Increasing Antibiotic Resistance in Shigella spp. from Infected New York City Residents, New York, USA

Kenya Murray, Vasudha Reddy, John S. Kornblum, HaeNa Waechter, Ludwin F. Chicaiza, Inessa Rubinstein, Sharon Balter, Sharon K. Greene, Sarah L. Braunstein, Jennifer L. Rakeman, Catherine M. Dentinger

Approximately 20% of Shigella isolates tested in New York City, New York, USA, during 2013–2015 displayed decreased azithromycin susceptibility. Case-patients were older and more frequently male and HIV infected than those with azithromycin-susceptible Shigella infection; 90% identified as men who have sex with men. Clinical interpretation guidelines for azithromycin resistance and outcome studies are needed.

Shigella bacteria are transmitted through the fecal–oral route by direct contact with an infected person, by ingestion of contaminated food or water, or by fomites. Shigellosis is associated with travel to disease-endemic areas, men who have sex with men (MSM), crowding, poverty, and attendance at childcare centers (1); illness is generally self-limited. Antibiotics may shorten the duration and decrease the illness severity (2,3). Because Shigella spp. may be resistant to ampicillin and trimethoprim/sulfamethoxazole (TMP/SMX), azithromycin and ciprofloxacin are often prescribed to treat shigellosis. In 2016, the Clinical Laboratory Standards Institute (CLSI) published MICs of azithromycin that indicated Shigella resistance; values are based on in vitro data and are not clinical breakpoints (4).

In 2013, public health laboratories in New York City (NYC), New York, USA, began testing susceptibility of Shigella isolates to azithromycin. We identified factors associated with infection with isolates that exhibited decreased susceptibility to azithromycin (DSA) or resistance to ciprofloxacin.

Author affiliations: Centers for Disease Control and Prevention/ Council of State and Territorial Epidemiologists Applied Epidemiology Fellowship, Atlanta, Georgia, USA (K. Murray); New York City Department of Health and Mental Hygiene, Queens, New York, USA (K. Murray, V. Reddy, J.S. Kornblum, H. Waechter, L.F. Chicaiza, I. Rubinstein, S. Balter, S.K. Greene, S.L. Braunstein, J.L. Rakeman, C.M. Dentinger); Centers for Disease Control and Prevention, Atlanta (C.M. Dentinger)

DOI: http://dx.doi.org/10.3201/eid2302.161203

The Study

After submission to NYC public health laboratories, representative colonies of Shigella isolates are identified with conventional biochemical tests and tested for susceptibility to ampicillin, cefixime, ciprofloxacin, azithromycin, and TMP/SMX using the Etest antibiotic gradient (bioMérieux, Durham, NC, USA). MICs are interpreted according to CLSI guidelines (5). After consultation with the Centers for Disease Control and Prevention (CDC), we defined DSA isolates as those with an MIC of azithromycin of ≥32 µg/mL (J. Whichard, CDC, pers. comm., 2013).

Using a standard questionnaire, we interviewed persons infected with DSA or ciprofloxacin-resistant Shigella isolates, diagnosed during March 22, 2013–May 31, 2015; we abstracted antibiotic use data from medical charts. Shigella-infected case-patients were matched to the NYC HIV Surveillance Registry (6). We determined neighborhood poverty level as described (7) and compared proportions of those infected by age group, sex, and HIV status using χ² tests. To identify factors associated with DSA or ciprofloxacin-resistant Shigella infection and with hospitalization, we used logistic regression analysis (SAS version 9.2; SAS Institute, Cary, NC, USA).

During 26 months, 978 Shigella isolates were submitted; 295 were associated with an outbreak (8) and analyzed separately, and 683 were defined as sporadic. Among patients with sporadic infections, 129 (19%) were infected with isolates displaying DSA, and 29 (4%) were infected with ciprofloxacin-resistant isolates; 5 isolates displayed both characteristics. The median age of case-patients was 27 years (range 0–93 years); 446 (65%) were male. Nearly all infections were caused by S. sonnei (65%) or S. flexneri (34%). Antibiotic resistance of isolates was as follows: 416 (61%) to ampicillin, 10 (1%) to cefixime, 29 (4%) to ciprofloxacin, and 481 (70%) to TMP/SMX (Table 1).

Persons infected with DSA or ciprofloxacin-resistant Shigella spp. were older and more likely to be male than those with DSA- or ciprofloxacin-susceptible isolates; no association with neighborhood poverty was found. Although most infections were caused by S. sonnei, most isolates displaying DSA were S. flexneri. Isolates displaying DSA or ciprofloxacin resistance were more likely to be ampicillin- and TMP/SMX-resistant than were azithromycin- and ciprofloxacin-susceptible isolates (Tables 1, 2).
Table 1.

| Characteristic | No. (%) case-patients | |
|---------------|----------------------|---|
| Male sex      | DSA, n = 129 | Ciprofloxacin resistant, n = 29 | Susceptible, n = 530 | Total, n = 683† |
| Age, y        | 120 (93) | 22 (76) | 306 (58) | 446 (65) |
| 0–17          | 3 (2)     | 7 (24)  | 254 (48) | 262 (38) |
| 18–64         | 119 (92)  | 19 (66)  | 261 (49) | 397 (58) |
| >65           | 7 (5)     | 3 (10)  | 15 (3)   | 24 (4)   |
| Race          | White     | 58 (45)  | 12 (41)  | 107 (20) | 174 (25) |
|              | Black     | 39 (30)  | 1 (3)    | 75 (14)  | 115 (17) |
|              | Other     | 3 (2)    | 4 (14)   | 11 (2)   | 17 (2)   |
|              | Unknown   | 29 (22)  | 12 (41)  | 337 (64) | 377 (55) |
| Ethnicity     | Hispanic  | 15 (12)  | 3 (10)   | 74 (14)  | 91 (13)  |
|              | Non-Hispanic | 78 (60)  | 15 (52)  | 131 (25) | 222 (33) |
|              | Unknown   | 36 (28)  | 11 (38)  | 325 (61) | 370 (54) |
| Borough       | Bronx     | 19 (15)  | 1 (3)    | 100 (19) | 120 (18) |
|              | Brooklyn  | 32 (25)  | 7 (24)   | 132 (26) | 230 (34) |
|              | Manhattan | 61 (47)  | 12 (41)  | 119 (22) | 191 (28) |
|              | Queens    | 16 (12)  | 7 (24)   | 111 (21) | 131 (19) |
|              | Staten Island | 1 (1)  | 2 (7)    | 8 (2)    | 11 (2)   |
| Neighborhood poverty, %‡ |<10 | 23 (18) | 8 (29) | 87 (17) | 117 (18) |
|              | 10–20     | 48 (38)  | 10 (36)  | 137 (27) | 195 (29) |
|              | 20–30     | 37 (29)  | 7 (25)   | 111 (22) | 152 (23) |
|              | 30–100    | 20 (16)  | 3 (11)   | 176 (34) | 199 (30) |
| HIV diagnosed | 76 (59) | 7 (24) | 101 (19) | 183 (27) |
| Antibiotic resistance by species§ | S. sonnei | 42 (33) | 23 (79) | 381 (72) | 443 (65) |
|              | DSA       | 42 (100) | 3 (13)  | 381 (100) | 42 (9)  |
|              | Ciprofloxacin | 3 (7)    | 23 (100) | 380 (100)§ | 23 (5)  |
|              | Ampicillin | 39 (93)  | 4 (17)   | 177 (46) | 218 (49) |
|              | Cefixime  | 1 (1)    | 2 (9)    | 4 (1)    | 6 (1)   |
|              | TMP/SMX   | 37 (88)  | 20 (87)  | 252 (66) | 308 (70) |
| S. flexneri  | 86 (67)   | 5 (17)   | 140 (26) | 230 (34) |
|              | DSA       | 86 (100) | 1 (20)   | 140 (100) | 86 (37) |
|              | Ciprofloxacin | 1 (1)    | 5 (100)  | 139 (100)§ | 5 (2)  |
|              | Ampicillin | 79 (92)  | 5 (100)  | 109 (78) | 192 (83) |
|              | Cefixime  | 2 (2)    | 1 (20)   | 1 (1)    | 3 (1)   |
|              | TMP/SMX   | 73 (85)  | 4 (80)   | 89 (64)  | 186 (72) |

† N = 683 sporadic cases. DSA, decreased susceptibility to azithromycin; TMP/SMX, trimethoprim/sulfamethoxazole.
‡ Percentage of census tract residents below federal poverty level, per American Community Survey, 2009–2013; 19 missing.
§ S. boydii (n = 7) and S. dysenteriae (n = 3) omitted.

Of the 683 shigellosis case-patients, 183 (27%) had diagnosed HIV infection. Among these, 76 (42%) were infected with DSA isolates, and 7 (4%) were infected with ciprofloxacin-resistant isolates; 108 (59%) were infected with S. flexneri, 73 (40%) with S. sonnei, and 1 each (0.5%) with S. boydii and S. dysenteriae. Of 47 (62%) HIV-diagnosed persons with DSA Shigella infection, 45 (95%) identified as MSM.

Of the 153 persons with DSA- and/or ciprofloxacin-resistant Shigella infection, chart reviews were completed for 111 (73%). Interviews were completed for 97 (64%), and isolates of 80 (82%) of those had DSA to Shigella, 15 (15%) had ciprofloxacin-resistant isolates, and 2 (2%) had isolates resistant to azithromycin and ciprofloxacin. Most case-patients were male (140 [91.5%]); of 120 who completed interviews or were listed in the HIV Surveillance Registry, 102 (85%) identified as MSM. Eleven (12%) of 93 interviewed case-patients who answered the question reported international travel. All interviewees reported symptoms; most common were diarrhea (98%) and abdominal cramps (82%). Median illness duration was 7 days (range 2–45 days). Of 31 (32%) reported hospitalizations, 28 (90%) were infected with DSA and 3 (10%) with ciprofloxacin-resistant isolates; median duration of stay was 3 days (range 1–10 days). Twenty-five (81%) hospitalized case-patients were infected with S. flexneri. In a model that considered age, sex, species (S. flexneri and S. sonnei), HIV status, and neighborhood poverty level, only infection with S. flexneri was associated with hospitalization (odds ratio 4.04, 95% CI 1.46–11.18).

Antibiotics, most commonly ciprofloxacin, were prescribed for 114 (89%) of 128 case-patients (for whom
HIV-positive MSM may be at increased risk for acquiring infections caused by antibiotic-resistant Shigella spp. due to transmission-facilitating behavior (10) or because of increased exposure to macrolides and fluoroquinolones used to treat sexually transmitted infections, which could increase selective pressure on Shigella organisms (12). HIV infection may increase the risk of acquiring and transmitting Shigella infection due to increased carriage and shedding time or altered immune response (2).

To limit the emergence of resistance, the NYC Department of Health and Mental Hygiene and CDC recommend that antibiotics be avoided in treating Shigella infections except in cases of severe illness or among those at risk for systemic infection (13,14). When antibiotics are prescribed, therapy should be modified on the basis of sensitivity testing; however, without CLSI-defined clinical breakpoints for azithromycin, this process will be challenging (4,14,15).

We were unable to compare illness, exposures, and treatments between persons infected with susceptible versus resistant Shigella spp. We may have overestimated resistance if persons with resistant strains were more likely to have severe or persistent infections, seek care, and have cultures obtained. The clinical significance of resistance is not clear. Finally, molecular characterization of isolates to describe resistance mechanisms and transmission patterns was not done.

Although Shigella infections are generally self-limited, resistant organisms could lead to complications among those who develop systemic infection if they cannot be adequately treated. Studies of clinical breakpoints for azithromycin susceptibility and clinical outcomes are needed. In the meantime, providers should avoid treating

Table 2. Characteristics associated with azithromycin or ciprofloxacin resistance among case-patients with Shigella flexneri and S. sonnei infections, New York City, New York, USA, March 22, 2013–May 31, 2015*  

| Characteristic | No. (%) case-patients | Crude OR (95% CI)§ | Adjusted OR (95% CI)§ |
|---------------|-----------------------|---------------------|-----------------------|
| Male sex      |                       |                     |                       |
| Resistant, n = 152† | Susceptible, n = 521‡  | 8.33 (4.50–15.40) | 3.27 (1.63–6.55) |
| Age, y        |                       |                     |                       |
| 0–17          | 8 (5.3)               | 251 (48.2)          | Referent              |
| 18–64         | 136 (89.5)            | 256 (49.1)          | 16.67 (8.00–34.73)   |
| ≥65           | 8 (5.3)               | 14 (2.7)            | 17.93 (5.86–54.64)   |
| Neighborhood poverty, %¶  |                       |                     |                       |
| <10           | 30 (19.7)             | 85 (16.9)           | Referent              |
| 10–20         | 58 (38.2)             | 135 (26.9)          | 1.22 (0.73–2.04)     |
| 20–30         | 41 (27.0)             | 108 (21.5)          | 1.08 (0.62–1.86)     |
| 30–100        | 23 (15.1)             | 174 (34.7)          | 0.38 (0.21–0.68)     |
| Species       |                       |                     |                       |
| S. flexneri   | 90 (59.2)             | 140 (26.7)          | 3.95 (2.71–5.76)     |
| HIV-diagnosed |                       |                     | 1.91 (1.25–2.92)     |
| Yes           | 82 (54.0)             | 99 (19.0)           | 4.99 (3.39–7.35)     |
|               |                       |                     | 1.44 (0.91–2.30)     |

* N = 683 sporadic cases. OR, odds ratio.
† S. boydii (n = 1) omitted.
‡ S. boydii (n = 6) and S. dysenteriae (n = 3) omitted.
§ Values reported in bold are significant, calculated by using bivariate or multivariable (sex, age, neighborhood poverty, species, and HIV diagnosis) logistic regression.
¶ Percentage of residents below federal poverty level, per American Community Survey, 2009–2013: 19 missing.

Data were available; 16 (13%) received antibiotics to which their Shigella isolates was not susceptible. Fifteen (17%) of 90 patients had taken antibiotics in the 4 weeks before illness onset; all were men, 10 (67%) were HIV-positive, and 12 (92%) of 13 for whom data were available were MSM.

Median illness duration for the 15 (52%) interviewed case-patients infected with ciprofloxacin-resistant Shigella spp. was 7 days (range 2–17 days); 3 (20%) reported hospitalization, and 5 (33%) reported recent international travel. Five (63%) of 8 case-patients for whom data were available identified as MSM.

**Conclusions**

In NYC, 19% of nonoutbreak shigellosis cases were caused by organisms with an azithromycin MIC ≥32 µg/mL, a much higher proportion than the national estimate of 3.8% (9). This finding is troubling because, when antibiotics are indicated, azithromycin is recommended (2,3).

**DISPATCHES**
otherwise healthy shigellosis patients with antibiotics. When antibiotics are indicated, providers should use available susceptibility results and monitor patient outcomes.

Acknowledgments
We thank Madeline Sankaran, Jasmine Abdelnabi, Jasmine Parks, Alexander Davidson, and Eric Peterson for their assistance with interviewing case-patients and data abstraction.

This study/report was supported in part by an appointment to the Applied Epidemiology Fellowship Program administered by the Council of State and Territorial Epidemiologists and funded by the Centers for Disease Control and Prevention Cooperative Agreement no. 5U38HM000414–5.

Ms. Murray is an antibiotic resistance data analyst at the New York City Department of Health and Mental Hygiene. Previously, she completed a 2-year fellowship in applied epidemiology there, sponsored by CDC and the Council of State and Territorial Epidemiologists. She has also worked as an epidemiologist in Zambia, focusing on infectious diseases among maternal and child populations. Her research interests include the epidemiology of infectious diseases and outbreak preparedness and response.

References
1. Goldberg M. *Shigella* infection: epidemiology, microbiology, and pathogenesis. UpToDate. Alphen aan den Rijn (the Netherlands): Wolters Kluwer; 2016 [cited 2016 Sep 9]. http://www.uptodate.com/home
2. American Academy of Pediatrics. Red book: 2012 report of the Committee on Infectious Diseases. 29th ed. Elk Grove (IL): American Academy of Pediatrics; 2012.
3. Agha RM. *Shigella* infection: treatment and prevention in adults. UpToDate. Alphen aan den Rijn (the Netherlands): Wolters Kluwer; 2015 [cited 2016 Sep 9]. http://www.uptodate.com/home
4. Clinical Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. 26th ed. CLSI supplement M100S. Wayne (PA): The Institute; 2016. p. 62.
5. Clinical Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing, 24th informational supplement. Report no. cM100. Wayne (PA): The Institute; 2014.
6. Drobni A, Pinchoff J, Bushnell G, Ly S, Yuan J, Varma JK, et al. Matching HIV, tuberculosis, viral hepatitis, and sexually transmitted diseases surveillance data, 2000–2010: identification of infectious disease syndemics in New York City. J Public Health Manag Pract. 2014;20:506–12.
7. Toprani A, Hadler JL. Selecting and applying a standard area-based socioeconomic status measure for public health data: analysis for New York City. New York: New York City Department of Health and Mental Hygiene; 2013.
8. New York City Health Alert Network. 2014 Alert #39: outbreak of shigellosis in Borough Park and Williamsburg. New York: New York City Department of Health and Mental Hygiene; 2014.
9. Centers for Disease Control and Prevention. National Antimicrobial Resistance Monitoring System: enteric bacteria human isolates final report. Atlanta: The Centers; 2013.
10. Baker KS, Dallman TJ, Ashton PM, Day M, Hughes G, Crook PD, et al. Intercontinental dissemination of azithromycin-resistant shigellosis through sexual transmission: a cross-sectional study. Lancet Infect Dis. 2015;15:913–21. http://dx.doi.org/10.1016/S1473-3099(15)00095-8
11. Bhattacharya D, Bhattacharya H, Sayi DS, Bharadwaj AP, Singhania M, Sugunan AP, et al. Changing patterns and widening of antibiotic resistance in *Shigella* spp. over a decade (2000–2011), Andaman Islands, India. Epidemiol Infect. 2015;143:470–7. http://dx.doi.org/10.1017/S0950268814000958
12. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations for the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Atlanta (GA): US Department of Health and Human Services; 2014.
13. Centers for Disease Control and Prevention. Ciprofloxacin- and azithromycin-nonsusceptible shigellosis in the United States. Atlanta: The Centers; 2015.
14. New York City Department of Health and Mental Hygiene. Increasing antimicrobial resistance of *Shigella* among men who have sex with men in NYC. 2016 Alert #41. New York: New York City Department of Health and Mental Hygiene; 2016.
15. Nüesch-Inderbinen M, Hein I, Zurluh K, Althaus D, Hächler H, Stephan R. *Shigella* antimicrobial drug resistance mechanisms 2004–2014. Emerg Infect Dis. 2016;22:1083–5. http://dx.doi.org/10.3201/eid2206.152088

Address for correspondence: Catherine M. Dentinger, New York City Department of Health and Mental Hygiene, Bureau of Communicable Diseases, 42-09 28th St, Queens, NY 11101, USA: email: cdentinger@cdc.gov