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Increasing Antimicrobial Resistance of *Shigella* Isolates in Israel during the Period 1984 to 1992

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Recent (1984 to 1992) trends in the antimicrobial resistance of *Shigella* isolates in Israel were studied by analyzing the results of 106,000 stool cultures, 3,511 of which yielded *Shigella* spp. Over the study period, resistance to trimethoprim-sulfamethoxazole (TMP-SMX) increased from 59 to 92% ($P = 0.0038$) and that to ampicillin increased from 13 to 86% ($P < 0.0001$). Resistances to nalidixic acid, chloramphenicol, and broad-spectrum cephalosporins remained low. *Shigella sonnei*, which currently accounts for 90% of *Shigella* infections, was more resistant than *S. flexneri* to TMP-SMX (81 versus 57%, $P < 10^{-6}$), ampicillin (42 versus 32%, $P < 10^{-5}$), and tetracycline (38 versus 28%, $P < 10^{-5}$). *S. boydii* and *S. dysenteriae* were relatively rare. Seasonality in antimicrobial resistance was found, with summer isolates being less resistant to TMP-SMX, ampicillin, or both than isolates obtained over the rest of the year ($P < 10^{-5}$). We conclude that the resistance of shigellae, especially *S. sonnei*, to TMP-SMX and ampicillin is increasing to ~90%. Resistance should be recorded locally, and empiric therapy for suspected shigellosis should be changed accordingly.

Appropriate antibiotic treatment of shigellosis has proven efficacious (8, 15, 22, 29). It shortens the duration of fever, diarrhea, and toxemia (1, 22) and probably also reduces the risk of lethal complications (10, 26). The concomitant shortening of the period in which the infecting organisms are excreted in stools is important epidemiologically to minimize spread of the infection, because shigellosis is usually disseminated by person-to-person transmission (1, 8, 22, 29).

Antibiotic treatment of suspected shigellosis, especially in children, has been complicated by the appearance of drug resistance. Initially susceptible to many antimicrobial agents, *Shigella* isolates resistant to a variety of agents have been reported in the United States, especially in Indian reservations and day care centers (4, 5, 11), and in Canada (25), Asia (3, 18), Europe (13), and Africa, most prominently among patients with AIDS (16). This development has necessitated the examination of new therapeutic options (1, 9, 28, 34) and repeated reevaluation of the treatment recommendations (29). Because resistance patterns are changing constantly and vary among geographic locations (20), their continual monitoring is mandatory.

Shigellosis is endemic to Israel, with a reported incidence rate about 20 times higher than that in the United States (7, 12). It is primarily prevalent among children aged 1 to 4 years (12). The purpose of the present study is to analyze current trends in the antimicrobial resistance of *Shigella* isolates, especially in light of the changing epidemiology of *Shigella* spp. (2). Resistance trends regarding ampicillin and trimethoprim-sulfamethoxazole (TMP-SMX), agents typically used to treat shigellosis, are analyzed in more detail.

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MATERIALS AND METHODS

Source of specimens. Stool cultures submitted during a 9-year period (1984 to 1992) were studied. The 106,000 specimens included 34,000 from the Microbiology Laboratory of Beilinson Medical Center, Petah Tiqva, Israel, a university hospital that serves as a tertiary-care center for an urban population of ~300,000. The other 72,000 specimens were from the Central Laboratory of the Sick Fund Health Insurance, which serves only ambulatory clinics that cater to a population of ~600,000. Both populations have good sanitary conditions. Only one *Shigella* isolate per patient per diarrheal episode was included in the analysis.

Microbiologic examinations. Stool specimens were cultured on salmonella-shigella agar, MacConkey-sorbitol agar, and selenite broth. *Shigella* species were identified biochemically by standard methods (14) and grouped serologically by slide agglutination with specific antisera (Wellcome Research Laboratories, Beckenham, England). Antibiotic susceptibility was determined by the disk diffusion method according to procedures established by the National Committee for Clinical Laboratory Standards (21). Quality control strains that were used include *Escherichia coli* ATCC 25922, coagulase-positive *Staphylococcus* strain ATCC 25923, and *Pseudomonas aeruginosa* ATCC 27853. Zone sizes for the controls were in acceptable ranges for the drugs tested.

Statistical analysis. The significances of differences in the proportions of antimicrobial resistance and of the relative prevalences of each *Shigella* species were determined by the chi-square test or the Fisher exact test (when the expected value in >20% of the cells was <5). Two-tailed tests were applied. Trends over the years were examined by Pearson's correlation coefficient.

RESULTS

From the stool specimens examined, 3,511 isolates of *Shigella* species were identified. Comparison of the isolates obtained from the ambulatory clinics ($n = 2,550$) and those obtained from the hospital ($n = 961$) showed no significant differences in antimicrobial susceptibilities of the two groups. Hospital and community isolates were therefore grouped together for the final analysis.

Trends in resistance to common antimicrobial agents. Resistance patterns to TMP-SMX, ampicillin, and nalidixic acid, which are usually used to treat shigellosis, are shown in Fig. 1. Resistance of *Shigella* isolates to TMP-SMX increased over the study period from 59% in 1984 to 92.5% in 1992 ($P = 0.0038$). Resistance to ampicillin, which was only 12.7% in 1984, increased to 86.3% in 1992 ($P < 0.0001$). In contrast, resistance

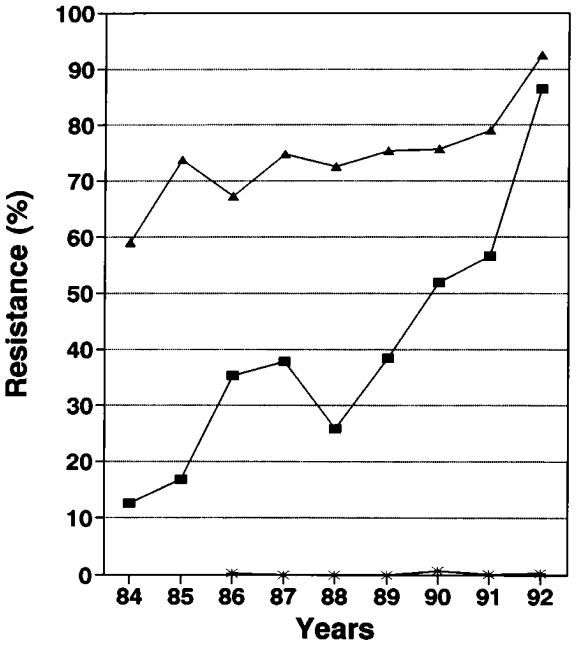

FIG. 1. Trends in antimicrobial resistances of 3,511 *Shigella* isolates to TMP-SMX (▲), ampicillin (■), and nalidixic acid (∗) from 1984 through 1992.

to nalidixic acid, which is not commonly used in our country, remained below 1% throughout the study period.

Trends in resistances of *Shigella sonnei* and *S. flexneri*. Of all 3,511 *Shigella* isolates obtained throughout the study period, *S. sonnei* accounted for 78.0% of the cases and *S. flexneri* accounted for 15.8%, while *S. boydii* and *S. dysenteriae* were relatively rare, accounting for 4.9 and 1.5% of the cases, respectively. Therefore, species-specific trends of resistance were analyzed for *S. sonnei* and *S. flexneri* (Fig. 2). Overall, *S. sonnei* was more resistant than *S. flexneri* to TMP-SMX (80.9 versus 56.8%, $P < 10^{-6}$), ampicillin (42.1 versus 32.2%, $P < 10^{-5}$), and tetracycline (37.9 versus 27.6%, $P < 10^{-5}$). Resistance of *S. sonnei* to TMP-SMX was already above 60% in 1984 and increased to 90% in 1992, while that of *S. flexneri* was above 50% in 1984 but did not increase in subsequent years (Fig. 2A). Resistance to ampicillin has increased in recent years for both species, reaching 83 and 40% for *S. sonnei* and *S. flexneri*, respectively (Fig. 2B).

Multiresistance of *S. sonnei* to both TMP-SMX and ampicillin has increased markedly since 1990, reaching a high rate of ~85% in 1992 (Fig. 3). This resistance rate was significantly ($P < 10^{-6}$) higher than that of *S. flexneri*. Although the multiresistance of *S. flexneri* has also increased in recent years, it was below 30% in 1992 (Fig. 3). Resistances of *S. boydii* were similar to those of *S. flexneri*, being 46, 22, and 26% to TMP-SMX, ampicillin, and tetracycline, respectively. The high resistance rates of *S. sonnei* are of particular importance because the relative prevalence of this species has increased in recent years, reaching about 90% of all *Shigella* isolates in 1992, while the relative prevalence of *S. flexneri* and *S. boydii*, the less resistant species, has decreased (Fig. 4).

Seasonality of antimicrobial resistance. We compared the resistances of shigellae isolated in the summer (June through September) and those isolated during the rest of the year (October through May) over the study period. The winter and spring isolates were combined because of the smaller number of isolates during these seasons. Summer isolates were less

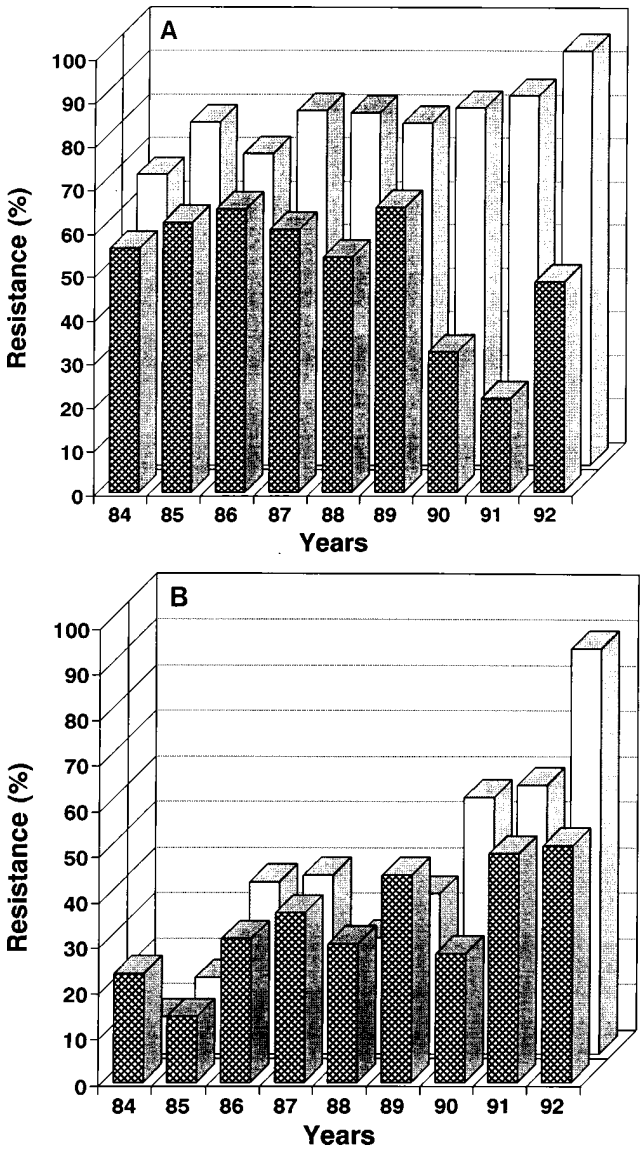

FIG. 2. Trends in resistances of *S. sonnei* and *S. flexneri* to TMP-SMX (A) and ampicillin (B) from 1984 through 1992. □, *S. sonnei*; ▨, *S. flexneri*.

resistant to TMP-SMX, ampicillin, or both ($P < 10^{-5}$; Table 1). The lower resistance rates of summer isolates were consistent for the various species of *Shigella* and with regard to the different antimicrobial agents mentioned above, although sometimes not for *S. boydii* or *S. dysenteriae*, perhaps because of the small number of isolates of the latter two species. The seasonality in antimicrobial resistance could not be explained by the relative prevalence of *Shigella* species, for which no significant seasonality was found.

Current resistance patterns. The resistances of *Shigella* isolates during the period 1991 to 1992 to multiple antimicrobial agents are shown in Table 2. Most *S. sonnei* isolates and about half of the *S. flexneri* isolates were resistant to TMP-SMX or ampicillin. Twenty-five to 50% were resistant to tetracycline or cefazolin. In contrast, a low level of resistance to nalidixic acid, chloramphenicol, broad-spectrum cephalosporins (cefotaxime and cefixime), gentamicin, and fluoroquinolones was found. The resistance rates of *S. flexneri* could have been skewed by the relative rarity of this species in 1991 to 1992.

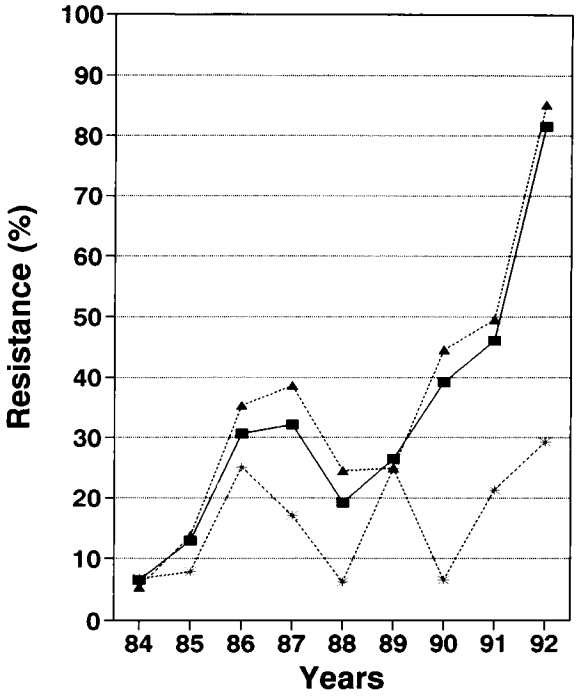

FIG. 3. Multiresistance to both TMP-SMX and ampicillin of all *Shigella* isolates (■), *S. sonnei* (▲), and *S. flexneri* (∗) from 1984 through 1992.

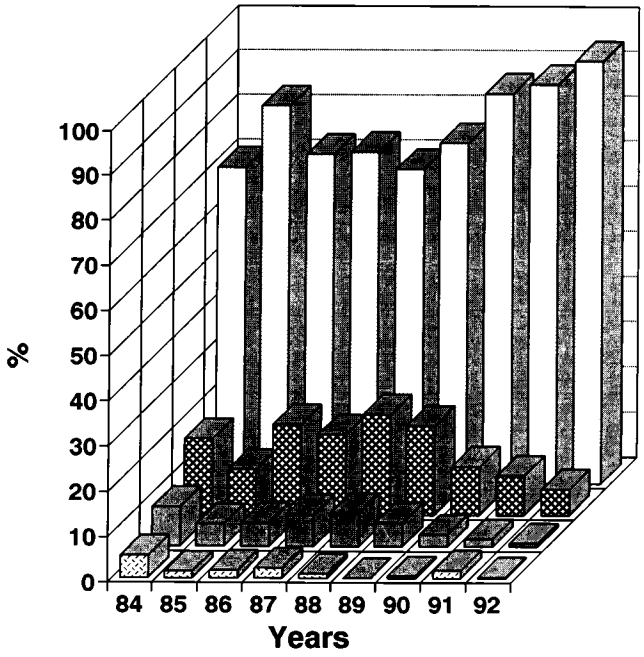

FIG. 4. Trends in the relative frequencies of the various *Shigella* spp. from 1984 through 1992. , *S. dysenteriae*; ■, *S. boydii*; ▨, *S. flexneri*; □, *S. sonnei.*

DISCUSSION

The present study demonstrates recent trends of increasing antimicrobial resistance of *Shigella* species in Israel. Resistance to antimicrobial agents usually used to treat suspected shigellosis in children, namely, TMP-SMX and ampicillin, has become profound. Although similar trends have been reported in other locations, resistance rates were usually lower than those in Israel (6, 11, 18, 25, 31). In developing countries, in Bangladesh in particular, very high resistance rates have been reported (19, 28). In Bangladesh and Africa, however, *S. flexneri* and *S. dysenteriae* are more prevalent and, of the latter, serotype 1 often shows multiple antibiotic resistance (26, 27). In addition, the introduction of nalidixic acid use in that location has been followed by rapid development of *Shigella* isolates resistant to nalidixic acid (18, 19). Nalidixic acid is used infrequently in Israel, while TMP-SMX and ampicillin are extensively used. In developed countries the importance of international travel as a source of resistant *Shigella* isolates has been emphasized (13, 33), as have settings associated with relatively high resistance rates, such as day care centers and Indian reservations (4, 11). Outbreaks of infection by multiply resistant *Shigella* strains have been reported also in developed countries; for instance, a large outbreak which occurred recently among participants at a mass gathering in the United States was caused by *S. sonnei* resistant to TMP-SMX, ampicillin, and tetracycline (35).

By analyzing trends in the resistance patterns of the various *Shigella* species, we found that *S. sonnei* currently is significantly more resistant to common antimicrobial agents, mainly TMP-SMX and ampicillin, than are the other *Shigella* species, in contrast to the patterns noted in the past. These data need to be emphasized because *S. sonnei* is at present the predominant species in the United States, Israel, and other developed countries and its relative incidence is increasing, mainly in hospitalized patients (2, 17).

Another finding of the present study is the seasonality of the antimicrobial resistance of shigellae; namely, summer isolates of *Shigella* were significantly less resistant to TMP-SMX, ampicillin, or both, than were isolates obtained during the rest of

TABLE 1. Seasonality of antimicrobial resistance of *Shigella* isolates[a]

Organism(s)	No. of isolates		% Resistant to:					
			TMP-SMX		Ampicillin		Both	
	Summer	Rest of yr	Summer	Rest of yr	Summer	Rest of yr	Summer	Rest of yr
All *Shigella* isolates	1,566	1,790	66	82	38	45	27	35
S. sonnei	1,240	1,426	71	89	36	46	32	40
S. flexneri	217	263	49	64	30	33	12	17
S. boydii	78	85	47	44	18	27	12	20
S. dysenteriae	32	17	13	12	39	38		

[a] Resistances to antimicrobial agents commonly used against shigellosis were compared for isolates obtained during the summer months (June through September) and those obtained during the rest of the year (October through May). The differences in the susceptibilities of summer isolates and those obtained during the rest of the year were highly significant ($P < 10^{-5}$).

TABLE 2. Percentage of antimicrobial resistance of *Shigella* isolates during the period 1991 to 1992[a]

Antimicrobial agent	% Resistance for:		
	All *Shigella* isolates (n = 602)	*S. sonnei* (n = 557)	*S. flexneri* (n = 39)
TMP-SMX	90	86	40
Ampicillin	81	84	51
Amoxicillin-clavulanate	6	5	33
Nalidixic acid	0.3	0.3	0
Tetracycline	23	22	48
Chloramphenicol	6	2	43
Cefazolin	24	23	28
Cefotaxime	0.9	0.5	5
Cefixime	2	1	20
Gentamicin	6	5	16
Ciprofloxacin	0	0	0
Norfloxacin	0	0	0

[a] Only three isolates each of *S. boydii* and *S. dysenteriae* were recorded in 1991 to 1992.

the year. This finding has not been reported before and was unexpected, and its explanation is currently unclear. In other infections, more resistant microorganisms may be less virulent, but no epidemiological data are available on a distinct epidemiology or transmission of *Shigella* species during the colder months of the year. Selection of resistant strains by a more frequent use of antimicrobial agents during winter, for respiratory infections, is another speculation.

The high resistance rates of *Shigella* isolates to TMP-SMX and ampicillin mandate the consideration of other therapeutic options. For children, these are currently limited. Nalidixic acid has been efficacious against shigellosis, mainly in terms of clinical response but also with regard to the bacteriologic cure rate (28). Unfortunately, resistance to nalidixic acid appears relatively rapidly. This agent was introduced for the treatment of shigellosis in Bangladesh in 1986, and within 4 years a high rate of resistance had developed, mainly of *S. dysenteriae* serotype 1 (18). The new quinolones, such as ciprofloxacin and ofloxacin, are powerful agents against shigellosis in adults; in children, however, their use is not approved because of the damage to the growing cartilage that has been observed to occur in young animals (9, 29). Because of the problem of antimicrobial resistance, the practice of not using quinolones in children with shigellosis has been questioned (9). Oral broad-spectrum cephalosporins may present another therapeutic option. They are effective against *Shigella* species in vitro (23, 30) and have a good safety record (32). Two clinical studies using cefixime (1) and ceftibuten (24) showed promising results against culture-proven shigellosis.

Physicians should be aware of the increasing antimicrobial resistance of *Shigella* species, especially of *S. sonnei*, and of the increasing relative prevalence of this species. Since resistance varies according to the specific location, continuous local monitoring of resistance patterns is mandatory for the appropriate selection of empiric antimicrobial therapy for patients with suspected shigellosis. In addition, since resistance changes constantly, susceptibility testing should be performed on all clinical isolates and the empiric antibiotic treatment should be changed accordingly.

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