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Outbreak of Infections caused by *Shigella sonnei* with Reduced Susceptibility to Azithromycin, United States

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Shigellosis is the third most common enteric bacterial infection in the United States (9). The disease is caused by *Shigella* bacteria and symptoms include abdominal cramps, diarrhea that sometimes contains blood, nausea, vomiting, and fever. *Shigella sonnei* has a very low infectious dose, and the infection may spread from person to person or via contaminated objects, food, or water. In the United States, the incidence is highest among children <5 years old and multiple outbreaks of *S. sonnei* infections have been associated with daycare centers (2, 10).

In the United States., shigellosis is frequently treated with antimicrobial drugs because they can slightly shorten the duration and severity of illness (6). Increasing resistance to ampicillin and trimethoprim-sulfamethoxazole has led physicians to prescribe azithromycin for treatment of shigellosis (3, 10). Azithromycin is currently recommended by the American Academy of Pediatrics and the Infectious Diseases Society of America for the treatment of multidrug-resistant shigellosis, although azithromycin susceptibility testing guidelines and interpretive criteria are lacking for *Shigella* (1, 7). A study by Howie *et al.* showed the susceptible wild type distribution of minimum inhibitory concentrations (MICs) to range from 4 to 16 µg/ml (8). Isolates with higher azithromycin MICs have been confirmed to harbor *mphA*, a macrolide resistance gene encoding a macrolide-2'-phosphotransferase (4, 8).

In May 2012, Los Angeles County Department of Public Health investigated an outbreak caused by *S. sonnei* that sickened 43 people. Four representative isolates (2012C-3667 to 2012C-3670) were submitted to the Centers for Disease Control and Prevention (CDC). Two were obtained from asymptomatic, male employees of a bridge club, one of whom was a food handler. Two isolates were obtained from women in the same club. Both women were hospitalized with non-bloody diarrhea; one was ill for 7 days and reported vomiting and fever of

102°F; the duration of illness was not reported for the other. The ages of these four individuals ranged from 60 – 89 years.

The isolates yielded indistinguishable patterns by pulsed-field gel electrophoresis (PFGE) using *XbaI* (PulseNet pattern J16X01.0756). Susceptibility to 14 antimicrobial agents was determined by broth microdilution (Sensititre, Trek Diagnostics, Westlake, OH). All four isolates displayed resistance to streptomycin, sulfisoxazole, tetracycline, and trimethoprim-sulfamethoxazole. In addition, all four isolates displayed azithromycin MICs >16 µg/ml (Table 1). PCR-screening confirmed the presence of *mphA* in all four isolates (8). Plasmid DNA from two isolates was electroporated into *Escherichia coli* DH10B cells. *E. coli* transformants with elevated MICs to azithromycin (MIC >16 µg/ml) confirmed the *mphA* gene to be located on a plasmid. The plasmid type could not be determined by inc/rep typing (5).

To our knowledge, this is the first outbreak caused by *Shigella* isolates displaying elevated azithromycin MICs to be documented within the United States. The circulation of *Shigella* isolates with high azithromycin MICs is worrisome since it may limit the treatment options for multidrug-resistant infections, especially among children.

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Table 1. Minimum inhibitory concentrations (μg/ml) for four 2012 outbreak isolates of *Shigella sonnei*, two *Escherichia coli* DH10B transformants and *E. coli* DH10B.

Antimicrobial Agent*	Minimum inhibitory concentration (μg/ml) for:						
	2012C-3667	*2012C-3668*	*2012C-3669*	*2012C-3670*	*DH10B-3668*	*DH10B-3670*	*DH10B*
Ampicillin	2	2	4	4	4	4	4
Amoxicillin/CLA	4	4	4	4	2	4	2
Azithromycin	>16	>16	>16	>16	>16	>16	2
Cefoxitin	2	2	2	2	8	8	8
Ceftriaxone	≤0.25	≤0.25	≤0.25	≤0.25	≤0.25	≤0.25	≤0.25
Chloramphenicol	4	4	4	4	≤2	≤2	≤2
Ciprofloxacin	≤0.016	≤0.016	≤0.016	≤0.016	≤0.016	≤0.016	≤0.016
Gentamicin	2	1	1	1	0.5	0.5	0.5
Kanamycin	≤8	≤8	≤8	≤8	≤8	≤8	≤8
Nalidixic acid	1	1	1	1	1	1	1
Streptomycin	>64	>64	>64	>64	>64	>64	>64
Sulfisoxazole	>256	>256	>256	>256	>256	>256	≤16
Tetracycline	>32	>32	>32	>32	≤4	≤4	≤4
Trimethoprim-sulfamethoxazole	>4	>4	>4	>4	>4	>4	≤0.125

*CLA, clavulanic acid