Detection, Risk Factors and Antibiogram of *Shigella dysenteriae* and *Shigella flexneri* in Young Children with Acute Gastroenteritis in Uyo Metropolis, Nigeria

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ABSTRACT

Shigella plays an important role as causative agent of acute gastroenteritis, especially in developing countries. This study aimed to determine the prevalence of shigellosis, antibiogram and predisposing factors in children aged five years and below having acute gastroenteritis in Uyo metropolis, Akwa Ibom State. This was a descriptive cross-sectional study involving 250 young children with acute gastroenteritis seen at the paediatric unit of University of Uyo Teaching Hospital, Uyo; St. Luke's Hospital, Anua and Nedeke Children's Hospital, Uyo from October 2018 to March 2019. Fresh stool samples were collected using a clean universal container and cultured using MacConkey and Deoxycholate citrate agar. Biochemical identification and serotyping using polyvalent antisera were conducted. Shigella were detected in 8(3.2%) of the children's stool samples. Shigella species identified were S.dysenteriae, 4(2.4%) and S.flexneri, 2(0.8%). Majority of the children with shigellosis were males, 6(4.6%), and children aged 13-24 months had the highest prevalence of the infection, 3(4.7%). St. Luke's Hospital, Anua had the highest number of infection, 4(8.0%) and overall Shigella infection. Children whose parents/caregivers mostly used sachet water, 4(10.3%) and borehole water, 2(4.3%) for drinking were significantly affected with shigellosis (p=0.006). Findings revealed that shigella remains one of the bacterial pathogens causing acute gastroenteritis among children in Uyo with S.dysenteriae as the predominant species. All the shigella isolates exhibited multi-drug resistance and ingestion of contaminated water was a risk factor. These findings are of immense public health concern.

Keywords: Shigellosis, Children, Acute Gastroenteritis, Uyo

INTRODUCTION

Acute gastroenteritis also described as infectious diarrhoea is one of the leading causes of illness and death in infants and children throughout the world, especially in developing countries.[1] Gastroenteritis is a medical condition characterized by inflammation of the gastrointestinal tract (gut) that involves the stomach and the small intestine, resulting in some combination of diarrhoea, vomiting, abdominal pain and cramping. Worldwide, bacteria pathogens account for about 15% of the cause of acute gastroenteritis, with the most common types being *Escherichia coli, Salmonella* species, *Shigella* species and *Campylobacter* species.[2]

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Shigella is a group of bacteria among the diarrhoeal pathogens that continues to play a major role in aetiology of invasive intestinal infections leading to dysentery.[3] *Shigella i*s transmitted by the faecal-oral route, including direct person-to-person contact and indirectly through ingestion of contaminated food or water.[4] Clinically, shigellosis manifests as watery or bloody diarrhoea and presents a serious challenge to public health authorities worldwide.[5] WHO has previously estimated that each year, about 80 million persons are affected by shigellosis globally, especially in developing countries and predominantly in children.[6] A decade ago, *Shigella* species was reported as the leading cause of childhood diarrhoea in developing countries with case-fatality rates of up to 28% reported in Kenya.[7,8]

Shigella is a highly contagious, Gram-negative, non-motile bacilli belonging to the family e*nterobacteriaceae*. The genus shigella includes four species: *S.dysenteriae, S.flexneri, S.Boydii* and *S.sonnei*, also designated groups A, B, C and D,

respectively.[9] Shigella serogroup and serotype are identified by slide agglutination using polyvalent and monovalent antisera, respectively. Except for *S.sonnei*, each *Shigella* species/group can be divided into serotypes based on reactivity with monovalent antisera: *S.dysenteriae* (15 serotypes), *S.flexneri* (6 serotypes and 2 variants), and *S.boydii* (20 serotypes).[10] *S. sonnei* and *S.boydii* usually cause relatively mild illnesses in which diarrhoea may be watery or bloody. In Lagos, Nigeria, *Shigella flexneri* was reported as the main cause of endemic shigellosis[11] and is characterized by long-term persistence of sublineages in shigellosis-endemic regions with inadequate hygienic conditions and unsafe water supplies.[12] *S.dysenteriae* are the more rarely isolated species and has been associated with past large-scale shigellosis epidemics.[13]

Shigella dysenteriae serotype 1 is the aetiologic agent of epidemic dysentery and differs from other dysentery-causing bacilli by its capacity to form a powerful exotoxin known as Shiga toxin (Stx).[14] Illnesses with *Shigella dysenteriae* are accompanied by fever, vomiting, stomach cramps, short-lived diarrhoea and passage of scanty stools of mucus with pus and blood.[5] It is most likely to occur in children, especially among those in crowded households and those with pre-existing poor nutritional status.[15] It produces severe disease associated with life-threatening complications.[16] Although dysentery is normally self-limiting in adults, it can be fatal in infants and young children. Haemolytic-uraemic syndrome (a complication resulting in bleeding, anaemia and kidney failure) and leukaemoid reaction (blood findings resembling leukaemia) complicate infection caused by *S. dysenteriae* type 1 and may be fatal in some cases.[17] The highest rates of complications occur in malnourished infants. Nevertheless, even well-nourished children can develop a more severe form of the disease, which in most cases may be fatal.[18]

Resistance of *Shigella* species to sulfonamides, tetracyclines, ampicillin, and sulfamethoxazole-trimethoprim has been reported worldwide and these agents are not recommended as empirical therapy unless local microbiologic data suggest susceptibility.[19] Similarly, a study in Lagos, Nigeria suggested exclusion of these antibiotics as first-line drugs in the treatment of shigellosis due to reported drug resistance.[20] The WHO's guidelines recommended the use of ciprofloxacin as the drug of choice to reduce mortality and morbidity rates associated with the disease including reduction in organism-excretion time among those infected.[6] However, rising cases of multidrug resistance and resistance to ciprofloxacin have been reported for shigella isolates from Asian and some African countries.[21] The third-generation cephalosporin (ceftriaxone) and the macrolide (azithromycin), which the WHO recommends as second-line therapy, are expensive, restricting their use.[6]

There is dearth of information on the epidemiology of shigellosis and no antibiotic usage policy to guide treatment of shigellosis among young children in Akwa Ibom State. This study was therefore aimed to investigate the prevalence of shigella infection, antibiogram and plausible predisposing factors in children five years and below having acute gastroenteritis in Uyo metropolis, Akwa Ibom State.

MATERIALS AND METHODS

Study Area

This study was conducted in Uyo, the capital of Akwa Ibom State located in south-south geographical zone of Nigeria. Uyo metropolis has a population size of about 427,873[22] and is a fast-growing city, both economically and population wise. The city lies on the geographical coordinates of 5° 3'0" N Latitude and 7° 56'0" E Longitude and located in the rainforest belt with an elevation of less than two feet above sea level. Despite its present status of being a developing state capital and Akwa Ibom State being adjudged as one of the cleanest States in Nigeria, Uyo is still dotted with overcrowding, unsafe drinking water, dirty surroundings and poor drainage systems. Uyo is a tableland and

suffers perennial flooding during rainy seasons. The temperature hovers around 26°C while annual rainfall is 362.5mm[3]. The climate presents two distinct seasons; rainy season (May to October) and dry season (November to April).

Study Population

The study population included children aged 5 years and below with acute gastroenteritis who attended the paediatric clinics of University of Uyo Teaching Hospital (UUTH) (tertiary public health facility); St. Luke's Hospital, Anua (secondary public health facility) and Nedeke Children's Hospital, Uyo (privately-owned health facility). Children with diarrhoea for seven days or more, with or without fever, mucus and bloody stool were included in the study while those that had been on antibiotic therapy within two weeks prior to study were excluded.

Ethical Consideration

Ethical approval was obtained from the Health Ethics Review Committee, University of Uyo Teaching Hospital, Uyo. Only children with acute gastroenteritis whose caregivers had consented to participate after full explanation of the study protocol were enrolled and were at liberty to withdraw from the study at any time during the research without any cohesion to continue.

Data Collection

A structured close-ended questionnaire was used to obtain relevant information from children's parents/caregivers. Information such as child's age, gender, source of drinking water, method of feeding, nutritional status, and type of stool passed were collected from either parents or caregivers. Other information obtained included child's clinical information, predisposing factors such as frequency of child bathing/day, method/type of child feeding, type of accommodation, and socio-economic status of parents/caregivers.

Sample Collection

Freshly passed stool samples were collected from 250 children in a wide-mouth clean container, labelled with patient's data (date, time of collection and patient's name) and added to Cary-Blair transport medium (Oxoid, UK) before it was transported to microbiology laboratory, University of Uyo Teaching Hospital, Uyo for analysis.

Isolation of *Shigella* Organism

Freshly passed stool samples were introduced into Selenite-F enrichment broth and directly cultured on MacConkey agar (MaC) and Deoxycholate Citrate Agar (DCA) (Oxoid, UK). All cultures were incubated aerobically at 37°C for 18 to 24 hours. Suspected colonies were subcultured on MaC agar to obtain pure colonies. Discrete colonies were stored in Mueller Hinton agar for biochemical test and serotyping.

Biochemical identification and serotyping of *Shigella* species

Species identification was carried out using Microbact 24E (MB24E) system (Oxoid, UK) as directed by the manufacturers. Serotyping of *Shigella species* was done using slide agglutination method with commercially prepared polyvalent antisera (Oxoid, UK) for *S. dysenteriae (*group A*), S. flexneri* (*group B*), *S. boydii* (group C) and *S. sonnei* (group D).

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing was carried out on Mueller-Hinton agar using the modified Kirby-Bauer disk diffusion method. The commercially available antibiotic-impregnated paper disks (Oxoid, UK) and inoculums standardadized using McFarland (0.5) standard. Standard antimicrobial concentrations of ampicillin (10µg), ceftriaxone (30µg), ceftazidime (30µg), cefuroxime (30µg), imipenem (10µg), gentamicin (10µg), sulfamethoxazole/trimethoprim (23.75/1.25µg), ofloxacin (5µg), ciprofloxacin (5µg), cefotaxime (30µg),

aztreonam (30µg) and amoxicillin/clavulanic acid (20/10µg) were used following the Clinical and Laboratory Standards Institute (CLSI) guidelines and zone interpretative criteria.[23] *Escherichia coli* ATCC 25922 was used as the reference strain.

Extended-Spectrum -Lactamase production Test

Extended-Spectrum -Lactamase (ESBL) detection was carried out using the Double Disk Synergy Test (DDST) for ESBL production in Enterobacteriaceae.[24] Ceftazidime and cefotaxime disks (30µg each) were placed 20mm apart (centre-to-centre) around a disk containing amoxicillin (20µg)/clavulanic acid (10µg). The inoculated agar plates were incubated at 37°C for 24 hours. Enhancement of inhibition zone of any one of the test antibiotics towards the clavulanate-amoxicillin disk was regarded as presumptive ESBL production.

Statistical Analysis

Data were analyzed using SPSS version 20. Chi-square (^{2}) was used to test for relationship between the variables and $p<0.05$ was considered significant.

RESULTS

The frequency distribution of shigella infections per healthcare facility is presented in Table 1. Of the 250 children studied, 8 had shigella infection, giving a prevalence of 3.2%. Males were the majority, 6 (2.4%), and St. Luke's Hospital, Anua had the highest prevalence, 4(8.0%) followed by Nedeke Children Hospital, Uyo, 3(3.0%), while children in UUTH had the lowest prevalence, 1(1.0%).Children in the age ranges of 13-24 months and 25-36 months had the highest prevalence of Shigella infection, 3/64(4.7%) and 2/46 (4.3%), respectively. The two *Shigella* species detected were *Shigella dysenteriae*, 6/250(2.4%) and *Shigella flexneri*, 2/250 (0.8%). Males and children 13-24 months old were the majority with *S. dysenteriae* infection (Table 2). There was no statistically significant variation in the rates of infection between the age groups and among gender ($p>0.05$). The most common clinical features in children infected with s*higella* were fever, loss of weight, vomiting, and blood in stool. All children infected with *Shigella flexneri* had mucus but no blood in stool while among those infected with *Shigella dysenteriae,* one-third (33.3%) and two-thirds (66.7%) had mucoid and bloody stool, respectively.

Majority of the parents/caregivers whose children were infected with shigella had secondary education, 7/8(87.5%) while children with the least infection were recorded among parents/caregivers with either primary or post-secondary education. Parents/caregivers that earned an average income of 2,000-5000 naira weekly had children with the highest rate of shigella infection, 2/8(25%*)* (Table 3). Respondents (parents/caregivers) who mostly used sachet water for drinking had a higher rate of *S. dysenteriae* infection, 10.3% followed by those that used borehole water, 4.3%. Also, *S. dysenteriae* infection was commoner in children under 12 months of age, who were fed a combination of breast milk and solid food (9.1%) compared with those either exclusively breastfed or given a combination of breastmilk and infant formula. In children aged 18 months or older, shigella infection was highest in those fed a combination of infant formula and solid food (8.3%), and in particular *S.dysenteriae* infection (5.6%), compared to others fed solid food alone. In terms of size of accommodation, the highest rate of *Shigella dysenteriae* infection occurred among those in detached one-bedroom apartments, 33.3% and two-bedroom apartments, 12%. Among these variables, only source of drinking water was significantly associated with shigella infection ($p<0.05$) (Table 4). The trend of shigella infection within the study period (October to March of the following year) shows that the highest number of cases occurred in January (n=4 cases) and February (n=3 cases). Other months recorded no case of shigella infection.

Most of the S.dysenteriae isolates were highly resistant to cefuroxime (83.3%), ciprofloxacin, ceftazidime, and amoxicillin

(66.7% each), and all isolates of *S. flexneri* were 100% resistant to cefuroxime, ceftazidime, and amoxicillin but 100% susceptible to ciprofloxacin. Generally, the two *Shigella species* exhibited high susceptibility rates to imipenem and ceftriazone (100% each), ofloxacin and sulfamethoxazole/trimethoprim (83.3% each) (Figure 1). All (100%) shigella isolates *(S. dysenteriae and S. flexneri)* in this study exhibited multi-drug resistance (MDR). Majority of the MDR strains were from St. Luke's Hospital, Anua (4 strains) followed by Nedeke Hospital (3 strains) with drug resistant combinations ranging from 3-6 (Table 5). None of the shigella isolates were extended-spectrum beta-lactamase (ESBL) producers.

Table 1: Frequency distribution of children infected with s*higella* by gender and healthcare facility

Facility	No. Tested	Male (%)	Female (%)	Total (%)
University of Uyo Teaching Hospital, Uyo	100	1(1)	0(0)	1(1.0)
St. Lukes Hospital, Anua	50	3(6)	1(2)	4(8.0)
Nedeke Childrens Hospital, Uyo	100	2(2)	1(1)	3(3.0)
Total (%)	250	6(2.4)	2(0.8)	8(3.2)

Table 2: Frequency distribution of *Shigella dysenteriae* and *Shigella flexneri* by age and gender (N = 250)

Variable	No. Tested	*Shigella dysenteriae** No. positive (%)	*Shigella flexneri*** No. positive (%)	Total (%)	χ^2	P-value
Age (month)						
1-12	74	2(2.7)	1(1.4)	3(4.1)	5.03	0.28
13-24	64	3(4.7)	0(0)	3(4.7)		
25-36	46	1(2.2)	1(2.2)	2(4.3)		
37-48	39	0(0)	0 (0)	0(0)		
49-60	27	0(0)	0 (0)	0(0)		
Gender						
Female	119	1(0.8)	1(0.8)	2(1.7)	1.69	0.19
Male	131	5(3.8)	1(0.8)	6(4.6)		
Total (%)	250	6(2.4)	2(0.8)	8(3.2)		

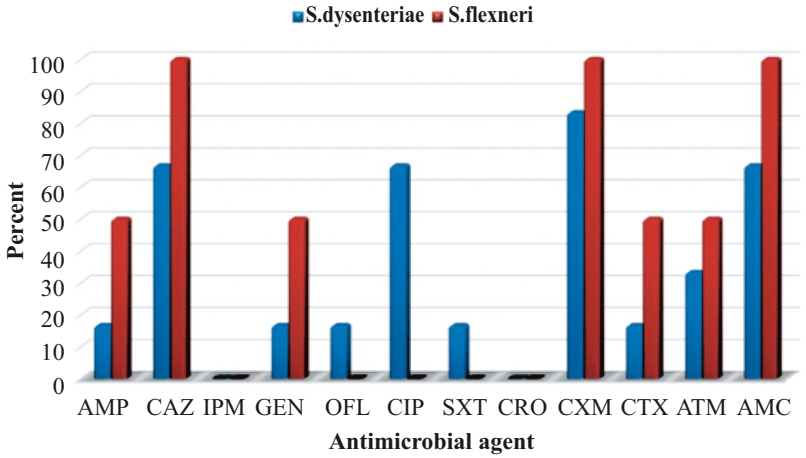
Table 3: Socio-economic characteristics of parents/caregivers of children infected with shigella

Variable	No. of parents/ caregivers with infected children (n=8) (%)
Level of education	
• Primary	0(0)
• Secondary	7(87.5)
• Post-secondary	1(12.5)
Level of weekly income (N)	
• <2,000	0(0)
• 2,000-5,000	2(25.0)
• 6,000-10,000	0(0)
• >10,000	3(37.5)
• Unstable	3(37.5)

Table 4:Factors associated with s*higella-i*nfected children

Variable	No. of respondent	*Shigella dysenteriae* (n=6)	*Shigella flexneri* (n=2)	χ^2	p-value
(i) Drinking water source					
• Sachet water	39	4(10.3)	1(2.6)	14.36	0.006*
• Borehole water	46	2(4.3)	1(2.2)		
• Filtered water	27	0(0)	0(0)		
• Bottled water	6	0(0)	0(0)		
• Boiled water	132	0(0)	0(0)		
(ii) No. of bathing/day					
• Once	2	0(0)	0(0)	3.01	0.22
• Twice	226	4(1.8)	2(0.9)		
• Thrice	22	2(9.1)	0(0)		
(iii) Method of feeding					
(a) < 12 months old					
• Exclusive breast milk	44	0(0)	0(0)	2	0.73
• Breast milk/formula	4	0(0)	0(0)		
• Breast milk/solid food	11	1(9.1)	0(0)		
(b) ≥18 months old					
• Formula/solid food	36	2(5.6)	1(2.8)		
• Solid food only	155	-1.9	1(0.6)		
(iv) Accommodation type					
(a) Detached					
• 1 room	3	1(33.3)	2(66.7)		
• 2 rooms	25	3(12)	0(0)		
• 3 rooms	66	0(0)	0(0)		
(b) Flat					
• 1 bedroom	61	1(1.7)	0(0)		
• 2 bedrooms	77	1(1.3)	0(0)		
• 3 bedrooms	18	0(0)	0(0)		

*Significant difference: p< 0.05



AMP= ampicillin; CRO= ceftriazone; GEN= gentamicin; OFL= ofloxacin; SXT= sulfamethoxazole/ trimethoprim; CIP= ciprofloxacin; CAZ= ceftazidime; CXM= cefurozime; IPM= imipenem; CTX= cefotaxime; ATM= aztreonam; AMC= amoxicillin/clavulanic acid.

Figure 1: Antimicrobial-resistant rates of *S. dysenteriae* and *S. flexneri* isolates in children.

Table 5: Multi-drug resistance (MDR) pattern of *S. dysenteriae* and *S. flexneri* by facility.

***Shigella* strains (facility)**	**Resistant antimicrobial agents***	**No. of drug combination**
Shigelladysenteriae		
F231 (Nedeke)	GEN, CAZ, AMC	3
M238 (Anua)	CIP, AMC, CXM	3
M215 (Nedeke)	GEN, AMP, AMC, CXM	4
M131 (Anua)	CIP, SXT, ATM, CAZ, CXM	5
M242 (Nedeke)	CIP, CTX, ATM, CAZ, CXM	5
M121 (Anua)	GEN, CIP, OFLÇAZ, AMC, CXM	6
Shigellaflexneri		
M226 (UUTH)	ATM, CAZ, AMC, CXM	4
F173 (Anua)	GEN, CTX, AMP, CAZ, AMC, CXM	6

*Extended spectrum beta-lactamse (ESBL) producers: none were ESBL producers

DISCUSSION

The prevalence of s*higellosis* in young children with acute gastroenteritis in Uyo in this study was 3.2%. Earlier studies in Yobe, Northeast-Nigeria and Benin city, south-south-Nigeria, reported 3.5% and 1.44% of *shigella* infection, respectively[25,26] while 3.8% and 4.8% prevalence had been reported in Iranian and Brazilian children, respectively.[27] The current study's low prevalence of 1.0% at UUTH compared to St. Luke's Hospital, Anua (8.0%) and the privately run Nedeke Children's Hospital (3.0%), is consistent with the low prevalence in the study among children at the University of Benin Teaching Hospital, a tertiary healthcare facility. These results mirror the common environmental conditions in communities where most of the children in this study are being nurtured. This includes substandard hygiene, unsafe water supplies, and densely populated areas and institutions[26]. Earlier studies in Abuja, Nigeria[28] and Gaborone, Botswana[29] had documented higher prevalence rates of shigella infection among children (18.8% and 21%, respectively). Apart from compromising sanitary environmental conditions, these findings underscore the need for relevant authorities to provide adequate resources and staff training at all levels of healthcare to promptly triage and manage gastroenteritis cases and refer cases with complications for better management. *Shigella dysenteriae* was the most prevalent *Shigella* species in this study, contrary to the report that S. *flexneri* is the predominant cause of endemic shigellosis in developing countries.[13]The preponderance of *Shigell adysenteriae* among children with gastroenteritis in this environment poses a serious public health concern because disease severity is associated with life-threatening complications.

The highest prevalence of s*higellosis* in children 2 years and below, compared to older children, is consistent with the report in Kogi.[30] The reason for this occurrence may multifactorial such as declining levels of maternally acquired antibodies (passive immunity), lack of active immunity in the infants, introduction of foods that may be contaminated with faecal bacteria and direct contact with human or animal faeces as the infant begins to grow.[31] In this study, one-third of young children infected with shigellosis did not present with mucoid and bloody stool usually associated with dysentery. This observation is in agreement with the report by Tickell et al.[32]

Among the risk factors of shigellosis in young children is the poor source of potable drinking water. In this study, shigellosis was significantly associated with source of drinking water especially among children whose parents/caregivers admitted to drinking mostly commercial sachet water (10.3%) and borehole water (4.3%). This is instructive going by the fact that faecal-contaminated commercial sachet water and borehole can be sources of pathogenic bacteria and if not adequately treated and monitored for consistent quality, can become

a reservoir of water-borne diseases, including dysentery.[33,34] Many commercial water companies lay claims to purification of their packaged water before being sold to the public. In Nigeria, the National Agency for Food and Drug Administration and Control registration number must be printed on the surface of water sachet/bottle as evidence of quality check. Findings in this study implicates drinking of contaminated water as a source of shigella infection. Moreso, water quality of some water production companies still fall short of the expected quality standard thereby exposing unsuspecting public to the risk of water-borne diseases.[35] Water contamination could occur as a result of poor water treatment, poor borehole sanitation and source of raw material for water production, long storage of sachet under unfavourable environmental conditions and above all, lack of good manufacturing practices.[36] Regular monitoring and assessment of borehole water sources are non-negotiable as they would help maintain quality groundwater for drinking and other sundry uses. In this study, cases of shigellosis among the children were recorded in the middle of dry season, particularly in January and February. This is because most samples were collected within that period and sample collection could not be extended to cover the rainy season due to time constraint. This was a limitation in this study.

Generally, there seems to be a global decline in dysentery caused by *S. dysenteriae* infection[13]. In addition, there is a decline in the prevalence of comorbidities such as malnutrition and measles owing to greater awareness campaigns by various agencies globally consequent upon which individuals are being better equipped to mount an immune response against s*higella* infection, therefore less likely to develop dysentery following s*higella* infection.[32] The use of antimicrobials in cases of uncomplicated diarrheoa has been discouraged except in cases involving dysentery, cholera, typhoid fever, etc.[37] Increased use of antibiotics has been associated with the global decline in dysentery but not without associated consequences such as the emergence of MDR-shigella strains.[32]Finding in this study where all the shigella isolates exhibited multi-drug resistance is worrisome, even though none was ESBL producer. The consequences of this occurrence include treatment failure, increased cost of treatment and death.[38] Also, the risk of continuous shedding of these MDR strains in stool may lead to an increasing risk of transmission of the disease among susceptible contacts. The development of MDR may not be unconnected with the popular practice of self-medication as well as the misuse and abuse of antibiotics dispensed as over-the-counter drugs in community pharmacies and chemists.[39]However, the drug of choice based on 80%-100% antibiotic susceptibility rates were: ciprofloxacin, imipenem and ceftriazone, ofloxacin and sulfamethoxazole/trimethoprim in line with WHO recommendations.[40]

CONCLUSION

Shigella infection is among the pathogens implicated in acute gastroenteritis among children in Uyo, with a prevalence of 3.2%, and *Shigella dysenteriae* is the predominant species with a prevalence of 2.4%. Children 13-24 months old and those whose parents/caregivers drink mostly commercial sachet water were most implicated. In most resource-limited settings, where bacterial culture is unavailable, reliance on the clinical presentation of dysentery alone in the diagnosis of shigellosis might inadequately identify those at risk of death because most may not present with dysentery. The overwhelming MDR pattern exhibited by the isolates are of immense public health concern. Primary prevention strategies such as improvements in safe drinking water and sanitation hold the key to reducing the infection.

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Competing Interest: None

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