

National antimicrobial stewardship and fluoroquinolone-resistant *Clostridium difficile* in China

Meng Xiao^{1,*}
Jing-Wei Cheng^{1,2,*}
Timothy Kudinha³
Fanrong Kong⁴
Ying-Chun Xu^{1,2}

¹Department of Clinical Laboratory, Peking Union Medical College Hospital, ²Faculty of Clinical Laboratory Diagnostics, Graduate School, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China; ³School of Biomedical Sciences, The Charles Sturt University, Leeds Parade, Orange, ⁴Centre for Infectious Diseases and Microbiology Laboratory Services, ICPMR–Pathology West, Westmead Hospital, University of Sydney, Westmead, NSW, Australia

*These authors contributed equally to this work

In a recent report, Dingle et al showed that national intervention programs aimed at judicious antimicrobial usage, especially restrictions to fluoroquinolones, contributed to a significant decrease in *Clostridium difficile* infection (CDI) in England.¹ This is considered an outstanding achievement in combating antimicrobial resistance worldwide.

China, one of the most populous and vast developing country in the world, has experienced extensive antimicrobial resistance crisis due to irrational antimicrobial use over several decades. To date, quinolones are still the first to second most common class of antimicrobial agents used in China. According to the most recent data from Center for Antibacterial Surveillance, China National Health and Family Plan Commission in 2015,² quinolones accounted for 13.2% of all antibacterial consumptions nationwide, which was only lower than third-generation cephalosporins (15.7%), but higher than second-generation cephalosporins (12.2%). Of note, the consumption of levofloxacin ranked in the first place (over 8.9%) among all antibacterial agents in China.

CDI is now a widely recognized problem especially in North America and Europe, resulting in increased awareness of the problem. In contrast, CDI has generally remained poorly understood in China, mainly due to limited clinical awareness, poor laboratory diagnostic capacity, and lack of targeted surveillance. Recent studies in China reported more cases of *C. difficile* ribotype-027 infections, including outbreaks, which indicated that the *C. difficile* problem is underestimated.^{3,4} During the period 2012–2016, our group carried out a study of healthcare-associated *C. difficile* infections in three tertiary general hospitals in Beijing, China. In 234 isolates collected from diarrhea patients, fluoroquinolone resistance was detected by sequencing of *gryA* and *gryB* genes, including scanning for resistance-related amino-acid substitutions. Genotyping was conducted in all isolates by toxin gene detection, multilocus sequence typing, and PCR-ribotyping.

Generally, 26.5% (54/234) of the studied isolates exhibited fluoroquinolone-resistant (FQR) genotypes. Determination of minimum inhibitory concentrations of levofloxacin for 110 randomly selected isolates revealed high concordance between susceptibility phenotypes and genotypes (107/110 isolates, 97.3%). Of note, nearly two thirds of FQR *C. difficile* isolates studied were of toxin gene A–B+ (60/97, 61.9%) type. Moreover, the toxin gene A–B+ *C. difficile* isolates were 100% FQR, compared to only 21.3% (37/174) of toxin gene A+B+ isolates ($p < 0.001$). Over half of FQR A–B+ isolates belonged to sequence type (ST) 81/ribotype-PU09 clone (34/60, 56.7%), followed by

Correspondence: Ying-Chun Xu
Department of Clinical Laboratory,
Peking Union Medical College Hospital,
Shuaifuyuan Street No. 1, Beijing 100730,
China
Tel/fax +86 10 6915 9766
Email xycpumch@139.com

ST37/ribotype-017 (23/60, 38.3%). Furthermore, these two clones were also the first and second predominant clones among all FQR isolates (35.1% [34/97] and 23.7% [23/97], respectively). However, based on the review of patients' medical records and further multiple locus variable numbers tandem repeat analysis (data not shown) of the isolates, it was found that none of the CDI cases was associated with nosocomial outbreak. In comparison with A–B+ isolates, a more divergent clonal background, including 15 STs and 19 ribotypes, was identified among 37 FQR A+B+ isolates. Among these, the predominant clone was ST3/ribotype-001 (12/37, 32.4%), which was only the third most common FQR clone overall (12/97, 12.4%). In addition, over half of ST3/ribotype-001 isolates were fluoroquinolone-susceptible (17/29, 58.6%). The prevalence of ST1/ribotype-027 isolates was very low (2/234, 0.9%), although both the isolates were FQR. However, due to challenges in accessing the clinical data of patients, the relationship between FQ exposure history of the patients and toxigenic profile and susceptibility of the isolates was not analyzed.

The molecular epidemiology of *C. difficile* in China seems to be quite different from that in England and America, where ST1/ribotype-027 A+B+ isolates predominated among FQR *C. difficile* isolates, but A–B+ clones were rare.^{1,5} However, the study by Dingle et al¹ revealed a significant decline of FQR isolates in both the major A+B+ clones (such as ST1/ribotype-027) and A–B+ clones (such as ST37/ribotype-017), mostly due to the implementation of national fluoroquinolone use regulations.

To curb antimicrobial resistance, the government of China has taken more active efforts since 2011,⁶ including establishing mandatory management strategies for appropriate clinical use of antimicrobials. In 2016, a new and enhanced national action plan involving 14 ministries was further established to combat antimicrobial resistance.⁷ Interventions in clinical consumption of FQs were implemented as part of these national actions. Consequently, in tertiary hospitals, FQ consumption decreased from 10.45 defined daily doses (DDDs)/100 patient days to 6.23 DDDs/100 patient days in 2015.² In the three hospitals involved in this study, FQ consumption also decreased from 9.64 DDDs/100 patient days to 6.48 DDDs/100 patient days during the study period. At national level, to combat certain “superbugs,” such as *C. difficile* and the recently reported *Enterobacteriaceae* carrying *mcr-1* gene,⁸ will require more systemic national stewardship

interventions and follow-up studies. The success of the national CDI control program in England, as highlighted by the study of Dingle et al,¹ offers a good reference point and encouragement for China in its fight against antimicrobial resistance crisis, including CDI control. Meanwhile, as commented by Donskey,⁹ it is not clear if FQ restriction alone is sufficient enough to decrease CDI without enhanced infection control measures and cephalosporin restriction. More baseline research data and continued surveillance for *C. difficile* infections in China is urgently needed.

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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