Incidence, clinical presentation, and antimicrobial resistance trends in *Salmonella* and *Shigella* infections from children in Yucatan, Mexico

Mussareet B. Zaidi1,2*, Teresa Estrada-García1, Freddy D. Campos1, Rodolfo Chim1, Francisco Arjona1, Magda Leon1, Alba Michell1 and Damien Chaussabel4

1 Microbiology Research Laboratory, Hospital General O’Horan, Mérida, Yucatan, Mexico
2 Infectious Diseases Research Unit, Hospital Regional de Alta Especialidad de la Península de Yucatan, Mérida, Yucatan, Mexico
3 Department of Molecular Biomedicine, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Mexico City, Mexico
4 Benaroya Research Institute, Seattle, WA, USA

*Correspondence: Mussareet B. Zaidi, Departamento de Investigación, Hospital General O’Horan, Av. Itzaes x Jacinto Canek, Merida, Yucatan, C.P. 97000, Mexico. E-mail: mizaidi@prodigy.net.mx

**Results:** Among 2344 children with acute gastroenteritis, salmonellosis decreased from 17.7% in 2005 to 11.2% in 2011 (p < 0.001). In contrast, shigellosis increased from 8.3% in 2010 to 12.1% in 2011. Compared to children with *Salmonella*, those with *Shigella* had significantly more bloody stools (59 vs 36%, p < 0.001), dehydration (27 vs 15%, p = 0.031), and seizures (11 vs 3%, p = 0.03). In *Salmonella* (n = 365), there was a significant decrease in resistance to ampicillin (43 to 16%, p < 0.001), trimethoprim–sulfamethoxazole (44 to 26%, p = 0.014), and extended-spectrum cephalosporins (27 to 10%, p = 0.009). Reduced susceptibility to ciprofloxacin in *Salmonella* rose from 30 to 41% (p < 0.001). All ceftriaxone-resistant isolates harbored the *bla*CMY-2 gene. *qnr* genes were found in 42 (36%) of the 117 *Salmonella* isolates with a ciprofloxacin MIC ≥ 0.125 μg/ml. Four were *qnr*A1 and 38 were *qnr*B19. Resistance to ampicillin (45%) and trimethoprim–sulfamethoxazole (58%) was common in *Shigella* (n = 218), but isolates remained fully susceptible to ceftriaxone and ciprofloxacin.

**Conclusion:** Illness from *Salmonella* has decreased while severe *Shigella* infections have increased among children with gastroenteritis in the Yucatan Peninsula. While *Shigella* resistance to clinically important antibiotics remained unchanged, resistance to most of these, except ciprofloxacin, declined in *Salmonella* *bla*CMY-2 and *qnr* genes are common in *Salmonella* isolates.

**Keywords:** *Salmonella*, *Shigella*, incidence, antimicrobial resistance, beta-lactamase genes, *bla*CMY-2, *qnr* genes, Mexico

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Background: *Salmonella* and *Shigella* cause significant morbidity and mortality among children worldwide. Increased antimicrobial resistance results in greater burden of disease.

**Materials and Methods:** From 2005 to 2011, *Salmonella* and *Shigella* isolates collected from ill children at a major hospital in Yucatan, Mexico, were subjected to serotyping and antimicrobial susceptibility testing by disk diffusion and agar dilution. The identification of *bla*CTX, *bla*CMY, *bla*SHV, and *bla*TEM, and *qnr* resistance genes was conducted by PCR and sequencing.

**INTRODUCTION**

*Salmonella* and *Shigella* are associated with a high burden of illness among children in the developing world (Niyogi, 2005; Wese-Colburn and Bobal, 2009; Sokoloff et al., 2013). In Mexico, the disease patterns of these pathogens have undergone significant changes in the last decades. During the early 1970s, *Shigella dysenteriae* type 1 and *Salmonella* Typhi caused severe outbreaks among the local population. The epidemic strains of *S. Typhi* and *S. dysenteriae* were both multidrug resistant (MDR) to chloramphenicol, tetracycline, streptomycin, and sulfonamides, harbored on different plasmids (Datta and Olarte, 1974). Subsequently, *S. dysenteriae* infections decreased, while *Shigella flexneri* became the predominant species isolated from endemic infections. *S. dysenteriae*, nonetheless, was still prevalent among visitors to the Yucatan Peninsula during the late 1980s (Centers for Disease Control [CDC], 1988). Typhoid fever also sharply declined, while non-typhoidal *Salmonella*, extremely prevalent along the food chain, was identified as one of the main causes of gastroenteritis in hospitalized children. *Salmonella* Typhimurium, commonly carrying resistance to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline, was the most common serotype encountered in Yucatan (Zaidi et al., 2006). Extended-spectrum cephalosporin (ESC)-resistant S. Typhimurium isolates first emerged in 2002, and rapidly spread throughout the state causing severe diarrhoea and fatal systemic infections in infants (Zaidi et al., 2007).

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1 Microbiology Research Laboratory, Hospital General O’Horan, Mérida, Yucatan, Mexico
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4 Benaroya Research Institute, Seattle, WA, USA

*Correspondence: Mussareet B. Zaidi, Departamento de Investigación, Hospital General O’Horan, Av. Itzaes x Jacinto Canek, Merida, Yucatan, C.P. 97000, Mexico. E-mail: mizaidi@prodigy.net.mx

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**Conclusion:** Illness from *Salmonella* has decreased while severe *Shigella* infections have increased among children with gastroenteritis in the Yucatan Peninsula. While *Shigella* resistance to clinically important antibiotics remained unchanged, resistance to most of these, except ciprofloxacin, declined in *Salmonella* *bla*CMY-2 and *qnr* genes are common in *Salmonella* isolates.

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In the past 25 years, the combination of the widespread use of oral rehydration solutions, rising antimicrobial resistance, and regional socioeconomic changes has modified the epidemiology and the impact of these enteric pathogens (von Seidlein et al., 2006; Parry and Thrall, 2008). There is a clear need to update relevant epidemiologic data (Sansometti, 2006) as there are few studies from Latin America. Monitoring for ESC and fluoroquinolone resistance is particularly important because these compounds are among the few therapeutic options available for severe Salmonella and Shigella infections. In this study, the main objectives were (1) to analyze trends in incidence and antimicrobial resistance of Salmonella and Shigella infections in children with gastroenteritis and/or systemic infections who sought medical attention at a major hospital in the Yucatan Peninsula, (2) to compare the clinical presentations of the ill children, and (3) determine the prevalence of extended-spectrum beta-lactamases, CMY-2 and Qnr in Salmonella and Shigella isolates.

**MATERIALS AND METHODS**

The Hospital General O’Horan is a tertiary-care public hospital that receives patients from throughout the state of Yucatan and neighboring states in southeast Mexico. The Pediatrics Emergency Department has an active surveillance program for diarrheal pathogens, current since 2000, which includes children with mild to severe gastroenteritis as well as those with systemic infections. Stool cultures are systematically collected from children with diarrheaea. Blood cultures are also routinely collected from children who appear septic or develop hematological, neurological, or other extraintestinal complications.

**CLINICAL AND EPIDEMIOLOGICAL DATA**

A trained nurse administered standardized questionnaires to collect demographic and clinical information on the children’s diarrheal episodes.

**MICROBIOLOGY**

Stool samples were collected in sterile containers containing Cary-Blair media. Samples were inoculated onto XLD, Hektoen Enteric, and brilliant green agars as well as tetrathionate and Rappaport broths and incubated at 35°C for 18–24 h. Broths were subcultured to XLD and brilliant green agar plates and incubated for another 18–24 h. Identification of Salmonella and Shigella isolates were performed with conventional biochemical tests. Salmonella isolates were serotyped by the Kauffmann–White scheme using commercial antisera (Recton Dickinson, Franklin Lakes, NJ, USA). All Shigella isolates were serogrouped; serotyping was performed on S. dysenteriae isolates only. Antimicrobial susceptibility testing was routinely performed for ampicillin, chloramphenicol, gentamicin, nalidixic acid, trimethoprim–sulfamethoxazole, ciprofloxacin, ceftriaxone, ceftazidime, and tetracycline by disk diffusion (CLSI, 2012a). Minimum inhibitory concentrations (MICs) for ciprofloxacin, azithromycin, ceftriaxone, nalidixic acid, and furazolidone were determined by agar dilution (CLSI, 2012b). Susceptibility and resistance breakpoints used for azithromycin were 16 and 32 μg/ml, respectively (Sjöland-Karlsson et al., 2011) and 2 μg/ml and 8 μg/ml for furazolidone (Rampling et al., 1990). Ceftriaxone and/or cefotaxime non-susceptible isolates were tested on a secondary panel of beta-lactam antimicrobials that included cefepime, ceftaxime, cefotaxim, imipenem, meropenem, amoxicillin–clavulanic acid, and piperacillin–tazobactam. According to resistance phenotypes, these isolates were also screened for AmpC beta-lactamase production with a combination disk method using cefotaxim (30 μg) and cefoxitin with boronic acid (30 μg + 300 μg; Jacoby et al., 2006).

**GENETIC CHARACTERIZATION OF bla and qnr GENES**

All ceftriaxone-resistant isolates (MIC ≥ 4) were tested for the presence of beta-lactamase genes. A multiplex PCR was used for the detection of genes encoding the CTX, SHV, TEM, and OXA enzymes according to previously published methods (Britha et al., 2002; Edelstein et al., 2003). Detection of the bla<sub>TEM</sub> gene was performed using a previously described assay (Zhao et al., 2001). Salmonella isolates with ciprofloxacin MICs ≥ 0.125 μg/ml were tested for qnrA, qnrB, and qnrS genes following published methods (Robicsek et al., 2006).

Specific group primers used for the study are listed in **Table 1**. Control strains were kindly provided by Patrick McDermott (U.S. Food and Drug Administration) and Jesus Silva-Sanchez (Instituto Nacional de Salud Publica, Mexico).

**Data Analysis**

Amplified products were separated by gel electrophoresis on 2% agarose and stained with ethidium bromide. Sequencing was performed using both forward and reverse PCR primers on a ABI Prism 3130 XL Genetic Analyzer (Applied Biosystems). Sequences were analyzed using the National Center for Biotechnology Information’s BLAST network service (http://www.ncbi.nlm.nih.gov/BLAST/). Sequences were compared to the original gene sequences reported in the GenBank database of accession numbers K01749, X91846, AY070225, EU432277, FJ460235 (Sutcliffe, 1979; Bauernfeind et al., 1996; Jacoby et al., 2006; Weiner et al., 2009). Sequences for qnrA and qnrB19 were submitted under accession numbers KF517418 and KP917417, respectively.

| Table 1 | Description |
|---------|-------------|
|          |             |

**ETHICS**

The data was obtained from two different studies that were approved by the Hospital General O’Horan Research and Ethics Committee; written informed consent was obtained from the children’s guardians to collect stool samples and use the data for scientific purposes. For this analysis, clinical and microbiological data were entered on new databases; a unique numerical code was assigned to each patient and personal identifiers were removed to ensure anonymity.
RESULTS

EPIDEMIOLOGY

From January 2005 to December 2011, 2344 children under 10 years of age who were admitted to the hospital for acute gastroenteritis were included in the study. One child with fever and malaise without gastroenteritis, whose blood culture was positive for S. Typhi, was also included. Children came from 94 localities within the state of Yucatan and from 35 other cities or towns in the neighboring states. Eight hundred ninety-one (38%) were under 1 year of age, 1176 (54%) were between 1 and 4 years of age, and 186 (8%) were between 5 and 9 years of age. Salmonella gastroenteritis decreased from 17.7% of all cases in 2005 to 11.2% in 2011, but there was a precipitous rise from 8.3% in 2010 to 12.1% in 2011, although the difference was not significant (p < 0.001). Shigella infections increased during this period, with a precipitous rise from 8.3% in 2010 to 12.1% in 2011, but the difference was not statistically significant (Figure 1A). A total of 365 Salmonella and 218 Shigella isolates were collected. The five most commonly isolated Salmonella serovars from ill children remained constant; S. Typhimurium was consistently the top serovar (19–21%) followed by S. Agona (9%), S. Muenchen (6–7%), S. Muenster (6–11%), and S. Enteritidis (5–7%). The S. Typhi isolate was susceptible to all tested antibiotics. Similarly, there was no change in the distribution of Shigella species; S. flexneri was predominant (68–76%), followed by S. sonnei (16–17%), S. boydii (5–12%), and S. dysenteriae (2%). S. dysenteriae strains belonged to type 3 (two isolates) and type 2 (two isolates).

CLINICAL PRESENTATION

Prospectively obtained clinical data was available for 112 patients with Shigella and 118 patients with Salmonella. Compared to children with Salmonella, those with Shigella had more fever ≥38.5°C (36 vs 37%, p = 0.001, OR = 2.7, 95% CI = 1.4–5.3), bloody stools (59 vs 36%, p < 0.001, OR = 2.6, 95% CI = 1.5–4.6), dehydration (27 vs 15%, p = 0.031, OR = 2.0, 95% CI = 1.0–4.1), and almost four times as many seizures (11 vs 3%, p = 0.03, OR = 3.4, 95% CI = 0.98–13.0, Figure 1B).

ANTIMICROBIAL RESISTANCE

Ampicillin resistance in Salmonella decreased from 63% in 2005 to 16% in 2011 (p < 0.001), while trimethoprim–sulfamethoxazole resistance decreased from 44% to 26% (p = 0.014). Likewise, resistance to ceftriaxone and other ESC, most commonly observed in S. Typhimurium, decreased from 27% to 10% (p = 0.009). Trends for the different time periods throughout the study are shown on Table 2 and Figures 2A–C. MIC50 and MIC90 values for the whole study period were, respectively, 0.83 and 0.5 μg/ml for ciprofloxacin, 0.125 and 64 μg/ml for ceftriaxone, and 8 and 16 μg/ml for azithromycin.

Reduced susceptibility to ciprofloxacin (MIC ≥0.12 and ≤1 μg/ml) was found in 113 Salmonella isolates evenly distributed throughout the study period. 77 of these (68%) were resistant to nalidixic acid, and was most commonly seen in S. Typhimurium (34%), S. Enteritidis (16%), S. Albany (9%), S. Muenster (6%), S. Muenchen (5%), and S. Reading (5%).

The percentage of isolates with reduced susceptibility to ciprofloxacin rose from 30% in 2005 to 41% in 2011 (p < 0.001). The number of isolates with MIC ≥1 μg/ml, however, peaked during 2007–2009 (14%) and then decreased in 2010–2011 (7%), although the difference was not significant (Figure 2A). Isolates with ciprofloxacin MIC = 2 μg/ml were first detected in 2007 in S. Enteritidis strain (2008 and 2011), and one S. Enteritidis strain (2009).

Sixty-one ceftriaxone and ceftazidime resistant isolates were uniformly resistant to cefotaxime, cefotaxin, aztreonam,

| PCR name | Primer name | Sequence (5’–3’) | Length (bp) | Amplicon size (pb) |
|----------|-------------|------------------|-------------|-------------------|
| Multiplex TEM, SHV, CTX, OXA | tem-F | TCTTGGAAAGCAGAAGG 20 | 1150 | 1150 |
| | tem-R | ACGTCAGTCAGAAGG 20 | 1150 | 1150 |
| | shv-F | GATCCAAAGGATATGTTG 19 | 702 | 702 |
| | shv-R | TTAGGGTGCCATGCTCCTG 19 | 702 | 702 |
| | ctx-F | TTTCTGATGTCAGTCACAA 23 | 544 | 544 |
| | ctx-R | CGATATCGTTGGTGCCAATA 22 | 1000 | 1000 |
| CMY | cmy-F | GACAGCCTCTTTCTCCACA 19 | 1000 | 1000 |
| | cmy-R | TGGAGGAAGGCTACGTA 18 | 1000 | 1000 |
| Multiplex qnrA, qnrB and qnrS | qnrA-F | ATTTCTACGCGGATGTTG 20 | 516 | 516 |
| | qnrA-R | GATCGGAAAGGATAGTCTA 20 | 516 | 516 |
| | qnrB-F | GATCGGAAAGGATAGTCTA 20 | 469 | 469 |
| | qnrB-R | GATCGGAAAGGATAGTCTA 20 | 469 | 469 |
| | qnrS-F | ATCTTTCCCCAACCCTGAA 20 | 417 | 417 |
| | qnrS-R | TAAATTTCGACCATGTTG 20 | 417 | 417 |

Table 1 Specific group primers used for PCR assays for beta-lactamase and qnr genes.
and amoxicillin/clavulanic acid; 52% were resistant to piperacillin/tazobactam. All isolates were susceptible to cefepime, and amoxicillin/clavulanic acid; 52% were resistant to trimethoprim–sulfamethoxazole.

### Table 2 | Antimicrobial susceptibility in Salmonella isolates from ill children in Yucatan, Mexico, 2005–2011. Percentage of resistance*

| Year of isolation | AMP* | CRO* | CAZ* | AZT | CIP | NAL | CHL | FZD | GEN | STX* | TET |
|------------------|------|------|------|-----|-----|-----|-----|-----|-----|------|-----|
| 2005–2006 (n = 147) | 33.3 | 19.7 | 19.7 | 4.8 | 0   | 29.2 | 33.4 | 30.8 | 12.2 | 38.1 | 52.4 |
| 2007–2008 (n = 138) | 25.4 | 18.1 | 18.1 | 3.6 | 2.2 | 37.7 | 31.9 | 28.4 | 9.4 | 34.1 | 45.7 |
| 2010–2011 (n = 80)  | 20.0 | 8.8  | 8.8  | 5.0 | 1.2 | 31.3 | 33.8 | 28.7 | 7.5 | 28.8 | 42.5 |

*Includes resistant and intermediate strains.

### Discussion

Illness from Salmonella has decreased in the Yucatan Peninsula while severe Shigella infections have increased among children with gastroenteritis requiring hospitalization. There is a high frequency of resistance to ampicillin and trimethoprim–sulfamethoxazole in Shigella isolates, but these remain uniformly susceptible to ESC, ciprofloxacin, and azithromycin. While Shigella resistance to clinically important antibiotics over the last 7 years remained basically unchanged, resistance to most of these, with
the exception of ciprofloxacin, declined in Salmonella. Resistance to ESC continues to be prevalent among Salmonella isolates, and is mediated by the blaCTX-M-2 gene. qnr genes are widely distributed among our Salmonella population, but their overall frequency appears to be decreasing in recent years.

The increase in shigellosis in our pediatric population is a major public health concern, as a high proportion of our patients presented bloody diarrhea, high fever, and dehydration. The frequency of seizures (11%), moreover, is much higher than that reported in a recent study in Asia (3%; von Seidlein et al., 2006). This could be explained by the higher proportion of S. flexneri infections at our center and by the fact that our study was confined to children with diarrhea sufficiently severe to seek medical care at a hospital emergency room.

Our Shigella strains were frequently resistant to trimethoprim–sulfamethoxazole and ampicillin, the first line empirical therapy for bloody diarrhea at our public hospitals. Although all strains were susceptible to azithromycin, ESCs, and ciprofloxacin, none of these antimicrobials are provided in oral form by our government healthcare system, which services 70% of the population. Consequently, patients with therapeutic failure ultimately required hospitalization with parental ceftriaxone or out-of-pocket purchase of oral azithromycin or cefixime, escalating costs for both the public health sector and families.

Although the increase in Shigella gastroenteritis was not statistically significant, we believe, nonetheless, that our findings are epidemiologically and clinically significant, as the prevalence of Shigella gastroenteritis had never, during the last decade, reached 12%. It has remained at this level during 2012 and 2013—a worrisome trend that warrants close scrutiny by public health authorities.

Our results concur with those of other investigators who challenge the widely accepted notion of a worldwide decline in shigellosis. Recent studies using active or passive surveillance have detected high incidence rates of shigellosis in Peru, Thailand, and China (Chompook et al., 2005; Kosek et al., 2008; Xia et al., 2011). Unlike Southeast Asia (von Seidlein et al., 2006; Vith et al., 2009), where the dominant species has shifted from S. flexneri to S. sonnei, the former continues to be the major culprit of severe shigellosis in Yucatan, as is the case in Peru and China.

The troubling recent rise in shigellosis could well be linked to the current economy. Between 2008 and 2010, the number of people below the poverty line in Yucatan increased by 35,000 to the current economy. Between 2008 and 2010, the number of people below the poverty line in Yucatan increased by 35,000.

Salmonella isolates were distributed into two distinct populations, one which was susceptible and the other resistant to ceftriaxone. CLSI breakpoints for susceptibility and resistance in isolates from stools are 1 and 4 μg/ml, respectively. Breakpoints for susceptibility and resistance in isolates from systemic infections are 0.06 and 1 μg/ml, respectively.

Salmonella isolates from ill children at a state referral hospital in Yucatan, Mexico, 2005–2011. Thin black lines indicate breakpoints for resistance. Number of isolates for each period was as follows: 2005–2006, n = 147; 2007–2008, n = 136, and 2009–2011, n = 85. (A) Ceftriaxone MICs. Reduced susceptibility to ceftriaxone in Salmonella rose from 28% in 2005–2006 to 33% in 2009–2010. Non-susceptibility (MIC ⩾ 2) first emerged in 2007 in a S. Anatum isolate and later appeared in S. Typhimurium multidrug-resistant, cefalosporin-resistant isolates. Black line is resistance breakpoint for isolates from stools; red line is breakpoint for systemic infections. CLSI breakpoints for susceptibility and resistance in isolates from stools are 1 and 4 μg/ml, respectively. Breakpoints for susceptibility and resistance in isolates from systemic infections are 0.06 and 1 μg/ml, respectively. (B) Ceftriaxone MICs. Resistance to ceftriaxone and other extended-spectrum cephalosporins significantly decreased from 19.7% during 2005–2006 to 8.8% in 2010–2011. Salmonella isolates were distributed into two distinct populations, one which was susceptible and the other resistant to ceftriaxone. CLSI breakpoints for susceptibility and resistance are 1 and 4 μg/ml, respectively. (C) Azithromycin MICs. No significant changes in azithromycin MICs were noted. Suggested breakpoints for susceptibility and resistance are 16 and 64 μg/ml, respectively.

FIGURE 2 | Minimum inhibitory concentrations to ciprofloxacin, ceftriaxone, and azithromycin in Salmonella isolates from ill children at a state referral hospital in Yucatan, Mexico, 2005–2011. Thin black lines indicate breakpoints for resistance. Number of isolates for each period was as follows: 2005–2006, n = 147; 2007–2008, n = 136, and 2009–2011, n = 85. (A) Ceftriaxone MICs. Reduced susceptibility to ceftriaxone in Salmonella rose from 28% in 2005–2006 to 33% in 2009–2010. Non-susceptibility (MIC ⩾ 2) first emerged in 2007 in a S. Anatum isolate and later appeared in S. Typhimurium multidrug-resistant, cefalosporin-resistant isolates. Black line is resistance breakpoint for isolates from stools; red line is breakpoint for systemic infections. CLSI breakpoints for susceptibility and resistance in isolates from stools are 1 and 4 μg/ml, respectively. (B) Ceftriaxone MICs. Resistance to ceftriaxone and other extended-spectrum cephalosporins significantly decreased from 19.7% during 2005–2006 to 8.8% in 2010–2011. Salmonella isolates were distributed into two distinct populations, one which was susceptible and the other resistant to ceftriaxone. CLSI breakpoints for susceptibility and resistance are 1 and 4 μg/ml, respectively. (C) Azithromycin MICs. No significant changes in azithromycin MICs were noted. Suggested breakpoints for susceptibility and resistance are 16 and 64 μg/ml, respectively.
Table 3 | Antimicrobial susceptibility in Shigella isolates from ill children in Yucatan, Mexico, 2005–2011. Percentage of resistance*.

| Year of isolation | AMP | CRO | AZT | CIP | NAL | CHL | FZD | STX | TET |
|-------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 2005–2006 (n = 79) | 39.8 | 0   | 0   | 0   | 0   | 16.4 | 57.5 | 57.5 | 83.6 |
| 2007–2008 (n = 79) | 44.3 | 0   | 0   | 0   | 1.3 | 24.1 | 26.4 | 59.5 | 50.4 |
| 2010–2011 (n = 66) | 34.8 | 0   | 0   | 0   | 12.1 | 25.8 | 59.0 | 59.0 | 59.9 |

*AMP: ampicillin; AZT: azithromycin; CIP: ciprofloxacin; CRO: ceftriaxone; FZD: fosfomycin; NAL: nalidixic acid; STX: streptomycin; TET: tetracycline.

†††Difference from 2005 to 2011: \( p < 0.001 \).

population of USA and Mexico strongly contrasts with reports from Europe and Asia. Recent studies from Spain (de Toro et al., 2011; Perez-Moreno et al., 2013) found an assortment of bls genes in human Salmonella isolates, including \( \text{bla}_{\text{TEM}} - 1 \), \( \text{bla}_{\text{MPC}} \), \( \text{bla}_{\text{CTX-M}} \), \( \text{bla}_{\text{SHV}} \), \( \text{bla}_{\text{PER}} \), \( \text{bla}_{\text{OXA-1}} \), and \( \text{bla}_{\text{OXA-23}} \), among which \( \text{bla}_{\text{CTX-M}} \), \( \text{bla}_{\text{TEM}} \), and \( \text{bla}_{\text{SHV}} \) were more frequently found in poultry isolates from the Netherlands (Dierikx et al., 2010). Likewise, \( \text{bla}_{\text{TEM}} \), \( \text{bla}_{\text{SHV}} \), \( \text{bla}_{\text{PER}} \), \( \text{bla}_{\text{OXA-1}} \), and \( \text{bla}_{\text{OXA-23}} \) are common in non-typhoidal salmonellae from humans and food-animals in India, China, and Korea (Menezes et al., 2010; Tamang et al., 2011a; Yu et al., 2011a). Diversification of beta-lactamase genes depends on a myriad of factors which include, among others, selective pressures in the environment as well as enzyme efficiency (Galán et al., 2013). Unraveling the complexity of the evolutionary processes that lead to the development of resistance and transfer of resistance genes may allow us to better explain their different distributions around the world.

Reduced susceptibility to ciprofloxacin and the presence of \( qnr \) genes was frequent in our Salmonella isolates, 32% presented MICs between 0.125 and 2 \( \mu \)g/ml, and 12% harbored a \( qnrA \) or \( qnrB \) gene. These findings are comparable with those of other reports from Latin America in which \( qnrB19 \) was the predominant variant. It has been detected in Salmonella isolates from food in Colombia (Karczmarczyk et al., 2010), and was highly prevalent in commensal enterobacteria isolated from healthy children in Peru and Bolivia (Pallecchi et al., 2009). Notably, it was also found in 32% of screened individuals living in a remote village in the Amazonas (Pallecchi et al., 2011). In contrast, a recent study conducted on Salmonella isolates from humans, retail meat and animals in the USA detected \( qnr \) genes in only 0.3% of human isolates, and none from animal sources (Sjolund-Karlsson et al., 2010). \( qnr \) genes are also reportedly low in China, Korea, and India (on the order of 5–3%), where \( \\text{aac(6’)-Ib-cr} \) is more commonly present (Menezes et al., 2010; Tamang et al., 2011b; Yu et al., 2011b; Chen et al., 2012; Kim et al., 2013). The origin and the mechanisms for widespread dissemination of \( qrnB \) genes is currently unfolding. Recent evidence points to the chromosome of Citrobacter spp. as the likely origin of plasmid-mediated \( qrnB \) (Jacoby et al., 2011). The presence of \( qrnB19 \) genes on small colE-type plasmids (Karczmarczyk et al., 2010; Pallecchi et al., 2010), as well as their insertion on transposons located on larger plasmids (Cattoir et al., 2008; Dionisi et al., 2009) are believed to contribute to their dissemination and persistence, even in the absence of selective pressure. This could explain its ubiquity in commensal fecal flora and horizontal transfer and spread among unrelated species.
Table 4 | Serotype distribution and antimicrobial susceptibility of Salmonella isolates positive for the qnr gene, Yucatan, Mexico, 2005–2011.

| Qnr variant | ID number | Serotype | Year of isolation | Resistance phenotypes to non-quinolone antibiotics | Ciprofloxacin MIC (μg/ml) | Nalidixic acid MIC (μg/ml) |
|-------------|-----------|----------|-----------------|---------------------------------------------------|--------------------------|---------------------------|
| A1          | yuhs03-35 | Enteritidis | 2010 | Nal, Fzd | 1 | 128 |
|             | yuhs05-13 | Havana | 2005 | Amp, Sxt, Tet | 0.5 | 32 |
|             | yuhs05-87 | Havana | 2005 | Amp, Sxt, Tet, Nal | 0.5 | 16 |
|             | yuhs05-106 | Havana | 2005 | Amp, Sxt, Tet, CRO | 0.5 | 16 |
| B19         | yuhs07-5 | Adelaide | 2007 | Nal, Fzd | 0.12 | 32 |
|             | yuhs07-44 | Adelaide | 2007 | Nal | 0.5 | 64 |
|             | yuhs07-71 | Adelaide | 2007 | Nal | 1 | 64 |
|             | yuhs08-31 | Adelaide | 2008 | Nal | 1 | 64 |
|             | yuhs07-40 | Agona | 2007 | Nal | 0.5 | 32 |
|             | yuhs08-34 | Agona | 2008 | Nal | 1 | 64 |
|             | yuhs07-38 | Anatum | 2007 | Amp, Sxt, Tet, Nal, Cro | 1 | 64 |
|             | yuhs07-53 | Anatum | 2007 | Amp, Sxt, Tet, Nal | 2 | 128 |
|             | yuhs05-10 | Derby | 2009 | Tet, Nal | 0.5 | 64 |
|             | yuhs07-61 | Enteritidis | 2007 | Nal, Fzd | 1 | 64 |
|             | yuhs06-57 | Enteritidis | 2008 | Nal, Fzd | 1 | 64 |
|             | yuhs08-59 | Enteritidis | 2008 | Nal, Fzd | 1 | 64 |
|             | yuhs09-1 | Enteritidis | 2009 | Nal, Fzd | 2 | 64 |
|             | yuhs09-7 | Enteritidis | 2009 | Nal, Fzd | 1 | 64 |
|             | yuhs11-43 | Enteritidis | 2011 | Nal, Fzd | 1 | 64 |
|             | yuhs07-46 | Havana | 2007 | Sxt, Tet, Chi | 0.5 | 16 |
|             | yuhs07-28 | Muenchen | 2007 | Nal | 1 | 32 |
| B19         | yuhs07-41 | Muenchen | 2007 | Nal | 1 | 32 |
|             | yuhs08-1 | Muenchen | 2008 | Nal | 0.5 | 32 |
|             | yuhs06-10 | Muenchen | 2008 | Sxt, Nal | 0.5 | 32 |
|             | yuhs06-30-2 | Muenchen | 2008 | Nal | 0.5 | 32 |
|             | yuhs11-33 | Muenchen | 2011 | Nal | 0.5 | 32 |
|             | yuhs05-97 | Muenster | 2005 | Amp, Sxt, Tet, Nal, Chi, Fzd | 0.12 | 32 |
|             | yuhs07-74-2 | Muenster | 2007 | Sxt, Tet, Nal, Chi | 1 | 32 |
|             | yuhs07-75 | Muenster | 2007 | Sxt, Tet, Nal, Chi | 1 | 32 |
|             | yuhs10-7 | Muenster | 2010 | Sxt, Tet, Chi, Nal | 1 | 32 |
|             | yuhs11-10 | Muenster | 2011 | Sxt, Tet, Chi, Nal | 1 | 32 |
|             | yuhs06-59 | Reading | 2006 | Tet, Nal | 1 | 32 |
|             | yuhs06-60 | Reading | 2006 | Tet, Nal | 1 | 32 |
|             | yuhs06-65 | Reading | 2006 | Tet, Nal | 1 | 32 |
|             | yuhs07-78 | Typhimurium | 2007 | Amp, Tet, Nal, Cro, Chi | 1 | 32 |
|             | yuhs03-79 | Typhimurium | 2007 | Amp, Tet, Nal, Cro, Chi | 1 | 32 |
|             | yuhs07-9 | Typhimurium | 2007 | Amp, Sxt, Tet, Nal, Cro, Chi | 1 | 32 |
|             | yuhs08-60 | Typhimurium | 2008 | Amp, Sxt, Tet, Nal, Cro, Chi, Fzd, Gen | 2 | 64 |
|             | yuhs10-16 | Typhimurium | 2010 | Amp, Sxt, Tet, Nal, Cro, Chi | 0.25 | 32 |
|             | yuhs11-28 | Typhimurium | 2011 | Amp, Sxt, Tet, Nal, Cro, Chi | 2 | 64 |
|             | yuhs11-47 | Typhimurium | 2011 | Tet, Chi, Nal | 1 | 32 |
|             | yuhs07-20 | Untypable | 2007 | Nal | 1 | 32 |

AMP, ampicillin; CHL, chloramphenicol; CRO, ceftriaxone; FZD, furazolidone; GEN, gentamicin; NAL, nalidixic acid; STX, trimethoprim-sulfamethoxazole; TET, tetracycline.
It is likely that many of our isolates with decreased susceptibility to ciprofloxacin have mutations in the quinolone resistance determining region, which was not assessed in this study. Furthermore, several of our nalidixic acid-susceptible isolates with reduced susceptibility to ciprofloxacin are likely to harbor other resistance genes such as aac(6’)-Ib-cr, qnr, aac(6’)-Ib-cr, and qnr that have been reported by other investigators. A more thorough search for plasmid-mediated genes, nucleotide mutations in the DNA gyrase and topoisomerase IV genes, as well as plasmid characterization will be conducted in the future.

It is noteworthy that the prevalence of 
\( \text{bla}_{CMY-2} \) and qnr genes decreased during the study period, possibly due to a reduced selective pressure in the regional Salmonella population. Although detected in several other serovars, the 
\( \text{bla}_{CMY-2} \) gene is mainly confined to our S. Typhimurium isolates for which the strain is the major reservoir (Zaidi et al., 2007). Our qnr genes, on the other hand, have dispersed more widely in the Yucatan Peninsula, all of the serovars harboring qnr genes are mainly associated with swine except for S. Enteritidis, which is poultry-associated, and S. Muenchen, which is more prevalent in cattle.

The encouraging decline in both the incidence and the antimicrobial resistance of Salmonella is likely due to interventions at the farm level. During recent years, swine producers in Yucatan have decreased the overall usage of antimicrobial compounds by the implementation of stricter biosecurity measures, greater use of vaccines, and stringent hygienic measures. Licensed veterinarians are solely responsible for determining the antibiotic regimens on farms (Jose Cervera, Asociacion Ganadera Local de Porcicultores de Merida, personal communication). Our previous molecular studies have shown that Salmonella strains in humans closely reflect those of locally produced food-animals, particularly swine (Zaidi et al., 2007). Improved farm management practices would thus have a direct impact on zoonotic pathogens such as Salmonella, but would be unlikely to have any effect on strictly human pathogens such as Shigella, an assumption supported by our study results. A comprehensive study in Denmark (World Health Organization [WHO], 2003) showed that an overall reduction in usage of antimicrobial compounds in food-animals was associated with decreased resistance in foodborne pathogens.

The epidemiology of Salmonella and Shigella in the Yucatan Peninsula, as in other regions of the world, is evolving. Typhoid fever and Shigella dysentery type infections, the major scourges four decades ago, are now rare. The new challenges, as evidenced from this study, are MDR, ESC-resistant Salmonella with rising resistance to ciprofloxacin and severe S. flexneri gastroenteritis. Our findings underscore the need to preserve critically important antibiotic classes such as ESC and fluoroquinolones. The agricultural sector in Mexico has taken important steps to reduce the burden of salmonellosis. Comparable action to ameliorate the impact of shigellosis is urgently required. If worsening socioeconomic conditions are a major determinant of this increase, action by health authorities alone will not suffice. Policy makers must take account of the full consequences of social inequality and act accordingly (Stiglitz, 2012).

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