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Shigellosis in Subjects with Traveler's Diarrhea versus Domestically Acquired Diarrhea: Implications for Antimicrobial Therapy and Human Immunodeficiency Virus Surveillance

Carlos Toro,* Ana Arroyo, Ana Sarria, Nuria Iglesias, Ana Enríquez, Margarita Baquero, and Concepción Ladrón de Guevara

Service of Microbiology and Parasitology, Carlos III Hospital, Madrid, Spain; IdiPAZ-La Paz University Hospital, Madrid, Spain; Tropical Medicine Unit, Service of Infectious Diseases, Carlos III Hospital, Madrid, Spain

Abstract. An increase of sexually transmitted shigellosis is currently being reported in developed countries. In addition, travel-related shigellosis can introduce resistant strains that could be disseminated within this new scenario. Epidemiological features and antimicrobial susceptibility of shigellosis depending on where infection was acquired were investigated. From 2008 to 2013, subjects with shigellosis were studied. Patients were classified according to acquisition of *Shigella* as traveler's diarrhea (TD) or domestically acquired diarrhea (DAD). Ninety cases of shigellosis were identified: 76 corresponding to the TD group and 14 to the DAD group. In the DAD group, most of patients were human immunodeficiency virus (HIV)-positive men who have sex with men (MSM), being shigellosis associated to male sex ($P = 0.007$) and HIV infection ($P < 0.0001$). *S. sonnei* (47.8%) and *S. flexneri* (42.2%) were the predominant species. The highest resistance was detected for trimethoprim/sulfamethoxazole (SXT) (81.8%), followed by ampicillin (AMP) (37.8%) and ciprofloxacin (CIP) (23.3%). Resistant *Shigella* strains were more frequent in subjects with TD than those with DAD, although only for CIP the difference was significant ($P = 0.034$). Continuous monitoring of patients with shigellosis is necessary to control the spread of resistant *Shigella* strains and for effective therapy. Men with shigellosis who have not traveled to an endemic area should be screened for HIV infection.

INTRODUCTION

Diarrhea is the most frequent morbidity among travelers returning from developing countries. *Shigella* is an important etiologic agent of traveler's diarrhea.[1] Only humans and higher primates carry *Shigella*. Transmission occurs via the fecal–oral route, through contaminated food, water, or fomites, and as few as 10 organisms can cause infection. *Shigella* is comprised of four major species: *S. dysenteriae*, *S. flexneri*, *S. boydii*, and *S. sonnei* with a worldwide distribution. *S. dysenteriae* and *S. flexneri* are the predominant species in resource-limited settings causing a more severe disease, while *S. sonnei* predominates in industrialized countries tending to cause milder disease.[2] In 1999, Kotloff and others[3] estimated that ~165 million cases of shigellosis (more than 100 million occurred in the developing world) with more than 1 million deaths. Over the last decade, the number of shigellosis-related deaths has declined significantly in developing countries; however, there were no substantial changes in the total number of cases of shigellosis episodes in these areas.[4] Among western countries, nearly 450,000 *Shigella* infections were reported each year in the United States.[5] In Spain, an average of 200 cases were reported annually in the last 5 years[6] and almost half of the cases detected in that country are probably imported through traveling abroad.[7]

Apart from foreign travel, risk factors for shigellosis in industrialized countries include children who are < 5 years or subjects in daycare centers. In addition, shigellosis has increasingly been reported in men who have sex with men (MSM).[8] Bader and others reported relatively long periods, up to 8 weeks, of symptom-free shedding of *Shigella* during the convalescent stage in MSM.[9] Besides, up to half of shigellosis cases in adults can be asymptomatic carriers.[9,10] These features may contribute to the transmission risk of shigellosis during oral–anal sexual practices. In fact, outbreaks in developed countries have been traced to networks of HIV-positive MSM.[11]

Shigellosis is characterized by abdominal cramps, diarrhea that sometimes contains blood, nausea, vomiting, fever, and tenesmus. In people without underlying diseases, shigellosis will typically resolve within 4–7 days, even without treatment. Antibiotic therapy reduces the duration of *S. dysenteriae* infection and, therefore, it is recommended for treatment of moderate to severe dysentery. Quinolones and cephalosporins are the drugs of choice[12]; however, resistance to fluoroquinolones and third- and fourth-generation cephalosporins has been reported, particularly among *Shigella* isolates acquired in southern and eastern Asia.[13,14] The possibility that travel-related infections may introduce *Shigella* to the HIV-positive population, with the implications about the introduction of resistant *Shigella* strains, is a matter of concern given the potential for increased transmission and severity of shigellosis in HIV-infected subjects.[15]

The aim of this study was to investigate the antimicrobial susceptibility of shigellosis over time and its possible relationships with epidemiological features to introduce measures for an improved diagnosis of the disease, thus avoiding the possible spread of resistance.

MATERIAL AND METHODS

Patients and strain identification. Adult patients (≥ 18 years old) with diarrhea due to *Shigella* species being attended in Carlos III Hospital located in Madrid, Spain—a center specializing in tropical medicine and HIV care—from September 1, 2008 to December 31, 2013 were studied. The stool samples were processed and the *Shigella* isolates were identified after performing standard techniques.[16] *Shigella* strains were serotyped by antiserum (Difco™, Becton Dickinson, Shannon, County Clare, Ireland). Systemic or invasive shigellosis was defined in those subjects in whom *Shigella* species were also isolated from a normally sterile site. Data from medical charts regarding age, sex, travel history (country of destination), HIV status, and risk exposure in HIV-positive patients infected with *Shigella* (categorized as intravenous drug users, MSM, female sex workers, or unknown) were retrospectively collected. Patients were classified into two different groups: those

*Address correspondence to Carlos Toro, Service of Microbiology and Parasitology, Hospital Carlos III, C/Sinesio Delgado 10, 28029 Madrid, Spain. E-mail: carlostororueda@hotmail.com

TABLE 1
Epidemiological characteristic and *Shigella* species distribution among subjects with diarrhea

	Total, *N* = 90	TD, *N* = 76	DAD, *N* = 14	*P* value
Age (mean ± SD) (years)	33.6 ± 11.4	33.5 ± 11.3	34.6 ± 12.4	ns
Sex (men) (%)	54 (60)	41 (53.9)	13 (92.9)	0.007
HIV (%)	14 (15.6)	2 (2.6)	12 (85.7)	< 0.0001
Shigella isolates				
S. sonnei (%)	43 (47.8)	38 (50)	5 (35.7)	ns
S. flexneri (%)	38 (42.2)	28 (38.2)	9 (64.3)	ns
S. boydii (%)	3 (3.3)	3 (3.9)	0 (0)	ns
S. spp. (%)	6 (6.7)	7 (7.9)	0 (0)	ns

DAD = domestically acquired diarrhea; HIV = human immunodeficiency virus; ns = not significant; TD = traveler's diarrhea.

subjects who came from foreign destinations developing diarrhea at their destination or within 1 week after returning were considered as patients with traveler's diarrhea (TD). Alternatively, subjects with diarrhea without travel history were included in the group of domestically acquired diarrhea (DAD).

Antimicrobial susceptibility. The antimicrobial susceptibility to ampicillin (AMP), amoxicillin plus clavulanic (AMC), cefotaxime (CTX), ceftazidime (CTZ), cefepime (CPM), trimethoprim/sulfamethoxazole (STX), ciprofloxacin (CIP), aztreonam (ATN), and imipenem (IMP) was tested by the microdilution system MicroScan® (Siemens, Camberley, United Kingdom) according to Clinical and Laboratory Standards Institute (CLSI).[17] The antimicrobial susceptibility to azithromycin (AZM) was retrospectively tested from frozen isolates by the E-test method (Biomérieux, Marcy l'Etoile, France). The breakpoint for susceptibility to AZM was a minimum inhibitory concentration (MIC) ≤ 16 mg/L.[18] Multidrug resistance (MDR) was defined as the presence of resistance to at least two unrelated antimicrobial agents.

HIV laboratory determinations. Plasma HIV-RNA was quantified using bDNA technology (HIV Quantiplex v3.0; Bayer Diagnostics or Versant HIV-1 RNA; Siemens, Barcelona, Spain). CD4 T-cell counts were determined by flow cytometry using specific labeled monoclonal antibodies (Beckman Coulter, Madrid, Spain).

Statistical analysis. Comparisons of proportions were done with the Fisher's exact test or χ^2 test for linear trend when appropriated. A P value of < 0.05 was considered to be statistically significant. Statistical analyses were performed using SPSS v.19 program (IBM, New York, NY).

RESULTS

Epidemiological distribution. A total of 90 *Shigella* strains were isolated from stool samples from subjects with diarrhea. No cases of systemic shigellosis were detected. Seventy-six (84.4%) corresponded to TD and the remaining 14 (15.6%) to DAD. Nearly half of *Shigella* isolates were identified as *S. sonnei* (*N* = 43, 47.8%), followed by *S. flexneri* (*N* = 38, 42.2%), *S. boydii* (*N* = 3, 3.3%), and in 6 isolates (6.7%) no species could be identified. Of 76 patients with TD, 37 (48.7%) came from Africa—most of them from Sub-Saharan Africa—30 (39.5%) from Asia—mostly from India—eight (10.5%) from Central and South America, and one (1.3%) from Russia. The geographical distribution of *S. sonnei* and *S. flexneri* isolates in the group of patients with TD was very similar: 16 *S. sonnei* and 15 *S. flexneri* were isolated from Africa, 17 *S. sonnei* and 10 *S. flexneri* from Asia, and 4 *S. flexneri* and 4 *S. sonnei* from central and South America. Of 14 subjects with DAD, 12 were HIV-positive men and nine of them were MSM. The other two remaining patients were a 70-year-old woman and a 33-year-old man, and there were no data about their HIV status. *S. flexneri* was isolated more frequently in this group of patients compared with TD, although the difference did not reach statistical significance (64.3% versus 38.2%; $P = 0.083$). Of 12 HIV-infected patients with DAD, the median of CD4 T cells was 479 cells/mm^3 (interquartile range [IQR], 393–589), and the median of HIV viral load was 4.2 log copies/mL (IQR, 1.6–5). Five patients were under antiretroviral therapy. Table 1 shows the epidemiological characteristics and *Shigella* species distribution between TD and DAD groups.

Yearly distribution. The distribution of the number of *Shigella* strains isolated in the 5-year study period showed a peak in 2011 with a light decrease in the following years (Figure 1). This decrease was due to a lower number of cases detected in patients with TD, while the cases identified in subjects with DAD remained relatively constant.

Antimicrobial susceptibility. Regarding the antimicrobial susceptibility of 90 isolates of *Shigella*, the highest resistance was detected for SXT (81.8%). Moderate resistance was found to AMP (37.8%) and CIP (23.3%). For the rest of antibiotics, the level of resistance was low (< 6%). MDR strains were detected in 44.4% (40/90) of cases. Table 2 shows the rate of antimicrobial resistance according to TD and DAD groups and *Shigella* species.

Shigella strains tested in the group of patients with DAD were susceptible to all antimicrobial agents except for penicillins and STX. In contrast, resistant *Shigella* isolates were observed against all antibiotics tested (but IMP) in subjects

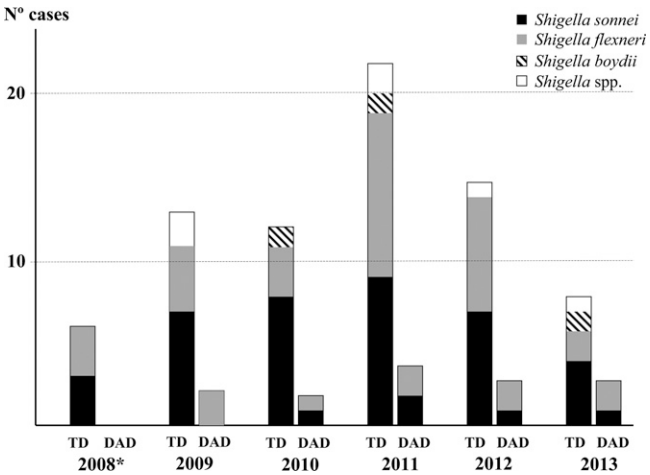

FIGURE 1. Number of cases of shigellosis by year, acquisition of diarrhea and *Shigella* species. *From September to December 2008.

TABLE 2
Antibiotic resistance in *Shigella* isolates according to acquisition of diarrhea and species

		TD			DAD		
Antimicrobial agent	Total	Total	*S. sonnei*	*S. flexneri*	Total	*S. sonnei*	*S. flexneri*
AMP (%)	34/90 (37.8)	27/76 (35.5)	**4/38 (10.5)***	**19/29 (65.5)***	7/14 (50)	**0/5 (0)†**	**7/9 (77.8)†**
AMC (%)	5/90 (5.6)	4/76 (5.3)	0/38 (0)	3/29 (10.3)	1/14 (7.1)	0/5 (0)	1/9 (11.1)
CTX (%)	2/90 (2.2)	2/76 (2.6)	2/38 (5.3)	0/29 (0)	0/14 (0)	0/5 (0)	0/9 (0)
CTZ (%)	2/90 (2.2)	2/76 (2.6)	2/38 (5.3)	0/29 (0)	0/14 (0)	0/5 (0)	0/9 (0)
CPM (%)	1/89 (1.1)	1/75 (1.3)	1/37 (2.6)	0/28 (0)	0/14 (0)	0/5 (0)	0/9 (0)
SXT (%)	72/88 (81.8)	61/74 (82.4)	32/37 (86.5)	21/28 (75)	11/14 (78.6)	5/5 (100)	6/9 (66.7)
CIP (%)	21/90 (23.3)	**21/76 (27.6)‡**	14/38 (36.8)	5/29 (17.2)	**0/14 (0)‡**	0/9 (0)	0/9 (0)
AZM (%)	1/23 (4.2)	1/19 (5)	1/7 (12.5)	0/10 (0)	0/4 (0)	0/3 (0)	0/1 (0)

AMC = amoxicillin plus clavulanic; AMP = ampicillin; AZM = azithromycin; CIP = ciprofloxacin; CPM = cefepime; CTX = cefotaxime; CTZ = ceftazidime; DAD = domestically acquired diarrhea; SXT = trimethoprim/sulfamethoxazole; TD = traveler's diarrhea.
In bold, statistically significant differences between groups: * $P < 0.0001$; † $P = 0.021$; ‡ $P = 0.034$.

with TD reaching statistical significance for CIP ($P = 0.034$). All but one resistant CIP strains were identified in subjects came from Asia (India and only one subject from Maldives) (Table 3). The rate of resistance was higher in *S. flexneri* in comparison with *S. sonnei* for AMP (67.6% versus 9.3%, $P < 0.0001$) and AMC (10.8% versus 0%, $P = 0.042$). This difference also was significant for AMP when analyzed by groups (Table 2). Although MDR was more frequent in *S. flexneri* compared with *S. sonnei*, the difference was not significant (54.1% versus 32.6%; $P = 0.070$).

A higher level of resistance of *S. flexneri* to AMP was observed in the group of subjects with TD who came from Africa and Asia (Table 3). There was no statistical difference in the isolation of MDR strains between the group of subjects with TD and DAD; however, when it was analyzed by travel destination among the group of TD patients, MDR strains were more frequent in subjects coming from Asia than those from Africa (80% versus 27%; $P < 0.0001$), and Asia in comparison with South and central America (80% versus 0%; $P < 0.0001$).

The evolution of antimicrobial susceptibility in the overall period of study in those antibiotics with an elevated rate of resistance strains (AMP, SXT, and CIP) showed only a significant decrease for SXT ($P = 0.011$) (Figure 2). However, it is noteworthy that for CIP the rate of resistant strains has decreased constantly from 2010.

DISCUSSION

In our study, shigellosis was found in two groups of patients, TD and DAD, with distinctive epidemiological features that correlated with different antimicrobial resistance profiles. Subjects with TD probably were infected with foreign *Shigella* strains acquired by faecal–oral transmission and more resistant to antimicrobial agents, while patients with DAD were infected by autochthonous *Shigella* isolates predominantly by sexual route and carried strains more susceptible to antibiotics.

Children were not included in the study; in other at-risk populations for this infection, only an elderly woman in the DAD group was detected. This bias is probably due to the fact that Carlos III Hospital is a center specializing in tropical medicine and HIV infection, thus receiving patients who are usually young or middle-aged people.[19]

The results show that patients with TD could introduce resistant *Shigella* strains and change the antimicrobial profile of susceptibility to most antimicrobial agents that seems to predominate in subjects with DAD. The introduction of resistant *Shigella* strains in populations of HIV-infected MSM may be worrisome. HIV infection raises the biologic susceptibility by immunosuppression and may increase carriage and shedding of *Shigella*[15] as a result. In addition, behavioral factors in MSM can contribute to outbreaks and spreading of resistant strains.[11,20,21] Therefore, increased monitoring and counseling for shigellosis would be recommendable, notably in HIV-positive MSM with diarrhea.

S. sonnei was the most frequent species detected in subjects with TD. Although *S. flexneri* is the most commonly isolated species in the developing world, in the last decade a shift in the predominant species have been occurred with a replacement of *S. sonnei* for *S. flexneri* in urban areas.[14,22–24] This fact can explain our results. In contrast, *S. flexneri* was the most frequent serotype isolated in DAD in our study in

TABLE 3
Antibiotic resistance in *Shigella* isolates in TD by travel destination and species

	Africa			Asia			South and central America		
Antimicrobial agent	Total	*S. sonnei*	*S. flexneri*	Total	*S. sonnei*	*S. flexneri*	Total	*S. sonnei*	*S. flexneri*
AMP (%)	13/37 (35.1)	**1/16 (6.3)***	**10/15 (66.7)***	11/30 (36.7)	**1/16 (5.9)†**	**8/10 (80)†**	2/8 (25)	1/3 (25)	1/4 (25)
AMC (%)	2/37 (5.4)	0/16 (0)	2/15 (13.3)	2/30 (6.7)	0/17 (0)	1/10 (10)	0/8 (0)	0/4 (0)	0/4 (0)
CTX (%)	0/37 (0)	0/16 (0)	0/15 (0)	1/30 (3.3)	1/17 (5.9)	0/10 (0)	0/8 (0)	0/4 (0)	0/4 (0)
CTZ (%)	0/37 (0)	0/16 (0)	0/15 (0)	1/30 (3.3)	1/17 (5.9)	0/10 (0)	0/8 (0)	0/4 (0)	0/4 (0)
CPM (%)	0/37 (0)	0/16 (0)	0/15 (0)	1/29 (3.4)	1/17 (5.9)	0/9 (0)	0/8 (0)	0/4 (0)	0/4 (0)
SXT (%)	32/36 (88.9)	15/16 (93.8)	12/14 (85.7)	22/29 (75.9)	13/16 (81.3)	6/10 (60)	6/8 (75)	3/4 (75)	3/4 (75)
CIP (%)	**1/37 (2.7)‡**	0/16 (0)	0/15 (0)	**20/30 (66.7)‡,¶**	17/14 (82.4)	5/10 (50)	**0/8 (0)¶**	0/4 (0)	0/4 (0)
AZM (%)	0/10 (0)	0/3 (0)	0/5 (0)	0/8 (0)	0/4 (0)	0/4 (0)	1/2 (50)	1/1 (100)	0/1 (0)
ATN (%)	0/36 (0)	0/16 (0)	1/14 (7.1)	3/29 (10.3)	2/16 (12.6)	1/10 (10)	0/8 (0)	0/4 (0)	0/4 (0)
IMP (%)	0/36 (0)	0/16 (0)	0/14 (0)	0/30 (0)	0/17 (0)	0/10 (0)	0/8 (0)	0/4 (0)	0/4 (0)

AMC = amoxicillin plus clavulanic; AMP = ampicillin; ATN = aztreonam; AZM = azithromycin; CIP = ciprofloxacin; CPM = cefepime; CTX = cefotaxime; CTZ = ceftazidime; DAD = domestically acquired diarrhea; IMP = imipenem; SXT = trimethoprim/sulfamethoxazole; TD = traveler's diarrhea.
In bold, statistically significant differences between groups: * $P = 0.001$; † $P = 0.0001$; ‡ $P < 0.0001$; ¶ $P = 0.0008$.

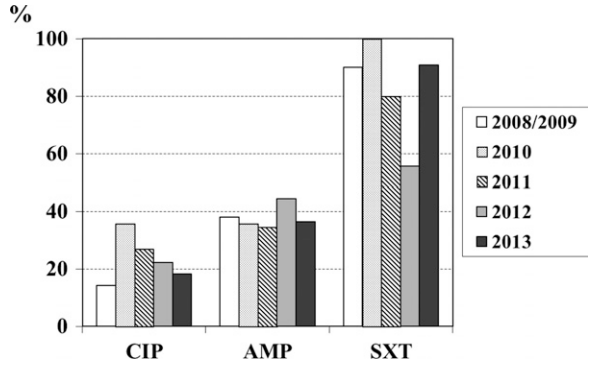

FIGURE 2. Evolution of rate of *Shigella* resistant strains to ciprofloxacin (CIP), ampicillin (AMP), and trimethoprim/sulfamethoxazole (SXT) by year.

spite of *S. sonnei* being the predominant species in developed countries. This may be because most of our subjects with DAD are HIV-infected MSM and it has been described that *S. flexneri* has replaced *S. sonnei* as the predominant species in this population. It has been suggested that *S. sonnei* is less pathogenic and less virulent than *S. flexneri* and could result in a higher number of asymptomatic and less severely ill individuals who will not be diagnosed.[8]

In this study, HIV-positive patients with shigellosis presented only diarrhea and no cases of systemic shigellosis were detected. A plausible explication is that most of our HIV-infected subjects had a preserved immune status with a CD4 T-cell count > 400 cells/mm^3. Keddy and others described that 70% of subjects that developed systemic shigellosis presented CD4 T-cell count < 50 cells/mm^3.[25] Therefore, although HIV infection may contribute to disease expression, shigellosis can be limited to the intestinal tract if the HIV immunosuppression is not severe.

The distribution of the number of *Shigella* isolates in patients with TD showed a peak in 2011 with a slight decrease in the following years. It seems feasible that this erratic pattern may be due to the limited sample size of the study. Pons and others found a decrease in the number of cases of TD due to *Shigella* in Spain in recent times (1995–2010).[26] One plausible explanation may be the improvement in the hygiene measures in the travelers' destinations.[27] More studies will be needed over time to confirm whether this declining trend will continue in the future. On the other hand, although the cases of shigellosis of HIV-positive MSM were scarce, their number was relatively constant throughout the study period, highlighting the need to intensify control measures in this at-risk population.

The evolution of resistance over time is a very important health issue. The level of resistance was high for SXT (81.8%), and a significant decrease in the rate of resistant strains was observed in the 5-year study period. The rate of resistance to AMP (37.8%) was moderate. Although a decline over time was not observed, its rate was lower than that detected in subjects with TD in last century.[28] This data may be related to changes to the therapy chosen for diarrhea. Because the proportion of isolates resistant to AMP and SXT increased substantially among *Shigella* isolates worldwide in the last decade, these drugs are no longer recommended as empirical therapy for shigellosis by the World Health Organization.[29]

We found that *S. flexneri* was more resistant than *S. sonnei* for AMP in both TD and DAD groups. These data are in concordance with other studies.[26,30] However, other authors have described the opposite: higher resistance rates for *S. sonnei* compared with *S. flexneri*.[14] It is feasible that exposure to selective pressure to antibiotic may be vary depending on the region studied, thus explaining this discrepancy.

The rate of resistance to CIP was remarkable (23.3%) and all cases were detected in subjects with TD from Asia (most of them from India) (Tables 2 and 3). In fact, CIP resistance has increased dramatically in the Indian subcontinent in recent years.[31] Therefore, although quinolones have been used as the drugs of choice for acute TD, the widespread use of these agents from specific areas, such as the Indian subcontinent, has produced an increase in the rate of resistance losing their utility in the treatment of subjects with TD from this area. No cases of CIP resistance were detected in the DAD group. However, it is noteworthy that Hoffman and others have found a 66% of resistance to this antimicrobial agent among HIV-positive MSM in Germany.[21]

Possible alternative treatments for shigellosis are the use of other antibiotics such as AZT. Although no clinical breakpoints are available for AZT, a MIC ≤ 16 mg/L is comparable to the MIC distribution in wild-type *Shigella* isolates and, therefore, expected to respond to treatment.[18] In fact, AZT treatment failure has been reported for patients who received this drug for infection with isolates of MIC > 16 mg/L.[32] In our study, one strain with an MIC > 16 mg/L was found. Unfortunately, the strains tested against AZT were scarce, as this antibiotic has not been used for treatment until quite recently. However, most of isolates studied in our work corresponded to strains isolated since 2011 (including the AZT resistant strain detected). Two recent reports have described *Shigella* isolates with increased MICs to AZT in HIV-positive patients, most of them with no travel-abroad history.[32,33] In addition, cases of *Shigella* strains with MICs elevated for this drug have already been documented in Asian countries.[34] These data suggest that AZT may be emerging with reduced susceptibility and MIC for this antimicrobial agent should always be determined in patients with shigellosis. Clinical outcome studies are required to establish clinical breakpoints and monitor the prevalence of genes and mobile elements associated with elevated azithromycin MICs.[35]

As for side effects of AZT, it can increase the risk of corrected QT interval (QTc) prolongation and cardiac arrhythmias and may increase the risk of cardiovascular death.[36] Additive QTc prolongation may occur when AZT is used with the antimalarial artemether, and therefore concomitant therapy should be avoided. Drug interactions have been reported with macrolides and antiretroviral protease inhibitors, as well as efavirenz and nevirapine. Increased anticoagulant effects have been noted when AZT is used with warfarin; monitoring prothrombin time is recommended for people taking these drugs concomitantly.[37] These problems discouraged the use of AZT as an empirical treatment of patients with TD and suggest caution in HIV-infected patients.

Finally, most of the *Shigella* strains were showing susceptibility to cephalosporins, ATN, and IMP. These findings are in concordance with other studies and it can be an alternative therapy in cases of complicated shigellosis. However, surveillance of these drugs is also necessary because some studies have found a remarkable resistance rate to the third-generation cephalosporins (between 12% and 20%).[14,38,39]

Our study has several limitations: first, the number of *Shigella* isolates from DAD group was scarce; second, the

study was performed in an HIV care center, so the cases of shigellosis among HIV-infected patients could be overrepresented. Besides, most of our patients with DAD were MSM subjects. Therefore, we cannot rule out that other collectives involved in high-risk sexual behaviors may be affected by shigellosis. More extensive studies are necessary to unveil the possible spread of resistant *Shigella* isolates domestically in all at-risk populations.

In conclusion, in subjects with diarrhea due to *Shigella*, epidemiological characteristic patterns that correlate with different antimicrobial susceptibility profiles were found. Resistant *Shigella* strains are circulating in our media and can be transmitted at high-risk population as HIV-positive MSM with the possibility of outbreaks. Individuals with HIV-positive MSM with diarrhea should require stool cultures for *Shigella* and antibiotic resistance investigation. In addition, men with shigellosis who have not traveled to an endemic area should be screened for HIV infection. Subjects with TD coming from Asia showed the highest level of resistance. In these subjects, CIP is not the first choice in empirical treatment and other drugs as AZT should be used cautiously. Continuous monitoring of patients with shigellosis is necessary to control the spread of resistant *Shigella* strains and for antimicrobial therapy recommendations.

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Authors' addresses: Carlos Toro, Ana Arroyo, Ana Sarria, Ana Enríquez, and Margarita Baquero, Service of Microbiology, Carlos III Hospital, Madrid, Spain, E-mails: carlostororueda@hotmail.com, anfa87@hotmail.com, anasavisa@gmail.com, aenriquez@salud.madrid.org, and margaritabaqueromochales@yahoo.es. Nuria Iglesias, Microbiology, IdiPAZ-La Paz University Hospital, Madrid, Spain, E-mail: nurinu@telefonica.net. Concepción Ladrón de Guevara, Service of Infectious Diseases, Tropical Medicine, Hospital Carlos III, Madrid, Spain, E-mail: mconcepcion.ladron@salud.madrid.org.

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