



## Review

# The importance of integrons for development and propagation of resistance in *Shigella*: the case of Latin America



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## ABSTRACT

In Latin America, the disease burden of shigellosis is found to coexist with the rapid and rampant spread of resistance to commonly used antibiotics. The molecular basis of antibiotic resistance lies within genetic elements such as plasmids, transposons, integrons, genomic islands, etc., which are found in the bacterial genome. Integrons are known to acquire, exchange, and express genes within gene cassettes and it is hypothesized that they play a significant role in the transmission of multidrug resistance genes in several Gram-negative bacteria including *Shigella*. A few studies have described antibiotic resistance genes and integrons among multidrug resistant *Shigella* isolates found in Latin America. For example, in Brazil, Bolivia, Chile, Costa Rica and Peru, class 1 and class 2 integrons have been detected among multidrug resistant strains of *Shigella*; this phenomenon is more frequently observed in *S. flexneri* isolates that are resistant to trimethoprim, sulfamethoxazole, streptomycin, ampicillin, chloramphenicol, and tetracycline. The gene cassette *sul2*, which is frequently detected in *Shigella* strains resistant to the sulfonamides, suggests that the sulfonamide-resistant phenotype can be explained by the presence of the *sul2* genes independent of the integron class detected. It is to be noted that *sul3* was negative in all isolates analyzed in these studies.

The high frequency of sulfonamide (as encoded by *sul2*) and trimethoprim resistance is likely to be a result of the recurrent use of trimethoprim sulfamethoxazole as a popular regimen for the treatment of shigellosis. The observed resistance profiles of *Shigella* strains confirm that ampicillin and trimethoprim-sulfamethoxazole are ineffective as therapeutic options. In-depth information regarding antibiotic resistance mechanism in this pathogen is needed in order to develop suitable intervention strategies. There is a pressing need for regional and local antimicrobial resistance profiling of *Shigella* to be included as a part of the public health strategy.

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## Introduction

*Shigellae* are global in terms of their prevalence and distribution<sup>1</sup> and shigellosis, which represents a significant cause of morbidity and mortality in developing countries, is still observed to be present in the industrialized nations.<sup>1–3</sup>

The disease process of shigellosis can be accurately summed up as an invasive infection of the human colon that encompasses a wide spectrum of clinical manifestations ranging from short-lasting watery diarrhea to acute inflammatory bowel disease that can cause fever, tenesmus as well as neurologic symptoms.<sup>4,5</sup>

On the basis of biochemical and serological characteristics, shigellae can be classified into four species: *Shigella dysenteriae*,<sup>6</sup> *S. flexneri*,<sup>7</sup> *S. sonnei*<sup>8</sup> and *S. boydii*.<sup>9</sup> The first three species include multiple serotypes. While *S. dysenteriae* and *S. flexneri* are the most commonly found species in developing countries, *S. sonnei* is responsible for most of the cases reported in industrialized nations.<sup>1,4</sup>

Prevalence of *Shigella* is predominantly observed in regions that have poor hygienic and environmental conditions as is common in developing countries. In industrialized nations, prevalence is found to be associated with groups or institutions such as day-care centers.<sup>2,5,9</sup>

The infective dose of *Shigella* is reportedly as low as 10–100 bacterial cells. Transmission occurs from person to person through the fecal and oral pathway, and also by consumption of contaminated food or water.<sup>1,5</sup> After an incubation period of 1–4 days, patients typically present with diarrhea, i.e., liquid stools that contain visible blood either with or without mucus.<sup>1</sup> Severe, acute complications of shigellosis may include acute hypoglycemia, seizures, toxic megacolon, hemolytic uremic syndrome, intestinal perforation, peritonitis, septicemia, etc., and can result in high mortality rates especially among infants and malnourished children.<sup>4,5</sup>

Shigellosis is endemic to most developing countries and is responsible for nearly 165 million cases and more than a million deaths annually. In the developing world, *Shigella* is associated with a high burden of illness particularly among children under five years of age, who present with the majority of cases (70%) and deaths (60%).<sup>1,10,11</sup> This pathogen is also frequently associated with epidemic outbreaks that are associated with high morbidity and mortality.<sup>1</sup>

## Methodology

The literature search for this review article included the following databases: SciELO (Scientific Electronic Library on Line), Science Direct, OVID, Clinical Key, EBSCOhost, PubMed (National Library of Medicine); LILACS (Latin American and Caribbean Center on Health Sciences Information) for peer-reviewed literature, and Google. The search terms used in English and Spanish were *Shigella*, antibiotic resistance, resistencia a antibióticos, integron, Latin America and América Latina.

## Emergence of multi drug resistance in *Shigella* isolates of Latin America

In Latin America, as in the rest of the world, the burden of shigellosis has been greatly increased by the emergence of microbial resistance toward antibiotics commonly used for therapy; this usually results in failure of treatment regimen.<sup>12–14</sup> Therefore, early and appropriate antibiotic therapy is crucial for reducing the duration of symptoms as well as for preventing the development of life-threatening complications.<sup>1</sup> Additionally, antibiotics also greatly reduce the excretion of the pathogen in stools which in turn reduces the spread of bacteria into the environment.<sup>13</sup>

Antibiotic resistant *Shigella* was initially noticed in 1940 in Japan when a serious outbreak of dysentery caused by *S. dysenteriae* was found to respond with decreasing effectiveness to sulfonamides, the principal antibacterial treatment available at the time. When antibiotics such as streptomycin, tetracycline, and chloramphenicol became available in that country, it was found that their efficacy was temporary as resistant strains were observed to develop soon after the drugs came into the clinical use.<sup>15,16</sup> Along similar lines, studies in Mexico have described resistance of the species toward tetracycline and chloramphenicol<sup>17</sup> and, in 1977, *Shigellae* strains resistant to ampicillin were isolated from similar epidemics in Mexico and Central America.<sup>18,19</sup> A few years later, an ampicillin resistant phenotype of *Shigella* was detected in Asian and African countries.<sup>20</sup>

Some reports in literature have documented an increased resistance to antibiotics such as gentamicin trimethoprim-sulfamethoxazole and  $\beta$ -lactams in Latin American countries.<sup>5,12,21–24</sup> In 2008, the first isolate of *Shigella* harboring the CMY-2 AmpC-lactamase enzyme was reported in Argentina.<sup>22</sup> This type of class C-lactamase is a clinically relevant cephalosporinase known to be produced by several Enterobacteriaceae strains; it is also known to mediate resistance to antibacterial agents such as cephalothin, cefazolin, cefoxitin, most derivatives of penicillin and  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations.<sup>25</sup>

The rapid emergence and propagation of resistance has shifted the recommended treatment modalities to ciprofloxacin and azithromycin.<sup>1</sup> Ciprofloxacin, a fluoroquinolone antibiotic formerly used as a backup drug, is now the drug of choice for all patients that present with bloody diarrhea irrespective of their age. Alarming, fluoroquinolone-resistant *Shigella* sp. is an emerging phenotype around the world including Latin America.<sup>12,13,24</sup> Recently, a multistate cluster of *Shigella sonnei* that had an uncommon pulsed-field gel electrophoresis profile and was resistant to ciprofloxacin was detected in the U.S. by the Centers of Disease Control and Prevention (CDC)-National Antimicrobial Resistance Monitoring System (NARMS).<sup>26</sup> According to CDC-NARMS, 109 out of the 126 (87%) *Shigella* isolates that were tested were found to be non susceptible to ciprofloxacin. Ciprofloxacin-resistant *Shigella* isolates were obtained from patients who had traveled to the Dominican Republic (one of five isolates tested) and India (one of one isolate tested), and also among non-travelers (four of seven isolates tested).<sup>26</sup>

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