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Laboratory-based surveillance of *Shigella* spp from human clinical cases in Colombia, 1997 to 2018.

Vigilancia por laboratorio de *Shigella* spp aislada de casos clínicos humanos en Colombia, 1997 to 2018.

Laboratory-based surveillance of *Shigella* spp Colombia, 1997 to 2018.

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Introducción. La shigelosis es endémica en países de bajos y medianos ingresos, ocasionando aproximadamente 125 millones de episodios de diarrea anualmente y 160,000 muertes, un tercio de estas producidas en niños.

Objetivo. Describir características y perfiles de resistencia antimicrobiana en aislamientos de *Shigella* spp., recuperados en Colombia durante 1997–2018.

Materiales y métodos. Se obtuvo los aislamientos de laboratorios en 29 departamentos de Colombia. La serotipificación la realizamos con antisueros específicos de *Shigella* y la determinación de perfiles de resistencia por Kirby-Bauer y concentración mínima inhibitoria frente a diez antibióticos.

Resultados. Se estudiaron 5.251 aislamientos de *Shigella* spp., obtenidos de materia fecal (96.4%) el (47.8%) de niños menores de cinco años. Las especies más frecuentes fueron *S. sonnei* (55.1%) y *S. flexneri* (41.7%). Se presentó resistencia a tetraciclina (88.1%), trimetoprim-sulfametoxasol-(SXT) (79.3%), ampicilina (65.5%), cloranfenicol (50.8%) y amoxicilina/acido-clavulanico (43.6%). En cefotaxime, ceftazidima, gentamicina y ciprofloxacina la resistencia no superó el (1%). En *S. sonnei*, el perfil de resistencia más frecuente correspondió a SXT en contraste con *S. flexneri* donde todos los perfiles fueron multiresistentes.

Conclusiones. La población menor de cinco años fue afectada por todas las especies de *Shigella* spp., esto debe ser considerado por legisladores en salud pública para tomar decisiones en lo que respecta a medidas de prevención y protección frente a esta enfermedad. Las características de resistencia antimicrobiana de los aislamientos de *Shigella* spp., en Colombia, ponen de manifiesto la importancia de combatir la diseminación en las dos especies más frecuentes en casos clínicos, *S. sonnei* y *S. flexneri*.

Palabras clave: disentería bacilar; vigilancia en salud pública; farmacorresistencia microbiana; ampicilina; cefalosporinas; fluoroquinolonas; combinación trimetoprim y sulfametoxazol; cloranfenicol.

Introduction: Shigellosis is endemic in low and middle-income countries, causing approximately 125 million diarrhea episodes annually, leading to around 160.000 deaths. One third of these deaths are associated with children.

Objective: describe characteristics and antimicrobial resistance profiles of *Shigella* species recovered in Colombia from 1997 to 2018.

Materials and methods: we obtained isolates from laboratories in twenty-nine Colombian states. Serotyping was performed with specific antiserum and antimicrobial resistance via Kirby-Bauer and minimal inhibitory concentration for ten antibiotics according to Clinical and Laboratory Standards Institute recommendations.

Results: In total 5251 isolates of *Shigella* spp. were studies. Most isolates were obtained from stool 96.4%. Also, 2511(47.8%) were from children under five years of age. Two most frequent species were founded *S. sonnei* (55.1%) and *S. flexneri* (41.7%). The highest rate of resistance was found for tetracycline (88.1%), followed by trimethoprim-sulfamethoxazole (SXT, 79.3%) and ampicillin (65.5%). 50.8% of isolates were resistant to chloramphenicol, 43.6% to amoxicillin/clavulanic acid whilst resistance to cefotaxime, ceftazidime, gentamicin, and ciprofloxacin did not reach 1%. In *S. sonnei*, the most frequent resistance profile corresponded to SXT (92%), whereas for *S. flexneri* the most frequent antibiotic profiles were multidrug resistant.

Conclusions. In Colombia the population under five years is affected by all *Shigella* species. These findings should be considered to guide funders and public health officials to make evidence-based decisions for protection and prevention measures. The antimicrobial resistant characteristics found in this study underlie

the importance of combating the dissemination of the most frequently isolated species *S. sonnei* and *S. flexneri*.

Key words: Dysentery, bacillary; public health surveillance; drug resistance, microbial; ampicillin; cephalosporins; fluoroquinolones; trimethoprim, sulfamethoxazole drug combination; chloramphenicol.

Diarrhea is a major global health issue, causing 1.3 million deaths each year. Of these deaths, 500.000 are children less than five years of age, among those (1). Shigellosis is endemic in most low and middle-income countries and is the most important cause of bloody diarrhea worldwide (2). Recent estimates attribute *Shigella* spp. to cause approximately 125 million diarrhea episodes annually, leading to around 160.000 deaths, with a third of these associated with young children (1,3). The Global Enteric Multicenter Study revealed that *Shigella* spp. was the most prevalent causative agent in children aged 2 to 5 years who experienced diarrhea and suggested that induced burden may be twice as high as previously estimated (4).

The *Shigella* genus is divided into four species and into multiple serotypes dependent on O-antigen and also biochemical differences: *Shigella dysenteriae* (serogroup A, 15 serotypes), *Shigella flexneri* (serogroup B, 19 serotypes), *Shigella boydii* (serogroup C, 20 serotypes) and *Shigella sonnei* (serogroup D, 1 serotype) (5). This pathogen is spread by direct contact with an infected person or by ingesting contaminated food or water. The infective dose can be as few as 10 organisms, thus this foodborne pathogen is of global importance based on wide distribution, water quality concerns and is an important risk for public health (6). *S. sonnei* and *S. boydii* usually cause relatively mild illness in which diarrhea may be watery or bloody while *S. flexneri* is the chief cause of endemic shigellosis in low and middle-income countries (7).

Many observations have concluded that *Shigella* species are geographically stratified based on the level of economic development in each country. *S. flexneri* is the primary infectious species in the low and middle-income countries, *S. sonnei*

rates increase with economic development. *S. boydii* is most commonly restricted to Bangladesh and South-East Asia and rarely occurs outside of these regions. *S. dysenteriae* type 1 (Sd1) occurs sporadically in outbreaks (8). Emerging multidrug-resistant *Shigella* isolates have exacerbated the public health impact of shigellosis, leading to increased morbidity, mortality and treatment costs (2,9).

Considering that *Shigella* is a major contributor to the global diarrhea burden, vaccination can be an effective way of preventing this disease. However, there are at least 50 recognized *Shigella* serotypes and the serotype distribution of *Shigella* species differs by geographical region, which complicates vaccine development (10).

In Colombia, organisms of public health significance include *Shigella* and *Salmonella*. These species form part of the surveillance of acute diarrheal diseases performed at department public health laboratories and National Microbiology Laboratory (INS). Considering the importance of better understand the behavior of *Shigella* species at a national level, in this report we present the population age, temporal and geographical characteristics of the isolates, and antimicrobial resistance profiles of *Shigella* species recovered in Colombia from 1997 to 2018.

Materials and methods

Strains recovered from patients were collected in hospitals or public health laboratories located in Colombia. Recovered strains were sent to the microbiology laboratory of National Health Institute (INS), as part of the acute diarrheal disease surveillance program, for confirmation with biochemical identification tests following standardized procedures, as well as serotyping using commercial polyclonal and monoclonal typing antisera (Eurobium) (11). Antimicrobial resistance was

determined using the Kirby-Bauer test against tetracycline (TE) (30 µg), chloramphenicol (C) (30 µg), nalidixic acid (NA) (30 µg), amoxicillin/clavulanic acid (AMC) (10 µg) and ciprofloxacin (CIP) (5 µg). Also, an automated instrument, Microscan ® (Siemens), obtained the minimal inhibitory concentration (MIC) for ampicillin (8-16 µg/ml); cefotaxime (CTX) (2-32 µg/ml), ceftazidime (CAZ) (1-16 µg/ml), ciprofloxacin (CIP) (1-2 µg/ml), gentamicin (GM) (4-86 µg/ml) and trimethoprim-sulfamethoxazole (SXT) (2/38 µg/ml) according to recommendations of the Clinical and Laboratory Standards Institute corresponding to yearly updates (12). Statistical significance (p value) was calculated with EpiInfo 7.

Results

We studied 5251 isolates of *Shigella* spp. recovered in twenty-nine different Colombian geographical states. Bogotá is the capital city of Colombia and was the principal place where isolates were obtained (3257 in total, 62%). Another five states recovered more than one hundred isolates: Antioquia 814 (15%), Valle 205 (3.9%), Norte de Santander 187 (3.6%), Nariño 157 (3%) and Boyacá 146 (2.8%). The additional 485 isolates were recovered from twenty-three other states.

Isolates were obtained mainly from the stool 96.4% (5063/5251) of patients ranging in age from newborn to ninety-two years old. The children under one year of age contributed 452 isolates (8.6%) and the patients between 2 and 5 years contributed 2059 isolates (39.2%). In patients ranging in age from 6 to 14, 1498 (28.5%) strains were recovered and in patients with more than fifteen years 904 (17.2%) were recovered (table 1).

Two species dominated the isolates, which together represented ninety-six percent of the strains: 2896/5251 (55.1%) isolates were *S. sonnei* and 2191/5251 (41.7%)

isolates were *S. flexneri*. Other species included *S*. *boydii* and *S*. *dysenteriae,* of which 103 and 14 isolates were detected respectively. Some of the isolates had characteristics typical of *Shigella* but it was not possible to identify to the species level so were therefore designated as nonserotypeable (NST) *Shigella*. NST accounted for about 47 isolates, none of which agglutinated with any antisera of the established *Shigella* serovars.

During the three first years of surveillance (1997–1999) *S. flexneri* was the dominant species, which decreased after 2002. At this time *S. sonnei* became the most dominant isolate for 15 years until 2016, whence this isolate again became the second most frequent strain (figure 1).

The highest resistance level was found for tetracycline 88.1%, followed by trimethoprim-sulfamethoxazole 79.3% and ampicillin in 65.5%. To chloramphenicol, 50.8% of isolates were resistant, whilst to amoxicillin/clavulanic acid 43.6%. Less than 1% of the isolates were resistant to cephalosporin (cefotaxime and ceftazidime), gentamicin and ciprofloxacin (table 2).

Geographical distribution, age and antimicrobial resistance evaluated for species:

Shigella sonnei

Geographical distribution: *S. sonnei* represented more than half of the Colombian *Shigella* spp. isolates evaluated (2896, 54.7%). From Bogotá, 66% (1975/2896) of the total isolates of this study were recovered. Initially in Bogotá 58 isolates were detected in 2001, whilst in 2002 101 isolates were detected. In Antioquia, 16% of isolates. The remaining 17.8% were detected from twenty-five different states; with an increase in its recovery from the year 2011 to 2014. In the

last few years, the largest number to isolates for this species were detected in those states (figure 2).

Twenty-three outbreaks were observed in nine different states (Antioquia, Bogotá, Boyacá, Cundinamarca, Nariño, Norte de Santander, Santander, Sucre and Valle) with eighty related isolates. The outbreak that grouped the most number of cases (12 in total) occurred in the department of Nariño in 2008. In the additional outbreaks from Nariño, the isolates recovered were varied.

Age: in the population under six years old, almost half of the isolates were recovered (48%, 1390/2896). In the 6 to 14 year bracket, *S. sonnei* was the species most frequently recovered 32.6% (943/2896, table 3).

Antimicrobial resistance: In *S. sonnei*, characteristically the major resistance was for trimethoprim-sulfamethoxazole 89.6% (2530/2825) and for tetracycline resistance was observed in more than 80% (2278/2714) of these isolates. For nalidixic acid, chloramphenicol, amoxicillin/clavulanic acid and ampicillin the resistance levels fluctuated between 7% (184/2574), 29.4% (803/2733), 32.8% (785/2391), and 52% (1469/2827) respectively (table 2). For ciprofloxacin cefotaxime, ceftazidime and gentamicin 14, 12, 10 and 7 of the isolates were resistant respectively.

Shigella flexneri

In Antioquia, 321/2191 of the total isolates (14.65%) were detected with increases in isolate numbers during the years 2000, 2006 and 2012. Another 627 (28.6%) were isolated from twenty-five different states, which represented an increase of the isolates recovered since 2016. For *S. flexneri,* eleven outbreaks were identified (figure 3) with thirty-seven related isolates from five states (Amazonas, Bogotá,

Cundinamarca, Meta, and Nariño). The most important outbreak occurred in Cundinamarca in 2001, during which 14 isolates were related with food consumed in a school. (figure 3)

Age: the *S. flexneri* isolates were recovered in similar proportion among the different age ranges. However, in children under six years old, almost half of the isolates (48.5%) were recovered (table 3).

Antimicrobial resistance: In *S. flexneri,* the major resistance was to tetracycline in 94.3% of isolates, ampicillin 83%, chloramphenicol in 80.8% and trimethoprim-sulfamethoxazole in 67.8% (table 2). Less than ten isolates were resistant to ciprofloxacin cefotaxime, ceftazidime, and gentamicin.

Other species

Geographical distribution: a total of 164 isolates included 103 *S. boydii*, 14 *S. dysenteriae* and 47 nonserotypeable *Shigella* isolates. The highest number of *S. boydii* were isolated in 2004 and 2006 with the largest number of isolates obtained being 42/103 (41%). S*. dysenteriae* only appeared in seven years during twenty-two years of surveillance. The greatest number of S*. dysenteriae* isolates recovered was six in 2018, which were from Arauca (3) Bogotá (2) and Norte de Santander (figure 4). S*. dysenteriae* was not related to outbreaks.

Age: the *S. boydii* was recovered mostly in the population under 14 years (71%) in contrast with S*. dysenteriae* which was recovered mostly from the ≥15 years old bracket. Nonserotypeable isolates were recovered in patients of all ages (Table 3).

Antimicrobial resistance: *S. boydii*, excluding ciprofloxacin, exhibited resistant to all evaluated antibiotics. More than 75% of *S. boydii* were resistant to ampicillin

and tetracycline, and the half of these isolates were resistant to trimethoprim-sulfamethoxazole.

S. dysenteriae was resistant to five of the ten evaluated antibiotics, with the resistance rate lower compared with other species. However, the highest percentage of resistance to nalidixic acid of *S. dysenteriae* was found when compared with other evaluated species (11.1%).

Isolates that were nonserotypeable had resistance to seven of the evaluated antibiotics, characteristically this group had the greatest resistance rate to ciprofloxacin (2.1%)(table 2).

Antimicrobial resistance evaluated per year and species:

B-lactams antibiotics:

Amoxicillin/clavulanic acid: *S. sonnei* resistance began to appear in 2006 when 24.6% of the isolates were found resistant; eleven years after in 2017 this resistance rate reached its highest level almost 66% ($p<0.05$). When this high resistance level was compared with the obtained value in 2018 (11.6%, Table 4) a significate decrease was observed ($p<0.05$).

During the first five surveillance years of *S. flexneri*, no resistance was recorded. Nonetheless between 2002 and 2005; levels from 22% to 40.9% were found; a year after in 2006 this increased significantly to 71.3% ($p<0.05$). Increases in the rate of resistance were stably maintained until 2018 when the resistance level had a significate decrease to 35.2% ($p<0.05$), which was similarly observed in *S. sonnei*. In the other species evaluated, resistance in nine of the twenty-two surveillance years occurred and the highest resistance level was detected in 2017 (50%, table 4).

Ampicillin: Since starting the surveillance in 1997 and for twelve years the resistance in *S. sonnei* remained above 50%. In 2010 rates of resistance increased significantly to 71.5% ($p<0.05$) and were stably maintained until 2018 when resistance rates decreased significantly to 25.9% ($p<0.05$). In contrast, *S. flexneri* resistance rates to ampicillin remained high in the same time frame between 62.7% and 92.8% (table 4). For the other species, there were only three years in which there were no resistant isolates 2008, 2015 and 2017 (table 4).

Cefotaxime and ceftazidime: Resistance to cefotaxime was found in 21 isolates including *S. sonnei* 12, *S. flexneri* 8 and *S. boydii* 1. In total, 16 resistant isolates were detected against ceftazidime, including 10 of *S. sonnei; S. flexneri* 4 and *S. boydii* 2 isolates.

Tetracycline: in *S. sonnei* since the first surveillance year we founded resistance levels in more than 90% of isolates, which decreases to 70% from 2013 and reached the lowest levels in 2018 with 41.2% of isolates. *S. flexneri* isolates were found to higher than 90% during seventeen years of surveillance, being the lowest in 2018 with 83.3%. Other species, presented fluctuations in resistance rates, including years without resistance isolates (2008 and 2017) and also resistance levels being one hundred percent in 1997, 1998, 2000, 2002, 2006 and 2007 (table 4).

Trimethoprim-sulfamethoxazole: In *S. sonnei*, resistance during the evaluated years remained constant, ranging from 75.9% to a maximum of 96.6% in 2006 and 2015 respectively. For *S. flexneri* until 2010, the resistance levels was exceeded 65%, and decreased later to 48.8% in 2018. With respect to other species, the resistance rates were more variable. For example, in some years such as 1998,

2008 and 2010 isolates were completely sensitive whilst in others years resistance rates reached 100% (as in 2017)(table 4).

Quinolones and fluoroquinolones: The resistance to nalidixic acid was highest for *S. sonnei* when compared with the other species. Resistance rates were stable below 10% until 2012 reaching a maximum in 2017 (38.1%). In *S. flexneri* in 2016 alone, the resistant isolates exceeded 20%. In other years this level did not exceed 6% Table 4. In ciprofloxacin, resistance was observed only in 24 isolates from evaluated species (*S. sonnei* 14, *S. flexneri* 9 and *S. boydii* 1).

Phenicols: the highest resistance rate was detected in *S. flexneri* from more than 70% of isolates during surveillance years. In isolates of *S. sonnei*, resistance rates were less than 30% until 2008, when rates began to increase toward (60.3%) in 2012. For others species the resistance levels were variable during the surveillance years (table 4).

Aminoglycosides: Gentamicin was evaluated within the aminoglycoside class. 12 resistant isolates were detected, seven were *S. sonnei*, four were *S. flexneri* and one was identified as *S. boydii*.

Resistance profiles:

The most frequent resistant profile was detected in 1001/5043 (19.8%) of isolates corresponding to a multidrug resistance (resistance in three or more antibiotic classes) TE-C-AMC-AMP-SXT (table 5). Rates of resistance were similar in *S. flexneri and S. sonnei* (table 5).

Other resistance profiles were specific for each species. In *S. flexneri* the most frequent were TE-C-AMP (91.6%), TE-C-SXT (87.7%), TE-C-AMC-AMP (83.5%) and TE-C-AMP-SXT (77.5%). Interestingly in *S. sonnei*, the main resistance profile,

corresponded to resistance to a single antibiotic SXT 92% (277/301), followed by resistance to two antibiotics TE-SXT 86% (825/959). Furthermore, less multidrug resistance profiles were detected compared with *S. flexneri;* TE-AMC-AMP-SXT 78.2%, AMP-SXT 77.9% and TE-AMP-SXT 75.6% were the most frequent resistance profiles (table 5).

Discussion

Diarrheal diseases continue to cause morbidity and mortality in low and middle-income countries. Estimates from 195 countries reveal that global diarrhea mortality among individuals older than 5 years has been dominated by *Shigella* spp (13). Also, *Shigella* spp. was the leading cause of diarrheal mortality among those older than 70 years (14,15).

In this report, most of the strains were isolated from patients under 6 years of age, indicating that age could be an important factor in acquiring *Shigella* infection in Colombia. Findings herein were supported by a prospective surveillance study also performed in Colombia. This prospective study determined the incidence of *Shigella* spp in acute gastroenteritis, finding 23% of the total isolates were associated with hospitalization and outpatient care in single and co-infections for children between 24 and 59 months of age (16). As described in the Global Enteric Multicenter Study (GEMS) study, the *Shigella* spp. burden increased proportionally with age, becoming the second most common pathogen identified among children 12 to 23 months of age, and the leading pathogen at 24 to 59 months of age (17). In this study, the dominant species was *S. flexneri*, in the three first years (1997 to 1999) and the three last years of surveillance (2016 to 2018). Since the year 2000 and for sixteen years (2000 to 2015) the dominant species became *S. sonnei*.

Indeed, *S. sonnei* was the most frequent isolate in all evaluated states. This 'replacement phenomenon' has been documented in many countries in different regions of the world like Asia and support the emergence of *S. sonnei* in economically transitional states, replacing *S. flexneri* as the most frequent agent of shigellosis (18,19).

S. sonnei and *S. flexneri* were the most common isolates herein, coinciding with reports at the global level. For example in the Americas, reports regarding incidence of several *Shigella* species such as in Ecuador which were found in an urban community and Chile in a periurban area (20,21). Additionally, the current global epidemiological burden for shigellosis is attributed to these two species, *S. flexneri*, which was conventionally associated with low and middle-income countries, and *S. sonnei* with high-income regions (19).

Noticeably, regions that had undergone significant industrialization reported increasing cases of *S. sonnei* compared to low and middle-income areas where *S. flexneri* levels remain high (22). The reasons for this shifting trend have been suggested to be an improvement of overall nutritional status (23), socioeconomic status and sanitation conditions (24).

Also, it has been suggested that this is mediated by a cross-immunity. In less-developed countries, repeated ingestion of *Plesiomonas shigelloides* bacteria through consumption of untreated surface waters may stimulate cross-protection against *S. sonnei,* as O antibodies might mediate protection (25).

In this study, the appearance of *S. flexneri* as the most frequent during the last three years of surveillance could be an indicator of decline in the quality of water supply and good sanitation in Colombian communities. It has been shown that an

increase in the provision of clean water and sanitation possibly disrupts the traditional transmission route of *S. flexneri* (26).

For the other evaluated species in this report, *S. boydii* and *S. dysenteriae*, we observed fewer isolates, coincident with other world-wide reports (10,17,27). Nevertheless, outbreaks of both species have been reported (28,29).

Isolates of *S. dysenteriae* in this study were recovered sporadically between one and two strains during the twenty-three years of surveillance. However, in 2018 six isolates were recovered from three different states, two of which are bordered (Arauca and Norte de Santander) and they had not previously reported isolates of these species. According to previous reports, these isolates indicate the possibility of an epidemic in these regions or other regions within Colombia (30).

These isolates were evaluated for the presence of Shiga-toxin and were found to be negative. Some isolates did not react with any *Shigella* serogroup/serotype-specific antisera in this study. Other studies have found similar results, with strains being identified as untypable by serotyping in many other countries (31-33).

In the antimicrobial resistance profiles of all species, the highest resistance levels were found for the three antibiotics tetracycline, trimethoprim-sulfamethoxazole and ampicillin. This trend was also observed in Africa, Asia, and South America, where ampicillin resistance rates were high for almost all *Shigella* species. In most of the studies observed in Africa and Asia, serogroups of *Shigella* developed resistance to tetracycline, chloramphenicol, and trimethoprim-sulfamethoxazole (34-36).

Additionally, in recovered isolates from this study, the resistance levels reached almost the fifty percent to amoxicillin/clavulanic acid. This trend was higher

compared with the Latin-American mean reported by Antimicrobial Surveillance Program, which found 27% of the isolates were resistant to amoxicillin/clavulanic acid which was still less frequent than 71% reported in Europe (35).

In cefotaxime, ceftazidime, gentamicin and ciprofloxacin the resistance rates were lower than 1%. In general, the antimicrobial resistance level for these antibiotics is similar across Latin America, where ceftriaxone is active against all *Shigella* spp. and the isolates resistant to fluoroquinolones are limited (35,37).

The antimicrobial resistance against specific species revealed that *S. sonnei* had the highest resistance level to trimethoprim-sulfamethoxazole. Indeed, resistant isolates of *S. sonnei* were found in all surveillance years. The resistance to amoxicillin/clavulanic acid reached its highest rate in 2017 and abruptly decreased more than fifty percent during 2018 which was unexpected taking into count the behavior of isolates reported herein.

With respect to *S. flexneri* isolates, a number as low as six percent was susceptible to tetracycline, classified to more than ninety percent of the population in the resistant category. Likewise, the ampicillin and chloramphenicol resistance was higher in *S. flexneri* isolates than in all other evaluated species. A similar situation has been revealed in other parts of the world, finding high rates of resistance to at least one common antibiotic such as ampicillin, tetracycline, and chloramphenicol (38,39).

In contrast to reports from other regions to gentamicin nalidixic acid and ciprofloxacin in *S. flexneri* (34) our resistant isolates did not reach high resistance levels. A similar situation occurred for cephalosporin, where resistant was less than one percent, which is similar to another report by Lima et al (40).

S. boydii isolate herein exhibited resistant levels to all antibiotics evaluated except ciprofloxacin. Interestingly this species had the highest resistance rates to cephalosporin and gentamicin. Regarding tetracycline, ampicillin, and trimethoprim-sulfamethoxazole, these trends are similar to previous reports (34). We found the highest percentage of resistance to nalidixic acid in *S. dysenteriae* amongst all the evaluated species. Results herein were similar to India and Bangladesh, in which a worrisome 82% resistance in this species was reported (41,42). In Egypt, Wasfy and colleagues found resistance levels above fifty percent to chloramphenicol, tetracycline and ampicillin (43,44). However, compared to other studies (31,45), isolates herein had lower levels of resistance to other antibiotics evaluated and indeed were completely sensitive to amoxicillin/clavulanic acid, ceftazidime, cefotaxime and ciprofloxacin.

An upsurge in fluoroquinolone resistance among *S. flexneri* and *S. sonnei* in high – income countries has been reported, although nalidixic acid resistance was common among *S. sonnei* isolates, the trend of fluoroquinolone resistance is slowly increasing (46,47). The oral fluoroquinolone ciprofloxacin can achieve high concentrations in the serum and stool and have activity against *Shigella* isolates. Yet ciprofloxacin prescription is avoided in children (48).

In Colombia, quinolones are not generally recommended for use in shigellosis and this may contribute to low levels of observed resistance. The macrolide azithromycin (AZM) is widely used in children and is recommended as an alternative therapy for the treatment of shigellosis in adults infected with multidrug-resistant isolates (49), however in vitro azithromycin susceptibility testing is not routinely performed by *Shigella* surveillance system in Colombia.

In the laboratory-based surveillance of *Shigella* spp. we determined that children under five years, were affected by all *Shigella* species. These findings should be considered to guide funders and public health officials to make evidence-based decisions for attention to the development of effective protection and prevention measures, like attainable vaccines. Characteristically in Colombia, an increased frequency of multidrug resistant S*. flexneri* was observed. In accord with international epidemiological trends, as countries increase their level of development and sanitation, *S. sonnei* is more likely to become more prevalent on a global scale. Combating the spread of global antibiotic resistance will be aided by focusing on surveillance of *S. sonnei*, while more localized efforts are needed to combat resistance in *S. flexneri*.

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Conflicts of interest

The authors declare no conflicts.

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Table 1. Age and sample distribution

	Age in years					
Sample Type	**<1**	**2- 5**	**6 - 14**	**>15**	**ND**	**Total**
Stool	435	2012	1469	834	313	5063
NC	6	24	15	18	18	81
Blood	8	10	4	36	6	64
Urine	2	11	4	13		30
Other	1	2	6	3	1	13
Total	**452**	**2059**	**1498**	**904**	**338**	**5251**

NC: information not collected

Table 2. Antimicrobial resistance isolates distribution in different *Shigella* species

Shigella species	**Antibiotics**									
	AMC	**TE**	**C**	**NA**	**CAZ**	**CTX**	**AMP**	**SXT**	**CIP**	**GM**
boydii	12.3	83.5	10.7	3.13	2.47	0.97	76.7	51.5	0	1.06
dysenteriae	0	41.7	7.14	11.1	0	0	28.6	42.9	0	0
flexneri	60.7	94.3	80.8	2.34	0.22	0.37	83	67.8	0.41	0.27
Shigella spp	12.5	63.8	27.7	9.76	0	0	61.4	65.9	2.17	0
sonnei	32.8	83.9	29.4	7.15	0.4	0.43	52	89.6	0.49	0.37
Total	**43.6**	**88.1**	**50.8**	**5.13**	**0.36**	**0.41**	**65.5**	**79.3**	**0.46**	**0.34**

AMC: Amoxicillin/clavulanic acid; TE: tetracycline; C: chloramphenicol; NA: Nalidixic acid; CAZ: Ceftazidime; CTX: cefotaxime; AMP: ampicilina; SXT: trimethoprim sulfametoxasol; CIP: Ciprofloxacin, GM: gentamicin.

Table 3. Age range and *Shigella* species distribution

	Shigella species					
Age in years	***boydii***	***dysenteriae***	***flexneri***	***Shigella spp***	***sonnei***	**Total**
≤ 1	6,8	0,0	11,2	9,9	6,7	8,6
2 to 5	30,1	28,6	37,2	34,1	41,3	39,3
6 to 14	34,0	7,1	23,5	15,4	32,6	28,5
≥ 15	22,3	57,1	22,4	30,8	12,5	17,2
NC	6,8	7,1	5,7	9,9	7,0	6,5

NC: information not collected

Table 4. Antimicrobial resistance isolates distribution per year in different *Shigella* species

Shigella species	n	year/antibiotic/resistance percentage																				
		97	98	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18
Tetracycline																							
sonnei	2714	100	95.0	85.7	95.2	94.9	96.3	97.4	90.8	92.3	92.4	92.0	93.7	82.8	85.6	81.6	86.3	70.0	70.2	70.3	64.2	62.5	41.2
flexneri	2137	96.2	96.2	97.9	95.5	97.6	98.1	98.3	95.8	96.9	97.7	95.7	95.1	90.5	99.1	91.4	91.7	91.2	95.0	90.6	87.0	95.9	83.3
Others	162	100.0	100.0	60.0	100.0	77.8	100.0	90.0	94.1	71.4	100.0	100.0	0.0	33.3	66.7	66.7	54.5	75.0	57.1	50.0	66.7	0.0	37.5
Nalidixic acid																							
sonnei	2574	0.0	0.0	0.0	0.0	0.0	0.6	1.3	1.1	2.4	4.2	1.7	2.1	4.0	3.0	7.0	12.8	18.6	9.4	14.1	6.3	38.1	25.0
flexneri	1882	0.0	0.0	0.0	1.9	1.2	0.9	0.0	2.4	3.1	1.1	2.9	0.0	4.8	3.4	1.3	0.7	2.2	3.4	0.0	20.0	6.0	5.3
Others	146	0.0	0.0	0.0	0.0	0.0	0.0	0.0	5.9	0.0	0.0	0.0	0.0	0.0	66.7	33.3	9.1	0.0	16.7	10.0	0.0	0.0	0.0
Amoxicillin/clavulanic acid																							
sonnei	2391	0.0	0.0	0.0	0.0	0.0	3.2	5.9	3.4	5.4	24.6	17.0	38.0	33.3	59.9	40.4	57.3	43.2	64.7	43.8	49.0	65.9	11.6
flexneri	1755	0.0	0.0	0.0	0.0	0.0	23.4	37.8	22.0	40.9	71.3	66.7	80.0	72.4	76.1	74.3	75.7	78.8	81.7	76.0	62.5	85.5	35.2
Others	130	0.0	0.0	0.0	0.0	0.0	0.0	11.1	0.0	9.5	27.3	28.6	0.0	0.0	33.3	0.0	9.1	0.0	28.6	22.2	0.0	50.0	0.0
Ampicillin																							
sonnei	2827	38.9	35.0	23.8	36.1	35.9	30.7	35.9	37.7	36.9	48.7	41.2	51.8	43.4	71.5	60.1	74.2	64.5	72.7	71.4	64.2	54.7	25.9
flexneri	2166	82.8	88.7	81.3	72.7	62.7	76.4	78.2	86.9	78.3	90.8	80.0	87.7	86.7	87.3	80.4	87.5	86.0	88.5	88.0	83.3	92.8	81.6
Others	160	50.0	100.0	40.0	66.7	66.7	87.5	90.0	88.2	66.7	100.0	100.0	0.0	50.0	66.7	50.0	54.5	25.0	40.0	0.0	33.3	0.0	33.3
Trimethoprim-sulfamethoxazole																							
sonnei	2825	94.4	85.0	76.2	91.6	89.7	92.0	94.8	87.4	94.6	96.6	89.3	95.0	91.9	89.7	75.9	79.0	92.2	94.2	96.9	94.3	87.3	86.6
flexneri	2166	82.8	73.6	85.4	83.0	83.1	80.2	84.9	78.6	78.3	79.3	71.4	69.1	66.7	56.8	58.8	50.0	57.4	56.4	88.0	51.9	48.5	48.8
Others	160	50.0	0.0	40.0	66.7	66.7	25.0	50.0	47.1	66.7	81.8	71.4	0.0	16.7	0.0	50.0	45.5	75.0	40.0	62.5	66.7	100.0	44.4
Chloramphenicol																							
sonnei	2733	11.1	5.0	0.0	1.2	2.6	0.6	9.2	13.7	11.9	16.8	11.4	30.3	20.2	42.5	37.7	60.3	51.4	59.9	54.3	53.8	50.0	21.6
flexneri	2149	69.0	88.7	75.0	64.8	83.1	74.5	84.0	75.6	78.1	87.4	85.5	87.7	85.7	86.3	83.6	85.4	83.1	85.0	75.0	75.9	74.2	76.6
Others	164	50.0	0.0	20.0	0.0	11.1	0.0	20.0	5.9	14.3	18.2	14.3	0.0	0.0	0.0	16.7	9.1	25.0	57.1	40.0	33.3	0.0	11.1

Table 5. Antimicrobial resistance profiles distribution in different *Shigella* species

Resistance profiles	*Shigella species*					
	flexneri **n (%)**	***sonnei*** **n (%)**	***boydii*** **n (%)**	***dysenteriae*** **n (%)**	***Shigella spp*** **n (%)**	**n isolates**
TE-C-AMC-AMP-SXT	555 (55.4)	442 (44.2)	3 (0.3)	0	1 (0.1)	1001
TE-SXT	125 (13)	825 (86)	4 (0.4)	1 (0.1)	4 (0.4)	959
TE-AMP-SXT	90 (16.9)	402 (75.6)	33 (6.2)	2 (0.4)	5 (0.9)	532
TE-C-AMP-SXT	410 (77.5)	109 (20.6)	3 (0.6)	1 (0.2)	6 (1.1)	529
TE-C-AMC-AMP	374 (83.5)	73 (16.3)	0	0	1 (0.2)	448
SXT	16 (5.3)	277 (92)	3 (1)	0	5 (1.7)	301
AMP-SXT	27 (17.5)	120 (77.9)	2 (1.3)	1 (0.6)	4 (2.6)	154
TE-C-AMP	141 (91.6)	8 (5.2)	4 (2.6)	0	1 (0.6)	154
TE-C-SXT	128 (87.7)	17 (11.6)	0	0	1 (0.7)	146
TE-AMC-AMP-SXT	30 (21.1)	111 (78.2)	1 (0.7)	0	0	142
Other profiles (n=78)	245 (36.2)	377 (55.7)	40 (5.9)	1 (0.8)	14 (2.1)	677
Total	**2141**	**2761**	**93**	**6**	**42**	**5043**

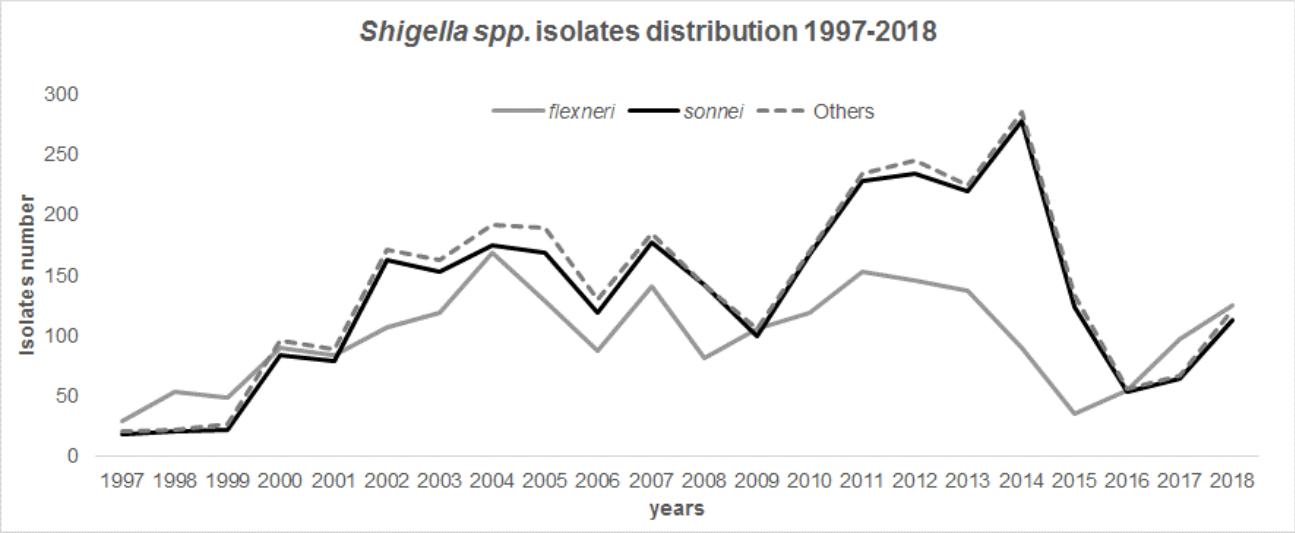

Figure 1. Distribution of *Shigella* spp. isolates in Colombia from 1997 to 2018. *Sh. flexneri* (grey), *Sh. sonnei* (black) and others species (dashed line). This information was based on the annual *Shigella* surveillance system in Colombia.

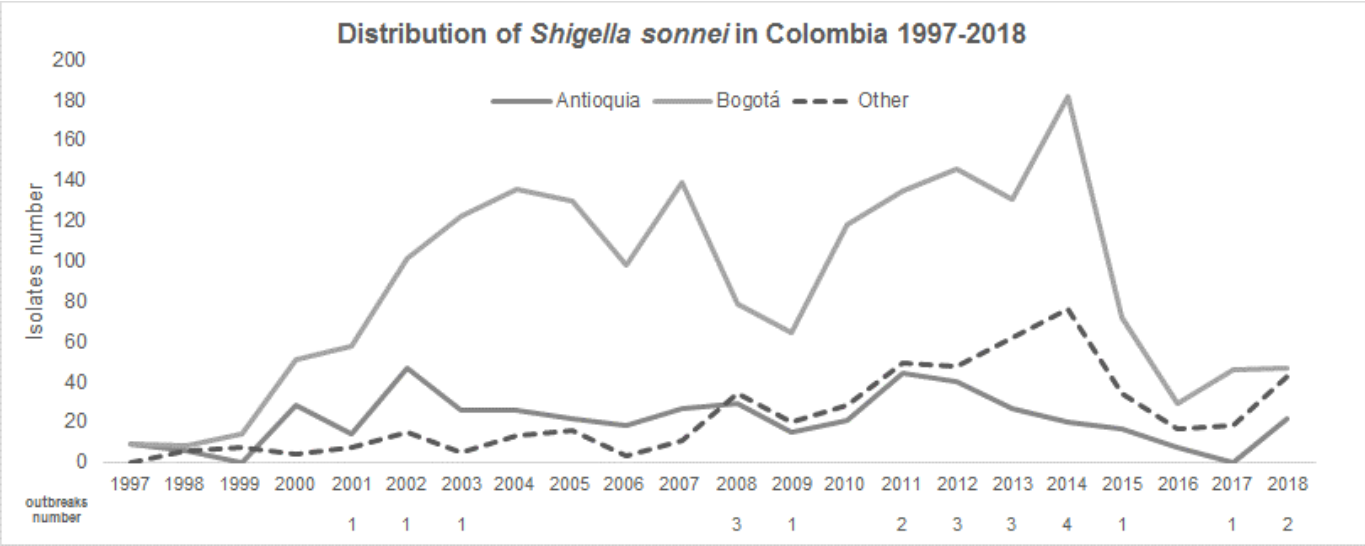

Figure 2. Comparison of number and distribution of *Shigella sonnei* isolates in Antioquia (black), Bogotá (grey) and others regions (dashed line) in Colombia from 1997 to 2018.

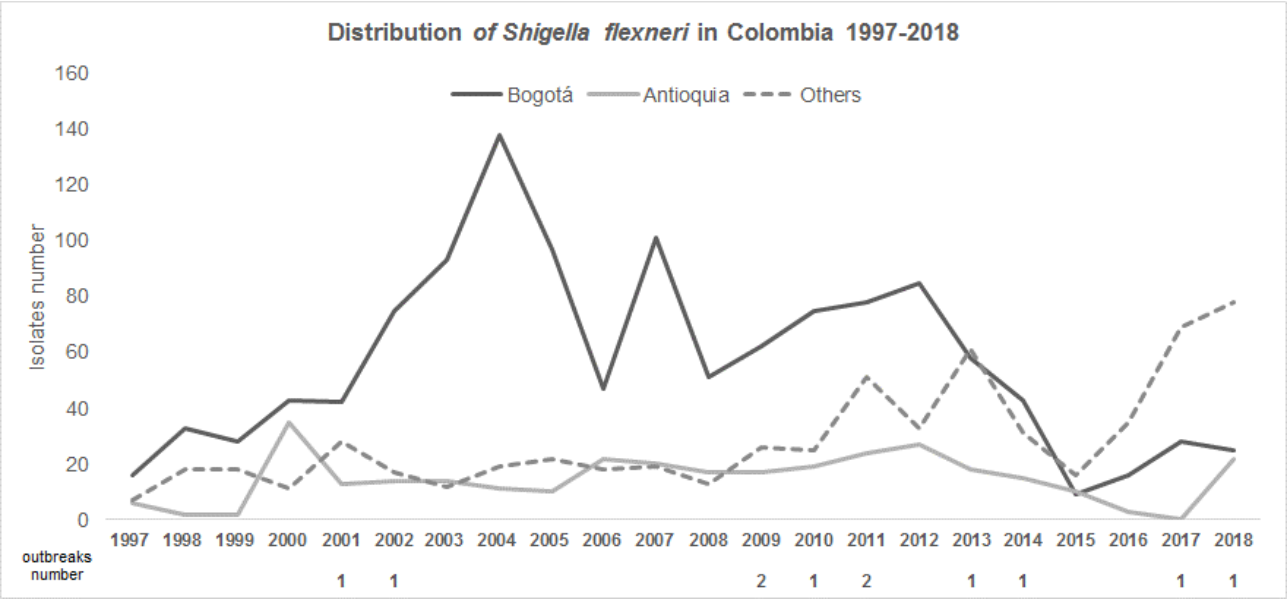

Figure 3. Comparison of number and distribution of *Shigella flexneri* isolates in Antioquia (grey), Bogotá (black) and others regions (dashed line) in Colombia from 1997 to 2018.

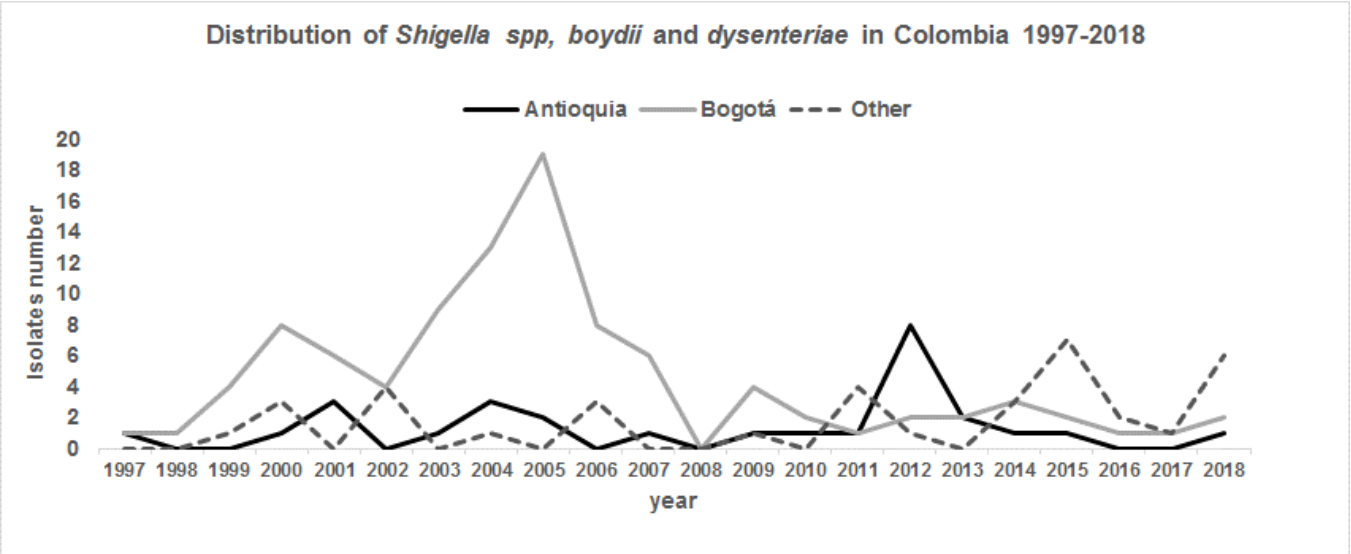

Figure 4. Comparison of number and distribution of *Shigella* species different to *sonnei* and *flexneri*, in Antioquia (black), Bogotá (grey) and others regions (dashed line) in Colombia from 1997 to 2018.