26 (81)	31 (74)
Tetracycline	283 (75)	27 (84)	17 (50)	177 (74)	31 (97)	31 (74)
Trimethoprim-sulfamethoxazole	346 (91)	29 (91)	31 (91)	218 (92)	31 (97)	37 (88)

*129 isolates did not have drug susceptibility tests done as antibiotics were probably not available when they were being tested

Chapter 4: Conclusions and Recommendations

Our study found that nearly a fifth of all diagnosed cases were from common households, although a low proportion of households ever saw more than one laboratory-confirmed case of shigellosis during the study period. While it is possible that some shigellosis cases identified through laboratory surveillance acquired their infection from outside of the household as opposed to within, their infection may have still placed their household contacts at risk. The majority of households with at least one shigellosis case contained five or more inhabitants and individuals living in those households were found to be at increased risk for *Shigella* infection as among households with at least one shigellosis case, those with five or more inhabitants were twice as likely to have a second shigellosis case diagnosed, than those with fewer inhabitants.

The current situation of household transmission of *Shigella* portrays an social inequity between those with the resources and knowledge to prevent transmission and those without. Along with previous literature, our study implicates the need for better nutrition, improved breastfeeding practices, less household crowding, increased access and use of safe drinking water, and improved sanitation and hygiene practices such as hand washing with soap, safe disposal of human waste and diapers, proper sanitization of soiled clothing and other fomites, control of flies, and safe handling and processing of food (De Schrijver et al., 2011; Ethelberg et al., 2004; Kotloff et al., 1999; Mintz & Chaignat, 2008; Njuguna et al., 2013; Ram et al., 2008; Rolfo et al., 2012; Sansonetti, 2006; von Seidlein et al., 2006; WHO, 2005). As confirmed shigellosis cases in Kibera were frequently identified from the same households, it is important that interventions focus on these prevention measures within households and among family members.

Ideally, a study of intra-household transmission would involve strain discrimination, which can be achieved using more robust serotyping methods such as molecular fingerprinting or genomic sequencing (Fernandez-Prada et al., 2004; Khan et al., 2006; Talukder, Dutta, & Albert, 1999; Tenover et al., 1995). Future studies should consider including such an analysis and should include a comparison group to see if the rate of diarrhea in households with a case of shigellosis is higher than in households without a laboratory confirmed diagnosis of any kind. Lastly, in addition to number of household inhabitants, future studies should consider an analysis of more detailed household characteristics such household structure, proximity to open sewage and water source, type of water source, age of primary case in household, highest level of education attained by the head of household, and number of household contacts under the age of five (Bovee et al., 2012; Breiman et al., 2011; Marathe, Lewis, Chen, & Eubank, 2011; Taffa & Chepngeno, 2005). These analyses should allow for a more accurate understanding of the intra-familial transmission of *Shigella.*

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