Reply to Chu et al., “Adoption of the New CLSI Fluoroquinolone Breakpoints for *Enterobacteriaceae*”

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We thank Chu and colleagues (10) for highlighting the potential impact of the 2019 revised Clinical and Laboratory Standards Institute (CLSI) *Enterobacteriaceae* fluoroquinolone breakpoints on the reporting of other members of this antibiotic class, in this case, nalidixic acid. As noted by the authors, this breakpoint revision was limited to ciprofloxacin and levofloxacin and did not include other members of the quinolone/fluoroquinolone class. In their analysis, Chu and colleagues noted that implementation of the revised levofloxacin breakpoint would lead to a 5- to 20-fold increase in their rates of levofloxacin-nonsusceptible/nalidixic acid-susceptible *Enterobacteriaceae* isolates. They also expressed concern over the potential for clinician confusion over such discordant results.

Although we agree with the authors that the reporting of levofloxacin resistant/nalidixic acid susceptibility has the potential to be confusing for clinicians, it is critical to note that the CLSI breakpoint for nalidixic acid is for urinary tract isolates only (1). In contrast, the breakpoint revisions for ciprofloxacin and levofloxacin were driven in large part by pharmacokinetic/pharmacodynamic data for non-urinary tract infections (e.g., bacteremia, pneumonia, etc.) (2). An increase in the proportion of nalidixic acid-susceptible isolates that would be levofloxacin intermediate or resistant once the revised levofloxacin breakpoints are applied is therefore not surprising. However, these data do speak to the potential need for urine-specific breakpoints for fluoroquinolones.

Importantly, a second reason for the breakpoint revision was the poor sensitivity of the previous breakpoints for the detection of low-level fluoroquinolone resistance mutations. Nalidixic acid is known to be a more sensitive agent for the detection of mutations in the quinolone resistance-determining regions (QRDRs) of topoisomerase than the previous ciprofloxacin and levofloxacin breakpoints (3–5). It is therefore not surprising, in looking closely at Chu et al.’s analysis, that the rates of levofloxacin-susceptible/nalidixic acid-resistant isolates would decrease 5-fold when the revised levofloxacin breakpoints are applied (i.e., from 24.6% to 4.8%). This speaks well to the poorer sensitivity of the previous breakpoints for low-level fluoroquinolone resistance detection.

Importantly, the data and concerns of Chu et al. highlight important differences in treatment and testing practices among different regions worldwide. The Infectious Diseases Society of America (IDSA) recommends that fluoroquinolones be reserved for more serious or complicated infections due to the plethora of adverse side effects associated with their use (6). With worldwide reported nalidixic acid resistance rates of >10% observed among *Escherichia coli* urine isolates, this agent is less attractive as empirical therapy than are other members of this class (e.g., ciprofloxacin) (7, 8). Nalidixic acid is not on formulary at our institutions, and to our knowledge, is not generally used clinically in the United States. Susceptibility testing against nalidixic acid in the United States has also declined, as evidenced by a dearth of laboratories

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reporting this antimicrobial in the College of American Pathologists (CAP) proficiency testing surveys. In the recent CAP D-C 2018 Bacteriology Survey, of 2,148 participants for an *E. coli* challenge, only 18 (0.8%) submitted antimicrobial susceptibility testing (AST) results for nalidixic acid. Indeed, the Vitek 2 (bioMérieux, USA), a commonly used automated commercial AST system in the United States, no longer includes nalidixic acid on AST panels currently available in the United States. Finally, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) does not have breakpoints for nalidixic acid against *Enterobacteriaceae* (*Enterobacteriales*) (9).

In closing, as discussed in detail in our review, revised breakpoints can prove challenging for laboratories to implement and can be confusing for clinicians to interpret. We agree with Chu et al. that it is important for clinical laboratories to examine the impact of implementing revised breakpoints on the potential for reporting discordant AST results within the same antibiotic class. However, we do not believe that the potential for discordant results should be used as a reason to avoid implementation of a breakpoint revision. Rather, we believe that the concerns raised by Chu et al. present an important opportunity for clinical microbiologists, infectious disease clinicians, and antimicrobial stewardship to collaborate and determine the best course of action so as to provide guidance for clinicians on appropriate interpretation and optimal antibiotic selection.

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