

**Title:** Laboratory Testing for Antimicrobial Resistance during the 1999-2000 Shigellosis Outbreak in Sierra Leone

**Activities:** Collect samples; Identify agent based on laboratory testing; Test for antiviral, antibiotic, and/or vaccine resistance

**Stakeholders:** Médecins Sans Frontières; Private sector laboratories; World Health Organization

**Phases:** Surveillance and preparedness; Detection; Early response; Intervention

**Years:** 1999-2000

**Countries:** Sierra Leone

**Agent:** Shigellosis

**Case study prepared by:** Emily Sherman, August 19, 2019

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Classified by the CDC as “microorganisms with a threat level of serious,”<sup>1</sup> *Shigella* bacteria are highly infectious<sup>2</sup> and have become increasingly resistant to common antimicrobials.<sup>3</sup> As such, during the 1999-2000 shigellosis outbreak in Sierra Leone, continual laboratory testing of *Shigella* samples for antimicrobial resistance (AMR) was necessary to support decision making for treating patients. While AMR occurs naturally in some bacteria, its spread can be expedited if patients are given antibiotics to which their infection is resistant.<sup>4</sup> Laboratory testing made known the exact drugs to which *Shigella* isolates were and were not resistant, and in doing so, allowed for the selection of effective medications and limited further development of AMR in *Shigella* strains.<sup>5</sup> Because shigellosis is a self-limiting disease,<sup>6</sup> only severe cases and those that

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<sup>1</sup> Antibiotic Resistance Threats in the United States, 2013. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.

<sup>2</sup> Muthuirulandi Sethuvel, D. , Devanga Ragupathi, N. , Anandan, S. and Veeraraghavan, B. (2017), Update on: *Shigella* new serogroups/serotypes and their antimicrobial resistance. *Lett Appl Microbiol*, 64: 8-18.

<sup>3</sup> Guerin, Philippe J., et al. "Shigella dysenteriae serotype 1 in west Africa: intervention strategy for an outbreak in Sierra Leone." *The Lancet* 362.9385 (2003): 705-706.

<sup>4</sup> Antimicrobial Resistance. World Health Organization. 15 February 2018.

<sup>5</sup> Liu H, Zhu B, Qiu S, Xia Y, Liang B, Yang C, et al. (2018) Dominant serotype distribution and antimicrobial resistance profile of *Shigella* spp. in Xinjiang, China. *PLoS ONE* 13(4): e0195259. <https://doi.org/10.1371/journal.pone.0195259>

<sup>6</sup> Muthuirulandi Sethuvel, D, et al. Update on: *Shigella* new serogroups/serotypes and their antimicrobial resistance.

were under the age of five, over the age of fifty, or malnourished were recommended for treatment with antibiotics.<sup>7</sup>

In November 1999,<sup>8</sup> Médecins Sans Frontières (MSF) personnel in Sierra Leone reported an abnormally high incidence of bloody diarrhea, a symptom of- among other things- shigellosis.<sup>9</sup> An outbreak was confirmed soon after when Institut Pasteur Abidjan<sup>10</sup> isolated *Shigella flexneri* from stool samples collected from the Western Area district.<sup>11</sup> On December 23, 1999, the Institut Pasteur in Paris isolated *Shigella dysenteriae* serotype 1 (Sd1) in six out of 19 stool samples collected in Kenema district.<sup>12</sup> Both the *Shigella flexneri* and Sd1 isolates were sensitive to the antibiotics ciprofloxacin and nalidixic acid. Shigellosis was laboratory confirmed in Koinadugu district and Moyamba district on January 19, 2000 when isolates from stool samples tested positive for Sd1.<sup>13</sup>

The Government of Sierra Leone requested assistance from the World Health Organization (WHO) on January 25, 2000 to help respond to the outbreak. The WHO's Regional Office for Africa sent a two-person team and 103,000 nalidixic acid tablets to Freetown, Sierra Leone. Medical staff at a laboratory in Connaught Hospital received a two-day training in the identification of *Shigella* species and were provided with necessary equipment for testing. Of 82 stool samples that were collected in the field and brought back to the laboratory, 72 were positive for Sd1 and sensitive to ciprofloxacin and nalidixic acid.<sup>14</sup>

In February 2000, the national reference laboratory in Freetown and field laboratory of Kenema district tested 69 samples, from which 20 strains of Sd1 were isolated. Had there not been long delays in transportation, it was expected that Sd1 would have been isolated in more of the samples. The isolates were sensitive to cefixime, gentamicin, ciprofloxacin, ofloxacin, ceftriaxone, and nalidixic acid, and resistant to amikacin, amoxicillin, amoxicillin-clavulanic acid, tetracycline, trimethoprim-sulfamethoxazole, and chloramphenicol.<sup>15</sup>

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<sup>7</sup> P.J. Guerin, C. Brasher, E. Baron, D. Mic, F. Grimont, M. Ryan, P. Aavitsland, D. Legros, Case management of a multidrug-resistant *Shigella dysenteriae* serotype 1 outbreak in a crisis context in Sierra Leone, 1999–2000, *Transactions of The Royal Society of Tropical Medicine and Hygiene*, Volume 98, Issue 11, November 2004, Pages 635–643, <https://doi-org.proxygt-law.wrlc.org/10.1016/j.trstmh.2004.01.005>

<sup>8</sup> Guerin, Philippe J., et al. "Shigella dysenteriae serotype 1 in west Africa: intervention strategy for an outbreak in Sierra Leone."

<sup>9</sup> Antibiotic Resistance Threats in the United States, 2013.

<sup>10</sup> Mike Ryan. Response to Shigellosis Outbreak Sierra Leone February 2000. World Health Organization.

<sup>11</sup> World Health Organization. 2000 - Dysentery in Sierra Leone. Disease Outbreak News. [https://www.who.int/csr/don/2000\\_01\\_24a/en/](https://www.who.int/csr/don/2000_01_24a/en/) 24 January 2000.

<sup>12</sup> P.J. Guerin, C. Brasher, E. Baron, D. Mic, F. Grimont, M. Ryan, P. Aavitsland, D. Legros, Case management of a multidrug-resistant *Shigella dysenteriae* serotype 1 outbreak in a crisis context in Sierra Leone, 1999–2000.

<sup>13</sup> World Health Organization. 2000 - Dysentery in Sierra Leone. Disease Outbreak News.

<sup>14</sup> Mike Ryan. Response to Shigellosis Outbreak Sierra Leone February 2000. World Health Organization.

<sup>15</sup> P.J. Guerin, et. al. Case management of a multidrug-resistant *Shigella dysenteriae* serotype 1 outbreak in a crisis context in Sierra Leone, 1999–2000.

In the choice between the use of ciprofloxacin and nalidixic acid, the WHO and MSF took different approaches. The WHO decided to first administer nalidixic acid, then ciprofloxacin if the nalidixic acid did not take effect. This was done for largely financial reasons; nalidixic acid was available at one-tenth of the cost of ciprofloxacin.<sup>16</sup> MSF chose to only use ciprofloxacin, which, compared to nalidixic acid in previous shigellosis outbreaks, had a significantly higher compliance rate (99.7% vs. 50%) and lower case fatality ratio (CFR) (0.9% vs. 13%).<sup>17</sup> There was also an argument to be made against the use of ciprofloxacin after nalidixic acid, because the mutation in *Shigella* that confers resistance to nalidixic acid also confers resistance to ciprofloxacin. This could result in an expedited acquisition of resistance to ciprofloxacin in *Shigella* strains.<sup>18</sup> MSF urged the WHO to reconsider its recommendation for the use of nalidixic acid in outbreaks of shigellosis dysenteriae type 1.<sup>19</sup>

In 2005, the WHO updated its guidelines for the control of shigellosis outbreaks, including those caused by Sd1. Because some *Shigella* strains acquired resistance to nalidixic acid in the years after the outbreak in Sierra Leone, the WHO changed its recommended first-line treatment from nalidixic acid to ciprofloxacin. The recommended second-line treatments were changed to pivmecillinam, ceftriaxone, and azithromycin.<sup>20</sup> A systematic review of the WHO's 2005 guidelines was published in May 2018. It concluded that the WHO's recommendations are still relevant, and that cefixime could also be used as a second-line treatment.<sup>21</sup> As of September 21, 2018, the WHO continues to recommend ciprofloxacin as the first choice treatment for shigellosis.<sup>22</sup>

*Shigella*'s AMR has evolved rapidly. Strains of *Shigella* have become resistant to the majority of the drugs that have been used to treat shigellosis in the past, including sulphonamides, tetracycline, chloramphenicol, ampicillin, co-trimoxazole, and nalidixic acid. *Shigella* is still generally susceptible to fluoroquinolones (including ciprofloxacin), ceftriaxone, pivmecillinam, and azithromycin; however, some isolates have now been found to be resistant to fluoroquinolones, ceftriaxone, and azithromycin. Increasingly widespread AMR in *Shigella*

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<sup>16</sup> Mike Ryan. Response to Shigellosis Outbreak Sierra Leone February 2000. World Health Organization.

<sup>17</sup> P.J. Guerin, et. al. Case management of a multidrug-resistant *Shigella dysenteriae* serotype 1 outbreak in a crisis context in Sierra Leone, 1999–2000.

<sup>18</sup> Mike Ryan. Response to Shigellosis Outbreak Sierra Leone February 2000. World Health Organization.

<sup>19</sup> P.J. Guerin, et. al. Case management of a multidrug-resistant *Shigella dysenteriae* serotype 1 outbreak in a crisis context in Sierra Leone, 1999–2000.

<sup>20</sup> World Health Organization. Guidelines for the control of shigellosis, including epidemics due to *Shigella dysenteriae* 1. <https://apps.who.int/iris/bitstream/handle/10665/43252/924159330X.pdf?sequence=1>

<sup>21</sup> Williams PCM, Berkley JA. Guidelines for the treatment of dysentery (shigellosis): a systematic review of the evidence. *Paediatr Int Child Health*. 2018;38(sup1):S50–S65. doi:10.1080/20469047.2017.1409454

<sup>22</sup> World Health Organization. Shigellosis. Operational Support & Logistics Disease Commodity Packages. Updated 21 September 2018. <https://www.who.int/emergencies/what-we-do/prevention-readiness/disease-commodity-packages/dcp-shigellosis.pdf?ua=1>

strains means the formulation of an effective and accessible shigellosis vaccine is urgently needed.<sup>23</sup>

**Please include case study summary text below this line.**

Shigella bacteria have become increasingly resistant to common antimicrobials, making it necessary to test laboratory samples for antimicrobial resistance (AMR) during the 1999-2000 shigellosis outbreak in Sierra Leone. *Shigella flexneri* were isolated from samples collected in the Western Area district, and *Shigella dysenteriae* serotype 1 (Sd1) were isolated from samples collected in Kenema district, Koinadugu district, and Moyamba district. All isolates were found to be sensitive to ciprofloxacin and nalidixic acid. However, there was debate amongst decision makers managing the outbreak response over which drug should be administered due to both financial and biological reasons.

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<sup>23</sup> Puzari, Minakshi, Mohan Sharma, and Pankaj Chetia. "Emergence of antibiotic resistant Shigella species: A matter of concern." *Journal of infection and public health* 11.4 (2018): 451-454.