MAJOR ARTICLE

Systemic Shigellosis in South Africa

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Background. Systemic disease due to shigellae is associated with human immunodeficiency virus (HIV), malnutrition, and other immunosuppressed states. We examined the clinical and microbiologic characteristics of systemic shigellosis in South Africa, where rates of HIV infection are high.

Methods. From 2003 to 2009, 429 cases of invasive shigellosis were identified through national laboratory-based surveillance. At selected sites, additional information was captured on HIV serostatus and outcome. Isolates were serotyped and antimicrobial susceptibility testing performed.

Results. Most cases of systemic shigellosis were diagnosed on blood culture (408 of 429 cases; 95%). HIV prevalence was 67% (80 of 120 cases), highest in patients aged 5–54 years, and higher among females (55 of 70 cases; 79%) compared with males (25 of 48 cases; 52%; $P = .002$). HIV-infected people were 4.1 times more likely to die than HIV-uninfected cases (case-fatality ratio, 29 of 78 HIV-infected people [37%] vs 5 of 40 HIV-uninfected people [13%]; $P = .008$; 95% confidence interval [CI], 1.5–11.8). The commonest serotype was *Shigella flexneri* 2a (89 of 292 serotypes [30.5%]). Pentavalent resistance occurred in 120 of 292 isolates (41.1%). There was no difference in multidrug resistance between HIV-infected patients (33 of 71 [46%]) and uninfected patients (12 of 33 [36%]; 95% CI, .65–3.55).

Conclusions. Systemic shigellosis is associated with HIV-infected patients, primarily in older girls and women, potentially due to the burden of caring for sick children in the home; interventions need to be targeted here. Death rates are higher in HIV-infected versus uninfected individuals.

Shigella are among the most ubiquitous of enteric pathogens and are a major cause of bacillary dysentery worldwide [1, 2]. *Shigella flexneri* serotypes are particularly common in the developing world, although changing patterns in serotype prevalence over prolonged periods of surveillance have been observed in some settings [3, 4]. Nearly 70% of episodes and 60% of deaths involve children under the age of 5 years. Infectious dose is low, and although the disease is primarily waterborne, fecal-oral transmission is an important route for acquisition of disease [2]. The organisms are highly adapted to mucosal invasion in the human host and have been associated with systemic disease [1]. Reports of resistance, including to the fluoroquinolones, are becoming more frequent [2, 5].

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Meta-analysis of published reports from Africa suggests that <1% of cause-specific bacteremias on the continent are due to *Shigella* [6]. *Shigella* bacteremia and systemic disease are nonetheless recognized as a problem in children, neonates being at an increased risk [7–14]. Since the advent of human immunodeficiency virus (HIV), cases in adults are increasingly recognized [7, 15–23]. Inadequate host immunity appears to play an important role in the development of systemic shigellosis, and factors besides HIV that have a role in development of disease include malnutrition in children, diabetes, and malignancy [9, 12, 13, 15, 24].

There are few reports in the literature that examine systemic shigellosis, and much of the knowledge is gleaned from case reports rather than analyses of series of patients [10, 13, 19, 21, 23, 25–30]. We aim to describe the epidemiology, clinical features, and the microbiology of patients with systemic shigellosis from 2003 through 2009 in South Africa, a country with an emerging economy and where seroprevalence rates for HIV are high, and the antenatal HIV prevalence among pregnant women in 2008 was 29.3% in women between 15 and 49 years of age [31].

METHODS

Case Definition

National active laboratory-based surveillance for invasive shigellosis has been performed by the Enteric Diseases Reference Unit (EDRU) of the National Institute for Communicable Diseases in South Africa since 2003, as described elsewhere [32, 33]. A case is defined as any patient from whom *Shigella* species are isolated from a normally sterile site such as blood and cerebrospinal fluid (CSF). All diagnostic microbiology laboratories in South Africa are encouraged to submit isolates from patients fulfilling the case definition to EDRU, and audits are conducted wherever possible to identify missing cases, which are then included in the database. Audits could not be conducted in KwaZulu-Natal or for all laboratories in the remaining provinces in 2003 and 2004, because not all laboratories were on a common laboratory information system. Additional clinical information is collected on cases at 24 sentinel hospitals in all 9 provinces, through patient interview, interviewing relatives, or bed letter review. This includes data on HIV status (HIV enzyme-linked immunosorbent assay results in older children and adults; HIV polymerase chain reaction [PCR] results in infants), other immunosuppressive conditions, admission and discharge dates, antibiotic exposure, and disease outcome. Outcome data (whether the patient survived hospitalization or died) were recorded on follow-up of the current hospitalization; no long-term follow-up was undertaken. Severity of acute illness was assessed by using the Pitt bacteremia score, a previously validated scoring system that is based on mental status, vital signs, requirement for mechanical ventilation, and recent cardiac arrest [34–36].

Laboratory Characterization

All *Shigella* isolates received are serotyped by the reference unit according to established methods (Mast Diagnostics, Bootie, England). Minimum inhibitory concentrations were determined for the following antimicrobials: ampicillin, amoxicillin-clavulanate, chloramphenicol, trimethoprim, sulfamethoxazole, co-trimoxazole, tetracycline, streptomycin, kanamycin, nalidixic acid, ciprofloxacin, ceftriaxone, and ceftazidime, using E test strips, according to the manufacturers instructions (AB-Biodisk, Solna, Sweden). Production of extended spectrum β-lactamase is tested for using the MAST laboratories double disk method, according to the manufacturer's instructions (MAST Diagnostics, Bootie, England).

Statistical Analysis

Univariate analysis was performed using the χ^2, Fisher exact, or Mantel-Haenszel test for comparison of categorical variables. The χ^2 test for trend was used to examine the number of isolates received year-on-year. Analysis was performed with Epi Info software, version 6.04d [37] and Stata software, version 9 (StataCorp Ltd, College Station, TX). Two-sided *P* values of <.05 were considered significant throughout.

RESULTS

All Cases

From January 2003 through December 2009, we identified 429 laboratory-confirmed cases of invasive shigellosis, for whom data on age were available for 387, and 292 were available to the reference unit for serotyping and susceptibility testing. Including audit cases, blood cultures were positive for *Shigella* for 408 of 429 patients (95%), the remaining patients had *Shigella* isolated from CSF (4 of 429 patients [1%]) or other sterile sites, including tissue biopsy or pleural fluid (17 of 429 patients [4%]). Eight patients had positive fecal cultures for *Shigella* in addition to the isolate from a sterile site.

The incidence of invasive *Shigella* increased from 0.11 to 0.13 per 100 000 population from 2005 through 2009, peaking in 2006 at 0.18 ($P = .935$). Data from 2003 to 2004 were excluded from this analysis as laboratory audits could not be done for these years. The incidence was highest in children younger than 1 year of age followed by children aged 1–4 years, with a second peak in persons aged 15–54 years (Figure 1). Patient ages ranged from 1 day to 84 years (median, 6 years), and 227 of 412 (55%) of patients for whom sex was recorded were female (sex was not recorded for 17 patients).

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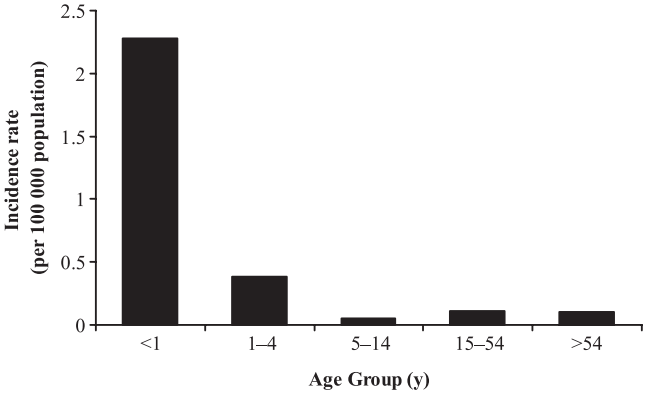

Figure 1. Incidence rates of all cases of invasive *Shigella* in South Africa in 2006 by age group (each year followed the same distribution).

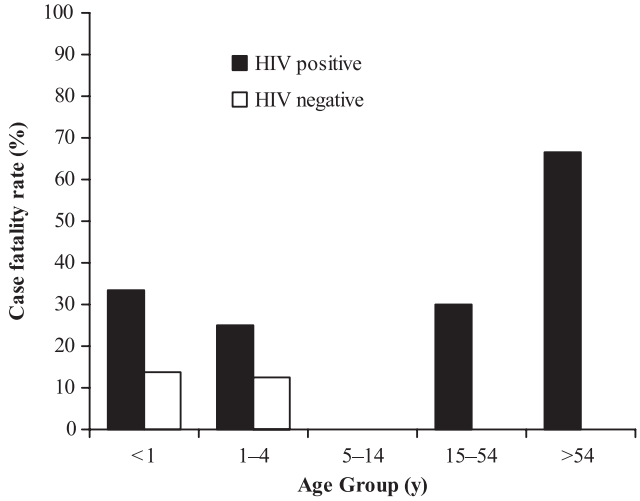

Figure 2. Case fatality rate of patients from sentinel sites with invasive shigellosis in South Africa by age group.

Clinical and Epidemiologic Features at Enhanced Surveillance Sites

HIV status was established for 120 of 210 patients (57%) admitted at enhanced or sentinel surveillance sites; 80 of these patients (67%) were HIV infected. The HIV prevalence among cases at sentinel sites was highest in patients aged 5–54 years and was significantly higher (55 of 70 cases [79%]) among females than males (25 of 48 cases [52%]; $P = .002$). HIV status was unknown in 38 of 86 (44%) of females and 48 of 86 (56%) of males at enhanced surveillance sites. There was no significant increase in HIV prevalence among tested patients by year (2003: 2 of 3 [67%]; 2004: 8 of 13 [62%]; 2005: 8 of 12 [67%]; 2006: 11 of 17 [65%]; 2007: 20 of 24 [83%]; 2008: 13 of 21 [62%]; 2009: 18 of 30 [60%]; $P = .602$). Other immunosuppressive states identified at sentinel sites that could have contributed to invasive shigellosis included kwashiorkor (protein energy malnutrition) in 19 children between birth and 5 years (6 of whom were HIV infected), diabetes mellitus (n = 2), renal impairment (n = 3), and malignancy (n = 1; adult patient). Presenting diagnoses at sentinel sites included diarrhea or dysentery (42 of 210 [20.0%]), bacteremia (122 of 210 [58.0%]), lower respiratory tract infection (34 of 210 [16.0%]), meningitis (3 of 210 [1.4%]) and other diagnoses (2 of 210 [1.0%]), with 7 of 210 diagnoses (3.0%) unknown.

Information on the length of hospital stay was available for 169 of 210 patients (80%). Time in hospital ranged from 0 to 106 days, with a median of 7 days. Fifty of 172 patients (29%) died; 50% of deaths occurred within the first 3 days of treatment, the remainder during the current hospitalization. One hundred twenty patients (70%) recovered or were transferred to chronic care/step-down facilities, and 2 patients (1%) refused hospital care. In children (age <15 years) the case fatality rate was 17% (15 of 86). Twenty-eight percent (5 of 18) of the HIV-infected children <5 years died as compared with 14% (5 of 37) of the HIV-uninfected children <5 years ($P = .236$) (Figure 2). Although protein energy malnutrition was associated with death in 4 of 5 HIV-uninfected children (80%), no contributing factor was recorded for 1 of 5 children (20%). There were no deaths in HIV-uninfected adults (0 of 2), but 39% (22 of 56) of HIV-infected adults died (Figure 2). Death was 3.2 times more likely to occur in adults than in children (32 of 79 adults [41%] vs 15 of 86 children [17%]; $P = .001$, 95% confidence interval [CI], 1.6–6.6). Overall, HIV-infected cases were 4.1 times more likely to die than HIV-uninfected cases (29 of 78 HIV-infected [37%] vs 5 of 40 HIV-uninfected [13%]; $P = .008$, 95% CI, 1.5–11.8) (Figure 2).

Severity of illness scores were fully recorded for a small number of patients only. Of the 135 patients with a calculated Pitt bacteremia score, 8 patients (6%) had a score ≥4, whereas the other 127 patients (94%) had a score <4. Having a Pitt bacteremia score of ≥4 was significantly associated with death (7 of 8 Pitt ≥4 [88%] vs 29 of 124 Pitt <4 [23%]; OR, 23; $P = .004$, 95% CI, 2.7–194.2). On presentation, the commonest sign of sepsis included pyrexia in 28 of 158 patients (18%), 37 of 144 patients (26%) were disorientated, and 3 of 144 patients (2%) were comatose. Mechanical ventilation was required for 8 of 158 patients (5%).

CD4 lymphocyte cell counts were available for 33 of 80 HIV-infected patients (41%), 9 (27%) of whom were children (<15 years); all children were 6 years of age or younger. Eight (89%) of these children had CD4 counts ≤750, and one (11%) had a CD4 count >1500. Of the adults, 18 (70%) had CD4 counts ≤50, 4 (15%) had CD4 counts between 51 and 200, and 4 (15%) had CD4 counts ≥350. One death

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occurred in an infant in whom the CD4 count was >350, the remaining patients survived. Data on access to co-trimoxazole prophylaxis was obtained for 125 patients, irrespective of HIV status. Of the 80 patients in whom HIV status was positive, 18 (23%) were on co-trimoxazole prophylaxis. Only 15 patients (10%) were receiving highly active antiretroviral therapy; 13 were <10 years of age.

Microbiological Findings

The numbers of isolates received increased from 11 in 2003 to 39 in 2005 and 54 isolates in 2009. In total, 292 viable isolates (68%) were received from 429 cases. The most common *Shigella* serotype isolated from invasive cases was *S. flexneri* 2a (30%), followed by *S. flexneri* 1b (16%) (Table 1). Pentavalent resistance occurred in 120 of 292 isolates (41%). Of the *S. flexneri* 2a isolates, 48 isolates (54%) were resistant to ≥5 antimicrobials and 2 isolates (2.3%) produced extended spectrum β-lactamase (ESBL; Table 1). Thirty-seven isolates (77%) of *S. flexneri* 1b were resistant to ≥5 antimicrobials, and 1 isolate (2.1%) was an ESBL producer. Pentavalent resistance was less common in the remaining serotypes, and only one other isolate had ESBL production (*S. sonnei* phase II). Resistance to the fluoroquinolone antibiotics in invasive *Shigella* was not documented, although nalidixic acid resistance occurred in 4 isolates (Table 1). No difference was noted in the occurrence of multidrug-resistant isolates between HIV-infected (33 of 71; 46%) and -uninfected patients (12 of 33 patients [36%]; $P = .334$; 95% CI, .65–3.55).

DISCUSSION

Invasive shigellosis is an uncommon complication of gastrointestinal disease. Previous studies have highlighted the predominance of the disease in children, as well as the role of protein energy malnutrition in children [12, 14, 27, 30, 38] and the association of the disease with HIV infection in adults [7, 19–21, 30, 39, 40]. There are rare reports of invasive shigellosis occurring in immunocompetent individuals [30, 41, 42]. Cell-mediated immunity has been postulated as being important in prevention of disease, and this is supported by current literature [7, 12, 16, 17, 19, 22, 26, 27, 43], but despite apparently high mortality, invasive shigellosis is infrequently reported from Africa [7, 14, 44]. We collected clinical and microbiological data on 279 patients who were treated around South Africa over an 8-year period, to better understand the features of this disease and compare the disease between HIV-infected and HIV-uninfected patients. Our study has confirmed previous findings and emphasizes the importance of this disease in older girls and women, as well as highlighting the higher death rates in HIV-infected versus HIV-uninfected patients.

Table 1. Antimicrobial Resistance Patterns in Major *Shigella* Serotypes Associated With Invasive Shigellosis

Serotype	Ampicillin	Chloramphenicol	Streptomycin	Sulfamethoxazole	Trimethoprim	Tetracycline	Nalidixic Acid	Ciprofloxacin	ESBL Production
S. flexneri type 2a (n = 89)	59 (66.3)	42 (47.2)	62 (69.7)	81 (91.0)	84 (94.4)	54 (60.7)	1 (1.1)	0 (0)	2 (2.3)
S. flexneri type 1b (n = 48)	41 (85.4)	37 (77.1)	41 (85.4)	36 (75.0)	48 (100)	43 (89.6)	0 (0)	0 (0)	1 (2.1)
S. sonnei phase I/II (n = 45)	6 (13.3)	1 (2.2)	38 (84.4)	42 (93.3)	44 (97.8)	32 (71.1)	0 (0)	0 (0)	1 (2.2)
S. flexneri type 3a (n = 33)	8 (24.2)	0 (0)	5 (15.2)	33 (100)	33 (100)	4 (12.1)	1 (3.0)	0 (0)	0 (0)
S. flexneri type 6 (n = 14)	6 (42.9)	2 (14.3)	5 (35.7)	14 (100)	14 (100)	2 (14.3)	0 (0)	0 (0)	0 (0)
S. flexneri variant X (n = 17)	11 (64.7)	5 (29.4)	8 (47.1)	16 (94.1)	17 (100)	11 (64.7)	0 (0)	0 (0)	0 (0)
S. flexneri variant Y (n = 9)	4 (44.4)	2 (22.2)	5 (55.6)	8 (88.9)	8 (88.9)	4 (44.4)	0 (0)	0 (0)	0 (0)
S. flexneri type 3b (n = 8)	4 (50.0)	2 (25.0)	5 (62.5)	7 (87.5)	7 (87.5)	4 (50.0)	1 (12.5)	0 (0)	0 (0)

Data are no. (%) unless otherwise indicated.

Abbreviation: ESBL, extended spectrum β-lactamase production.

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In this study, invasive disease was primarily associated with children under the age of 5 years, and adults aged from 15 to 54 years. This supports, in part, others' findings of disease prominence in malnourished and immunosuppressed children [7–11, 28, 38], as well as the role of HIV in adults [7, 16, 22, 23, 27, 30, 39, 40, 45], and mirrors the age-related distribution of HIV in South Africa. It emphasizes the importance of HIV status in affecting childhood mortality, as deaths in HIV-infected versus uninfected children <15 years of age were nearly doubled. The increased numbers identified over the 8-year period may potentially reflect improved collection practices by GERMS-SA rather than increasing numbers of cases of systemic shigellosis, due to challenges in conducting full audits in all provinces between 2003 and 2009. In those children aged <1 year who tested negative by PCR for HIV, we did not collect data on HIV exposure; that is, whether the mother was HIV infected but the child did not seroconvert. Proxy data, such as the use of perinatal nevirapine, were also not available for this subset of patients.

The strong correlation of HIV with invasive shigellosis in patients aged >15 years was expected, but it is notable that the disease predominated in this age group in South African patients, and 98% of patients identified in this study in this age group were HIV infected. These patients were frequently severely immunosuppressed, as evidenced by low CD4 counts. No other immunosuppressive condition, as previously described, was individually associated with invasive shigellosis, supporting the observation that it is a rare disease in adults, in the absence of HIV, even given the prevalence of other immunosuppressive conditions such as diabetes, malignancy, and renal failure [27, 30, 46]. We did not attempt to extrapolate the HIV data to those patients for whom the HIV status was unknown, as the numbers were small and there may have been selection bias among the patients who had blood cultures taken. Nonetheless, these data do emphasize the strong association between HIV and invasive shigellosis.

In common with other literature reports, most patients presented with clinical sepsis, which frequently followed or was associated with a history of gastroenteritis. There were no outstanding clinical features that would otherwise have given an indication of the bacteriological diagnosis. The Pitt bacteremia score of ≥4 was significantly associated with death. Previous authors have discussed the relevance of this clinical marker in association with mortality [34–36], and we found it to be a useful predictor for mortality in this group of patients.

The predominance of older women who were HIV infected with systemic shigellosis is noteworthy and may reflect the role of women in child-care practices in South Africa. The predominance of women who were HIV infected with invasive shigellosis in this study (79%) was greater than published figures for rates of HIV-infected women in South Africa [47]. Women may be more likely to be exposed to gastrointestinal pathogens that the child may carry, and in the presence of immunosuppression may hence be more prone to developing invasive disease. Moreover, although numbers are small, invasive shigellosis occurred in some HIV-uninfected elderly women, but there was only one case reported from an HIV-infected man over 54 years of age, supporting the argument for the burden of child care. This finding highlights a number of imperatives. First, as part of patient education in HIV clinics, interventions such as handwashing, which has been shown to be protective in preventing diarrhea, should be stressed, given the association in our patients with gastrointestinal disease [48]. Second, as almost no adults were receiving antiretrovirals in this study, it argues strongly that antiretrovirals should become more accessible to the South African population in need [49, 50].

It seems unlikely that serotype plays a role in invasion, as serotype distribution corresponds with the national data, which primarily reflect the serotype distribution in noninvasive shigellosis [32, 33]. Similarly, the occurrence of antimicrobial resistance is comparable to reports from other countries [51–54] and is unlikely to be related to the HIV seroprevalence in South Africa, but rather to antimicrobial usage patterns in the country, given that there was no significant difference in multidrug resistance between HIV-infected patients and HIV-uninfected patients with invasive disease. We are currently characterizing the ESBL produced by certain isolates [55], but postulate that these enzymes may have been acquired due to the number of patients who spend extended periods in the hospital environment, in the association with HIV and other immunosuppressive conditions. Although the serotypes associated with shigellosis in South Africa are well characterized, prevention of enteric infection through vaccination is not a consideration for the near future [2, 51, 56], and hence systemic infection in the immunosuppressed individual is likely to remain a problem in the absence of improved sanitation.

This study had a number of limitations. First, clinical data were collected at selected sites only and may not be relevant to all the cases. Second, clinical data may have been incomplete, where surveillance officers could not access the patient and relied on family members or patients' bed letters to complete the case report forms. Not all patients at enhanced sites had HIV results. It is possible that had these results been available, the differences in HIV infection between the sexes would have been less marked, but as the ratio of females to males in this group was 0.8, we believe this would not have seriously affected our results. As cases were based on a laboratory surveillance system rather than a bacteremia study, this study had limited influence on clinical

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management and patients therefore may not have had comprehensive access to laboratory diagnoses, such as having stool samples taken. This may also have influenced the numbers of cases in whom pyrexia was recorded or those who had dysentery symptoms.

In conclusion, we found that systemic shigellosis is primarily associated with HIV-infected patients in South Africa in all age groups, although other immune compromising features may contribute in children. Disease in adults particularly affects women of child-bearing age, who probably have the larger burden of caring for sick children in the home, and interventions need to be targeted at this group.

Notes

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