SHIGELLA-ASSOCIATED DIARRHEA IN CHILDREN IN SOUTH JAKARTA, INDONESIA

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Abstract. A surveillance of Shigella infections was conducted on 612 children aged 0-12 years-old presenting with diarrhea to Mampang and Tebet Community Health Centers in South Jakarta, Indonesia, during February 2005 through September 2007. Shigella was isolated from 9.3% of diarrhea patients in the health centers. *S. flexneri* which was found in 5.9% of patients, and was the most frequent species isolated, comprising 63.2% (36/57) of all *Shigella* species isolated. *Shigella* species were found significantly more often among children over 2 years old, and the rate of isolation increased with age. Stool with mucus and/or blood were the main characteristics of Shigella infection in these patients. Antibiotic multi-resistance was found in *S. flexneri* and *S. boydii* strains, in particular to ampicillin, chloramphenicol, tetracycline, and trimethoprim-sulfamethoxazole. None of the *Shigella* species showed resistance to nalidixic acid, norfloxacin, ciprofloxacin, or ceftriaxone

Key words: Shigella infections, children, diarrhea, Indonesia

INTRODUCTION

Shigellosis is becoming one of the leading causes of diarrhea morbidity and mortality in children under five years of age worldwide (Niyogi, 2005). In developing countries, where affected populations are immunologically compromised by poor nutrition and background infections, deaths attributed to shigellosis are common. Despite improvements in sanitary conditions and in the economic condition of the population over the past three decades, shigellosis remains a serious public heath problem in Indonesia and comprises the number one etiology of diarrhea (Subekti *et al*, 2001). Notable was the re-emergence of *S. dysenteriae* in several areas in Indonesia, including Jakarta, after a hiatus of over 15 years (Subekti *et al*, 2001).

Shigella infections are well known for their clinical severity in bacterial dysentery. Dysentery is characterized by blood, pus and mucus in the stool, which indicates colorectal inflammation and ulceration. These types of symptoms are common to infections by the genus *Shigella* which consists of four species pathogenic to humans: *S. dysenteriae*, *S. flexneri*, *S. boydii*, and *S. sonnei*. *S. flexneri* is the principal cause of endemic diarrheas in many developing countries and is generally associated with a severe, longer duration of diarrhea with blood in the stools (Subekti *et al*, 2001). Although shigellosis is endemic in Indonesia there are not many published reports found, especially in studies done in children.

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This surveillance investigated *Shigella* infections in children age 0-12 years old who sought treatment in community health centers. Since health consultation and treatment are costly, for illnesses that are not life-threatening the majority of people in Indonesia prefer taking their sick children to a health center, which is subsidized by the government and cheaper than the hospital (Subekti *et al*, 2001). As a result, certain bacterial infections that cause mild diarrhea may be found to be more prevalent in community health centers than in hospitals.

The aims of the study were to determine the *Shigella* species causing diarrhea in children in the area, to describe the clinical presentation of the disease among children treated in the health centers, and to investigate the prevalence of antimicrobial resistance of *Shigella* in South Jakarta, Indonesia.

MATERIALS AND METHODS

Subjects and specimen collection

During February 2005 - September 2007, a *Shigella*-associated diarrheal disease surveillance was conducted among pediatric patients in South Jakarta, Indonesia. The study sites involved community health centers. Diarrhea was defined as three or more loose stools during the previous 24 hours. Patients age 0-12 years old presenting to the community health centers with diarrhea as demonstrated by blood or mucus in their stools, regardless of the frequency of stools, were candidates for the study. Following informed consent obtained from the parent or guardian of the patient, the diarrheal children were enrolled in the study. Participating medical staff were instructed to obtain a rectal swab from the patient following the completion of a clinical data sheet containing patient information. A rectal swab was collected from each patient and the swab was placed in buffered glycerol saline (BGS) (Teague and Clurman, 1916). Specimens in BGS were held at 4ºC until the end of the normal working day, at which time they were transported in an ice box to the Microbiology Laboratory, Medical Faculty Trisakti University. Specimens were collected upon patient presentation to the community health center, before antibiotic treatment was initiated. Specimens collected at night were transported to the laboratory the following day.

Bacteriologic procedures

Rectal swab samples were processed immediately upon receipt. Each swab was streaked directly onto MacConkey (MAC) agar (DIFCO, Becton Dickinson, Sparks, MD) and xylose-lysine-deoxycholate (XLD) agar (DIFCO, Becton Dickinson, Sparks, MD). Inoculated plates were incubated at 37ºC, aerobically, for 18-24 hours. Non-lactose fermenting colonies that grew on MAC and/or XLD and resembled those of *Shigella* were selected and tested for their biochemical reactions on Kligler's iron agar, urea agar, and motility-indole-ornithine (Farmer, 2003). Isolate identification was confirmed by using API 20E (Biomerieux, France) and slide agglutination with specific *Shigella* antisera (Denka Seiken, Tokyo, Japan).

Antibiotic susceptibility testing was accomplished by the disk-diffusion method (NCCLS, 2001) employing nine antibiotics: ampicillin, chloramphenicol, tetracycline, trimethoprim-sulfamethoxazole, ceftriaxone, azithromycin, nalidixic acid, norfloxacin and ciprofloxacin.

Antibiotic disks were purchased from Becton Dickinson (Becton Dickinson, Cockeysville, MD).

Data analysis

Significant differences in isolation rates

Table 1
Distribution of *Shigella* isolated from children with diarrhea in South Jakarta Health Centers.

Isolate		Number (%) of isolates by age group				
	N =	0-11 mo 186	1-2yr 122	>2-5yr 108	>5-14yr 196	Total 612
S. dysenteriae		0 (0)	0 (0)	1 (0.9)	2 (1.0)	3 (0.5)
S. flexneri		4 (2.2)	7 (5.7)	8 (7.4)	17 (8.7)	36 (5.9)
S. boydii		1 (0.5)	1 (0.8)	1 (0.9)	2 (1.0)	5 (0.8)
S. sonnei		2 (1.1)	3 (2.5)	3 (2.8)	5 (2.6)	13 (2.1)
All *Shigella*		7 (3.8)	11 (9.0)	13 (12.0)	26 (13.3)	57 (9.3)

N, number of diarrheal cases

were determined by chi-square test using EpiInfo version 6 (Center for Disease Control and Prevention). A *p*-value <0.05 was considered statistically significant.

RESULTS

A total of 612 children age 0-12 years old reported to the health centers for treatment of diarrheal disease. Overall, 9.3% (57/612) of the diarrheal children were positive for *Shigella*. The proportions of distribution of the four subgroups of *Shigella* isolated from the pediatric patients are presented in Table 1. *S. flexneri,* which was found in 5.9% (36/612) of the patients, was the most frequent subgroup isolated, comprising 63.2% (36/57) of all *Shigella* species. *Shigella sonnei* was the second most common *Shigella* species isolated after *S. flexneri. S. sonnei* was found in 2.1% (13/612) of the diarrheal children in the health centers, or in 22.8% of culture confirmed cases. S. *boydii* was found in 0.8% (5/612), whereas *S. dysenteriae* was isolated in only 0.5% (3/612) of cases. Table 1 also shows the distribution of *Shigella* species by age group of the patients. Shigella infections increased with increasing age of patients, from 3.8% in the 0-11 month age group, 9.0 % in the 1-2 year old age group, 12.0% in the >2-5 year old age group and 13.3% in the >5-14 year old age group. *Shigella* species were isolated more often from children >2 years old. A total of 6.4% (39/612) of patients over 2 years old were positive for *Shigella*, whereas only 2.9% (18/612) of children under 2 years old were positive for *Shigella.*

Fever, dehydration and frequency of diarrhea of more than 10 episodes within 24 hours were not the major symptoms of the patients in this study (Table 2). Fever was found in only 16.7% and 15.4% of children with *S. flexneri* and *S. sonnei* infection, respectively. Dehydration and diarrhea of more than 10 episodes within 24 hours were found in 7.7% of children with *S. sonne*i and 8.3% with *S. flexneri*, but in none among those with *S. dysenteriae* and *S. boydii.* The majority (91.7%-100%) of children showed a frequency of diarrhea of less than 10 episodes within 24 hours.

Mucus in the stool, with or without blood, was the main characteristic of *Shigella* infection, found in 58.3% (21/36) of patients with *S. flexneri*, 69.2% (9/13) with *S. sonnei*, 80% (4/5) with *S. boydii* and 66.6% (2/3) in patients with *S. dysenteriae*. Although not significant ($p>0.05$), stool with

Table 2
Symptoms associated with Shigella infection in children in South Jakarta Health Centers.

Isolate	*N*	Number of patients with clinical symptoms (%)							
		Frequency of diarrhea				Stool characteristics			
		Fever	Dehydr	Diarrh <10	Diarrh ≥10	Loose	Watery	Mucous	Bl + Mu
S. dysenteriae	3	0 (0)	0 (0)	3 (100)	0 (0)	0 (0)	1 (33.3)	1 (33.3)	1 (33.3)
S. flexneri	36	6 (16.7)	3 (8.3)	33 (91.7)	3 (8.3)	3 (8.3)	12 (33.3)	16 (44.5)	5 (13.9)
S. boydii	5	0 (0)	0 (0)	5 (100)	0 (0)	0 (0)	1 (20)	3 (60)	1 (20)
S. sonnei	13	2 (15.4)	1 (7.7)	12 (92.3)	1 (7.7)	1 (7.7)	3 (23.1)	8 (61.5)	1 (7.7)

N, number of isolate; Dehydr, dehydration; Diarrh, Diarrhea; Bl, Blood; Mu, Mucous

Table 3
Antibiotic resistance of *Shigella* species isolated from diarrheal children.

Isolate	No. tested	Number (%) of isolates resistant to the antibiotic								
		Am	C	Te	SXT	Cro	Azm	Na	Nor	Cip
S. dysenteriae	3	1 (33.3)	1 (33.3)	2 (66.7)	1 (33.3)	0 (0)	1 (33.3)	0 (0)	0 (0)	0 (0)
S. flexneri	36	31 (86.1)	30 (83.3)	34 (94.4)	24 (66.7)	0 (0)	0 (0	0 (0)	0 (0)	0 (0)
S. boydii	5	1 (20)	1 (20)	4 (80)	3 (60)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
S. sonnei	13	2 (15.4)	2 (15.4)	12 (92.3)	12 (92.3)	0 (0)	1 (7.7)	0 (0)	0 (0)	0 (0)

Am, ampicillin; C, chloramphenicol; Te, tetracycline; Sxt, trimethoprim-sulfamethoxazole; Cro, ceftriaxone; Azm, azithromycin; Na, nalidixic acid; Nor, norfloxacin; Cip, ciprofloxacin

mucus and blood was found more often in children with *S. flexneri* infection than in those with *S. sonnei* infection (13.9% *vs* 7.7%), whereas watery diarrhea was found in only 20% to 33.3% of cases. Loose stool was seen in only a small number of patients (8.3% and 7.7% of children with *S. flexneri* and *S. sonnei*, respectively).

Table 3 shows the majority of *S. flexneri* specimens isolated in this study were resistant to ampicillin (86.1%), chloramphenicol (83.3%), tetracycline (94.4%), and trimethoprim-sulfamethoxazole (66.7%). No resistance was seen against ceftriaxone, azithromycin, nalidixic acid, norfloxacin or ciprofloxacin among *S. flexneri* isolates. While resistance to tetracycline and trimethoprim-sulfamethoxazole were seen in 92.3% of *S. sonnei* isolates, only a few isolates in this subgroup were resistant to ampicillin (15.4%), chloramphenicol (15.4%) or azithromycin (7.7%). All *S. sonnei* isolates were sensitive to ceftriaxone, nalidixic acid, norfloxacin, and ciprofloxacin. A number of *S. boydii* isolates were resistant to tetracycline (80.0%), trimethoprim-sulfamethoxazole (60.0%) and to ampicillin (20%), and chloramphenicol (20%);

but they were sensitive to ceftriaxone, azithromycin, nalidixic acid, norfloxacin and ciprofloxacin. All *S. dysenteriae* isolates were sensitive to ceftriaxone, nalidixic acid, norfloxacin, and ciprofloxacin; a small number showed resistance to ampicillin (33.3%), chloramphenicol (33.3%), trimethoprim-sulfamethoxazole (33.3%) and azithromycin (33.3%), but 66.7% were resistant to tetracycline.

DISCUSSION

There has been increasing recognition in recent years of the importance of *Shigella* as an enteric pathogen with global impact and of the development of resistant strains. It is estimated that each year 163.2 million episodes of endemic shigellosis occur in developing countries with approximately 1.1 million episodes (0.7%) resulting in death (Kotloff *et al*, 1999). Children under 5 years of age comprise the majority of cases and of fatalities (Kotloff *et al*, 1999).

Our results show *S. flexneri* was the predominant isolate in this study and comprised 63.2% (36/57) of all *Shigella* recovered from patients at the health center, followed by *S. sonnei* with 22.8% (13/57) as the next most common isolate (Table 1). This finding is in agreement with other reports from developing countries (Keusch and Bennish, 1998; Kotloff *et al*, 1999; Kavaliotis *et al*, 2000; Finkelstein *et al*, 2003) that *S. flexneri* is the predominant *Shigella* species while *S. sonnei* is the major *Shigella* isolate in developed countries. *S. flexneri* also comprised the most frequent subgroup isolated in several developing countries, such as Bangladesh and Pakistan, as well as Africa. In contrast to our findings the second most frequent *Shigella* isolated in those places was *S. dysenteriae* (Ahmed *et al*, 1997; Mache, 2001; Brooks *et al*, 2003; Gupta *et al*, 2003). We found *S. flexneri* and *S. sonnei* together caused 86.0% (49/57) of all *Shigella* infections in children in South Jakarta, Indonesia. Reports from northern Greece (Kavaliotis *et al*, 2000), Iran (MoezArdalan *et al*, 2003) and India (Dutta *et al*, 2002) found *S. flexneri* was the predominant species and *S. sonnei* was the second most frequent strain isolated. In northern Israel, *S. sonnei* was the most common species of *Shigella* found, followed by *S. flexneri.* Together these two species caused over 90% of infections among both hospitalized and non-hospitalized populations (Admoni *et al*, 1995). *S. sonnei* and *S. flexneri* were also found to be the major etiologies of shigellosis in Israel (Finkelstein *et al*, 2002), Turkey (Yurdakok *et al*, 1997), and the United States (Gupta *et al*, 2003).

Infection caused by *S. flexneri* is reportedly more severe than that caused by *S. sonnei* (Yurdakok *et al*, 1997; Keusch and Bennish, 1998; Kavaliotis *et al*, 2000), which suggests infection caused by *S. flexneri* was more serious and prompted the parents to bring their sick children to hospital rather than to health centers. A similar observation was reported by Gupta *et al* (2003) who stated although all *Shigella* species can cause dysentery, *S. sonnei* caused generally milder disease. Unlike in several countries (Ahmed *et al*, 1997; Mache, 2001; Brooks *et al*, 2003; Gupta *et al*, 2003) *S. dysenteriae* and *S. boydii* did not appear to be a major cause of diarrhea in Indonesia. They were isolated in a very small number of cases (0.5% and 0.8%, respectively) (Table 1) both species had been absent in Indonesia for almost 20 years (Subekti *et al*, 2001). *S. dysenteriae* was began to reemerge in 1998 in several cities in Indonesia, while *S. boydii* recently reappeared in North Jakarta in 2001 (Subekti *et al*, 2001, Agtini *et al*, 2005).

The isolation rates for *Shigella* increased with increasing age of the patient and reached significant percentages in children >2-5 years old(12.0%) and >5 -14 years old (13.3%) (Table 1). The lowest rate was seen in children under 1 year old (3.8%). These isolation rates are in agreement with those reported from Kolkata, India during 1995- 2000 (Dutta *et al*, 2002). The low shigellosis rate among children under age 1year old may be attributed to the protective immune properties of breast milk or the exclusion of Shigella-infected foods from their diet (Ahmed *et al*, 1997; Yurdakok *et al*, 1997). Most infants in Indonesia are breastfed until they are at least 1 year old. The increased number of shigellosis cases seen after age 1 year, when children are no longer breast feeding likely reflects the lack of natural anti-Shigella immunity of recently weaned children. The importance of breast feeding as a protective factor against shigellosis has been emphasized elsewhere (Ahmed *et al*, 1997; Khalil *et al*, 1998).

Shigella infection varied significantly by age group. *S. flexneri* was isolated in a greater number in children over 5 years old ($p<0.05$), as opposed to *S. sonnei* which was relatively constant among children greater than 1 year old. *S. dysenteriae* and *S. boydii* were isolated only rarely. Thus, they were difficult to analyze. However, they were recovered in a relatively high frequency from children over 1 year old.

Symptoms and signs, such as fever, dehydration, frequency of diarrhea more than 10 times within a 24 hour period and bloody stools, which were found in only a small number of cases in this community-based study, may be explained by the fact that many diarrhea cases, predominantly caused by *S. flexneri*, had severe disease and sought medical attention at a hospital. Symptoms of infection caused by *S. flexneri* and *S. sonnei* were similar. Diarrhea with mucus were the major characteristics of infection caused by these species. However, blood in the stool was found more often in *S. flexneri* infections, although this was not significant ($p>0.05$). Kavaliotis *et al* (2002) and Admoni *et al* (1995) reported that infection caused by *S. flexneri* resulted in a higher rate of bloody stools. In contrast to the findings by Admoni *et al* (1995) who found that *S. sonnei* infection frequently caused watery diarrhea only, our findings showed that diarrhea with mucoid stools were more frequent than watery stools in *S. sonnei* shigellosis ($p<0.05$). Compared to *S. sonnei*, Kavaliotis *et al* (2002) found that infection with *S. flexneri* resulted in a longer duration of fever and diarrhea, a higher number of cases with bloody stools and a longer hospital stay. It should be pointed out, however, that in individual patients there was no accurate way to distinguish between infections caused by the different species on the basis of clinical features (Admoni *et al*, 1995).

Antibiotics are always recommended for the treatment of childhood shigellosis (WHO, 1990), however, a main concern for treatment of shigellosis is the decision about the use or selection of antibiotics, since many *Shigella* species have developed resistance to antibiotics routinely used for diarrhea treatment. The increased resistance frequency of *Shigella* to ampicillin, chloramphenicol, tetracycline, and trimethoprim-sulfamethoxazole has been reported worldwide (Admoni *et al*, 1995; Yurdakok *et al*, 1997; Dutta *et al*, 2000; Kaviolits *et al*, 2000). Our data show that less than half of the number of *S. sonnei, S. dysenteriae*, and *S. boydii* cases were resistant to ampicillin and chloramphenicol, but resistance to these antibiotics was found in many *S. flexneri* isolates, which is the predominant species in Indonesia (Table 3).

A high frequency of resistance was seen in *S. flexneri* to trimethoprim-sulfamethoxazole. Therefore, ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole are no longer effective for the treatment of *Shigella* infections in this country. In Kolkata, India, the drug of choice for shigellosis is nalidixic acid, but due to emergence of resistant strains from various part of the country, norfloxacin, and ciprofloxacin have been used in day-to-day practice in the area (Dutta *et al*, 2000). The use of fluoroquinolones in pediatric patients is still controversial and is not recommended in Indonesia. Therefore, suitable alternative drugs should be sought for treatment of childhood shigellosis. Our data show resistance to nalidixic acid was not found even among *S. flexneri* isolates. Thus, at the present time nalidixic acid is the best choice for treating childhood shigellosis in Indonesia.

A limitation of this study was the relatively small number of isolates obtained which made analysis difficult, especially in regard to the symptoms and antibiotic resistance patterns. Therefore, further studies with large samples and coverage of a wider area of Jakarta are needed.

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