

# Decreased Outpatient Fluoroquinolone Prescribing Using a Multimodal Antimicrobial Stewardship Initiative

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**Background.** Fluoroquinolones are antibiotics prescribed in the outpatient setting, though they have serious side effects. This study evaluates the impact of stewardship interventions on total and inappropriate prescribing of fluoroquinolones in outpatient settings in a large county hospital and health system.

**Methods.** In an effort to decrease inappropriate outpatient fluoroquinolone usage, a multimodal antimicrobial stewardship initiative was implemented in November 2016. Education regarding the risks, benefits, and appropriate uses of fluoroquinolones was provided to providers in different outpatient settings, Food and Drug Administration warnings were added to all oral fluoroquinolone orders, an outpatient order set for cystitis treatment was created, and fluoroquinolone susceptibilities were suppressed when appropriate. Charts from October 2016, 2017, and 2018 were retrospectively reviewed if the patient encounter occurred in primary care clinics, emergency departments, or urgent care centers within Parkland Health & Hospital System and a fluoroquinolone was prescribed. Inappropriate use was defined as a fluoroquinolone prescription for cystitis, bronchitis, or sinusitis in a patient without a history of *Pseudomonas aeruginosa* or multidrug-resistant organisms and without drug allergies that precluded use of other oral antibiotics.

**Results.** Total fluoroquinolone prescriptions per 1000 patient visits decreased significantly by 39% ( $P < .01$ ), and inappropriate fluoroquinolone use decreased from 53% to 34% ( $P < .01$ ). More than 90% of inappropriate fluoroquinolone prescriptions were given for cystitis, while bronchitis and sinusitis accounted for only 4.4% and 1.6% of inappropriate indications, respectively.

**Conclusion.** A multimodal stewardship initiative appears to effectively reduce both total and inappropriate outpatient fluoroquinolone prescriptions.

**Keywords.** antimicrobial stewardship; fluoroquinolone; outpatient stewardship.

Fluoroquinolones are the third most commonly prescribed class of antibiotics in the outpatient setting due to ease of dosing, expanded spectrum of activity, and favorable pharmacokinetics [1]. However, despite their numerous benefits, fluoroquinolones are not free of adverse event concerns. In July 2008, the Food and Drug Administration (FDA) added a Boxed Warning to all fluoroquinolones for increased risk of tendinitis and tendon rupture, which was subsequently updated in February 2011 to include risk of worsening myasthenia gravis [2]. Then, in August 2013, the FDA mandated updates to the labeling to warn providers and consumers about the potential for irreversible peripheral neuropathy [3]. In May 2016, the agency

enhanced warnings about disabling and potentially permanent side effects involving the tendons, muscles, joints, nerves, and central nervous system [4]. Finally, in June 2018, the FDA reported additional increases in the risk of mental health side effects, dysglycemias, aortic dissections, and rupture of aortic aneurysms related to fluoroquinolone use. Therefore, the FDA determined that the risks of serious side effects outweighed the benefits of use of these agents to treat mild infections including uncomplicated bronchitis, sinusitis, and cystitis and that fluoroquinolone use in such situations should be reserved for when no alternative treatment options exist [5].

In addition to potential adverse drug events, overuse of fluoroquinolones also significantly contributes to the development of antibiotic resistance. In the 2 decades since their development and introduction, fluoroquinolones have become increasingly utilized for the treatment of urinary tract infections (UTIs). Fluoroquinolone-resistant *Enterobacteriaceae* isolated from female outpatients and male inpatients with UTIs were almost nonexistent until the mid-1990s [6]. Resistance to ciprofloxacin in urinary isolates doubled from 1.2% in 1998 to 2.5% in 2001 and has reached prevalence rates as high as 30% in 2013 [6–9]. The impact of ciprofloxacin prescribing on the

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emergence of fluoroquinolone resistance in uropathogens is well documented, with fluoroquinolone resistance rising in tandem with increasing rates of fluoroquinolone prescriptions [10–12]. Furthermore, epidemiological evidence has identified a strong correlation between simultaneous fluoroquinolone use and the rise of extended-spectrum  $\beta$ -lactamase (ESBL) resistance, which suggests that fluoroquinolone use is independently associated with the acquisition of ESBL resistance genes [13, 14].

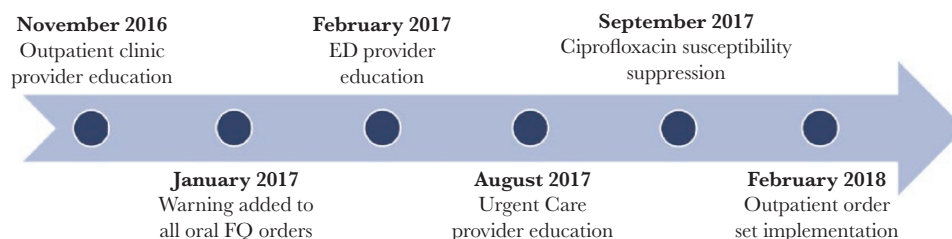
Finally, fluoroquinolones have been implicated as a major risk factor for the development of *Clostridioides difficile* infection by suppressing the normal bowel flora and allowing *C. difficile* to thrive. Therefore, restriction of fluoroquinolone usage is recommended by the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America clinical practice guidelines for the treatment of *C. difficile* infections as a method of preventing these infections [15, 16].

## METHODS

In November 2016, the Antimicrobial Stewardship Committee at Parkland Health & Hospital System (PHHS), a large public county hospital and health care system in Dallas, Texas, began a multimodal initiative to decrease outpatient usage of fluoroquinolones. Between this time and March 2018, the following 4 interventions were performed in the order listed as part of this multimodal initiative (Figure 1). Starting in November 2016, an infectious diseases (ID) pharmacist provided recurring education regarding the risks, benefits, and appropriate use of fluoroquinolones to the providers in the primary care clinics (PCCs) as part of their routinely scheduled quarterly forum. In addition, education was given by ID pharmacists and/or the medical director of stewardship, who is an ID physician, to advanced practice providers, residents, and attending physicians practicing in the emergency department (ED), urgent care centers (UCCs), and PCCs regarding antimicrobial stewardship in the outpatient setting (Table 1). In January 2017, FDA warnings were added to all oral fluoroquinolone orders as part of the order instructions in EPIC, the institution's electronic medical record (EMR) system (Supplementary Figure 1). Upon order entry by the provider, the warning appeared on

the top of the order window with instructions regarding prescribing practices. In September 2017, ciprofloxacin susceptibilities were suppressed from the provider-facing microbiology report if *Escherichia coli*, *Klebsiella* species, or *Proteus mirabilis* was isolated from the urine with documented susceptibility to third-generation cephalosporins. Finally, outpatient EPIC order sets were developed in late 2017 and went live in February 2018 to assist providers in the selection of guideline-recommended antibiotics for commonly encountered ambulatory infectious diseases such as urinary tract and skin and soft tissue infections (Supplementary Figure 2). The objective of this study was to evaluate the efficacy of the multimodal approach on total fluoroquinolone usage as well as percentage of inappropriate use in the ambulatory setting.

A retrospective chart review was performed on all outpatient visits during the months of October 2016, October 2017, and October 2018 in the PCCs, ED, and UCCs that resulted in a prescription for oral ciprofloxacin, moxifloxacin, or levofloxacin. The October 2016 cohort served as a baseline data set before the introduction of any stewardship interventions. The impact of multimodal stewardship interventions was measured by comparing the total number of outpatient fluoroquinolone prescriptions normalized per 1000 patient visits with the percentage of inappropriate indications. Inappropriate use was defined as an empiric fluoroquinolone prescription for cystitis, bronchitis, or sinusitis as documented during the patient's encounter in the setting of no documented history of infection with *Pseudomonas aeruginosa* or multidrug-resistant organisms (defined as a clinical pathogen with resistance to 3 or more classes of antibiotics) in the preceding 90 days or antibiotic allergies where a fluoroquinolone was the only oral treatment option. Of note, physician documentation of uncomplicated vs complicated cystitis was frequently unclear, so a decision was made to differentiate cystitis from pyelonephritis only. The results were analyzed using descriptive statistics. Categorical variables were compared between the 3 time periods using the chi-square test. Continuous variables were compared between the 3 time periods using the Kruskal-Wallis rank sum test because of non-normal data distributions. All statistical tests used  $<.05$  for statistical significance.



**Figure 1.** Stewardship intervention timeline. Abbreviations: ED, emergency department; FQ, fluoroquinolone.

**Table 1. Educational Sessions**

Forum Presented	Audience	Date Presented	Presenter
Primary care clinic provider quarterly forum	Primary care clinic providers	November 2016	ID pharmacist
Emergency department morning conference	ED residents and faculty providers	February 2017	ID physician
Population health quality leadership meeting	Primary care clinic providers	February 2017	ID pharmacist
Urgent care center morning conference	Urgent care advanced practice providers	August 2017	ID physician
Monthly morning conference for providers in the observation unit	Faculty & advanced practice providers	September 2017	ID physician
Weekly didactic session for family medicine residents	Family medicine residents	October 2017	ID physician
Advanced nurse practitioners monthly leadership meeting	Outpatient advanced practice providers	November 2017	ID physician
Internal medicine noon conference	Internal medicine residents	November 2017	ID physician
Primary care clinic quality leadership forum	Primary care clinic leadership, providers	February 2018	ID pharmacist & ID physician
Monthly urology advanced practice provider meeting	Urology advanced practice providers	March 2018	ID physician
Primary care clinic provider quarterly forum	Primary care clinic providers	May 2018	ID pharmacist & ID physician
Monthly clinic provider meeting	Primary care clinic providers	September 2018	ID pharmacist & ID physician

Abbreviation: ID, infectious disease.

## RESULTS

A total of 1033 outpatient fluoroquinolone prescriptions were reviewed and are described in Table 2. The median age of patients receiving fluoroquinolone prescriptions was slightly higher during the second time cohort compared with the first

and third cohorts ( $P < .01$ ). The prescriptions written during October 2018 were more evenly split between men and women when compared with the previous time periods ( $P = .01$ ). Ciprofloxacin was the predominant fluoroquinolone prescribed, constituting 89.6% of all fluoroquinolones prescribed in the

**Table 2. Patient Prescription Characteristics Across 3 Time Cohorts**

	October 2016 (n = 405)	October 2017 (n = 361)	October 2018 (n = 267)	PValue <sup>a</sup>
Total Fluoroquinolone Prescriptions				
Age, y	47 (36–57)	51 (38–60)	47 (34–57)	<.01
Female sex	246 (61)	221 (61)	133 (50)	<.01
Beta-lactam allergy	50 (12)	58 (16)	41 (15)	.30
Normalized fluoroquinolone prescriptions per 1000 outpatient visits	6.9	6.0	4.2	<.01
Fluoroquinolone type				
Ciprofloxacin	361 (89)	313 (87)	241 (90)	.01
Moxifloxacin	33 (8)	36 (10)	10 (4)	
Levofloxacin	11 (3)	12 (3)	16 (6)	
Indications for use				
Cystitis	212 (52)	174 (48)	92 (35)	<.01
Intraabdominal infection	65 (16)	62 (17)	52 (20)	
Pyelonephritis	35 (9)	36 (10)	34 (13)	
Lower respiratory tract infection	32 (8)	28 (8)	9 (3)	
Skin and soft tissue infection	21 (5)	20 (6)	28 (11)	
Bronchitis	4 (1)	13 (4)	5 (2)	
Sinusitis	3 (1)	3 (1)	2 (1)	
Other <sup>b</sup>	33 (8)	25 (7)	45 (17)	
Duration of therapy, d	7 (7–10)	7 (7–10)	7 (7–10)	.33
History of <i>P. aeruginosa</i> or MDRO	3 (1)	5 (1)	8 (3)	.07
Facility				
PCC	112 (28)	112 (31)	61 (23)	.09
ED	191 (47)	145 (40)	132 (49)	
UCC	102 (25)	104 (29)	74 (28)	
Inappropriate fluoroquinolone prescriptions	214 (53)	187 (52)	95 (36)	<.01

Data are presented as No. (%) or median (IQR).

Abbreviations: ED, emergency department; IQR, interquartile range; MDRO, multidrug-resistant organism; PCC, primary care clinic; UCC, urgent care center.

<sup>a</sup>No. (%) uses the chi-square test, and median (IQR) uses the Kruskal-Wallis test ( $P < .05$  is significant).

<sup>b</sup>Other: epididymitis (35), prostatitis (20), spontaneous bacterial peritonitis prophylaxis (8), otitis externa (7), upper respiratory tract infection (6), catheter-associated urinary tract infection (5), otitis media (3), musculoskeletal (2), pelvic inflammatory disease (2), *Helicobacter pylori* (2), corneal laceration (2), pelvic infection (1), balanitis (1), ruptured tympanic membrane (1), dental infection (1), orchitis (1), traveler's diarrhea (1), cystitis and intraabdominal infection (1), pancreatitis (1), urethritis (1).

outpatient setting across the 3 time periods ( $P = .01$ ). Patients with allergies to antibiotics or a recent history of multidrug-resistant organisms where a fluoroquinolone was the only antibiotic option constituted a similarly low percentage among the 3 time periods. The ED was the predominant prescribing site, with 468 of the 1033 prescriptions (47%) originating from this location. The proportion of indications for fluoroquinolone use changed significantly between the 3 time periods ( $P < .01$ ), although cystitis remained the predominant indication for fluoroquinolone use in all 3 time period cohorts. Additionally, >90% of prescriptions for this indication were deemed inappropriate.

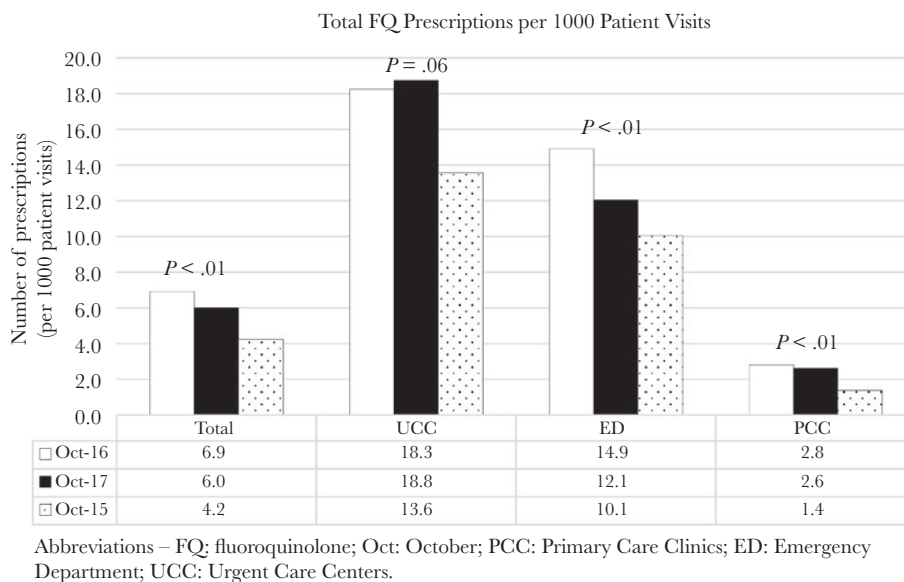
Despite 3 of the 4 antimicrobial stewardship interventions occurring between the first and second time periods, minimal change was seen in fluoroquinolone utilization. From October 2016 to October 2017, total fluoroquinolone use per 1000 patient visits decreased by 13% overall and did not differ by facility (Figure 2). Inappropriate fluoroquinolone use remained stagnant, with 53% of fluoroquinolone prescriptions considered inappropriate in October 2016 and 52% considered inappropriate in October 2017. Moreover, although the ED was the largest prescriber of fluoroquinolones, the PCCs had the highest inappropriate use as a percentage of total fluoroquinolone prescriptions (74%) (Table 3).

However, 2 years after interventions began and after implementation of all 4 interventions, total prescriptions per 1000 patient visits decreased significantly by 39% ( $P < .01$ ). The PCCs showed the greatest decrease in overall fluoroquinolone use at 51%, followed by the ED at 33%, both of which were statistically significant changes ( $P < .01$ ) (Figure 2). Only the UCCs did not show a significant decline in fluoroquinolone prescriptions, but

a trend toward decreased utilization was noted. Fluoroquinolone use specifically for cystitis decreased by 58% from 2016 to 2018. In addition, there was a statistically significant decrease in the proportion of inappropriate prescriptions from October 2016 to October 2018 (53% vs 36%;  $P < .01$ ). When comparing inappropriate use as a percentage of total fluoroquinolone use, the PCCs still had the highest percentage at 64%, without significant change, while the ED and UCCs experienced significant declines (Table 3).

## DISCUSSION

This study shows that a multimodal stewardship intervention can decrease the overall and inappropriate use of fluoroquinolones in the outpatient setting. The majority of fluoroquinolone prescriptions in our study were generated from the ED given the higher volume of patients seen there compared with the PCCs and UCCs; however, all areas showed a substantial decrease in fluoroquinolone use over the postintervention 2-year study period. Considerable reductions in inappropriate use were also observed from 2016 to 2018, with a change of >50% across all outpatient areas that may be attributed to continued education and antimicrobial stewardship efforts throughout the study period. Despite all interventions, cystitis remained the most frequent infection for which a fluoroquinolone was inappropriately prescribed. This may be due to providers' comfort with using fluoroquinolones for UTIs given historically lower rates of bacterial resistance to fluoroquinolones, lack of practice guideline updates for the treatment of cystitis, and the broad spectrum of empiric coverage and low cost of these antibiotics.



**Figure 2.** Total fluoroquinolone prescriptions by facility. Abbreviations: ED, emergency department; FQ, fluoroquinolone; Oct, October; PCC, primary care clinic; UCC, urgent care center.

**Table 3. Percentage of Inappropriate Fluoroquinolone Prescriptions by Facility Across 3 Time Cohorts**

Facility	October 2016, %	October 2017, %	October 2018, %	PValue <sup>a</sup>
Total	53	52	36	<.01
PCC	74	76	64	.22
ED	40	31	25	.01
UCC	53	55	31	<.01

Abbreviations: ED, emergency department; PCC, primary care clinic; UCC, urgent care center.

<sup>a</sup>Percentage uses the chi-square test ( $P < .05$  is significant).

Stewardship success using a variety of strategies has been previously reported in the literature. For example, in a Chinese study, multifaceted interventions, such as development of performance management strategies and advising on antibiotic prescriptions and training, were implemented by 13 clinical pharmacists, leading to a decrease in antibiotic prescriptions in both the outpatient and inpatient settings, improvement in resistance rates of *E. coli* and *P. aeruginosa* to fluoroquinolones, and reduction in incidence rates of methicillin-resistant *Staphylococcus aureus* [17]. Yu et al. noted that statewide tracking and reporting in New York State have increased the use of first-line agents (nitrofurantoin, trimethoprim/sulfamethoxazole, and fosfomycin) for the outpatient treatment of cystitis in males and females [18]. Changes in the prescription of antibiotics showed mixed results, except for fluoroquinolones, which had a reduction in usage in both sexes (females: 34.1% vs 29.1%;  $P < .0001$ ; males: 44% vs 39.3%;  $P < .0001$ ). In another study, implementation of a treatment selection tool and best-practice algorithm for the outpatient treatment of UTI led to a significant increase in the proportion of empiric orders that adhered to best practice (41 vs 66%;  $P < .001$ ), a change believed to be largely driven by decrease in ciprofloxacin usage (32% vs 11%) [19]. Similarly, a clinical decision status system interposed at the time of electronic prescriptions has decreased the proportion of unwarranted outpatient gatifloxacin and azithromycin prescriptions from 22% to 3.3% ( $P < .0001$ ) for the treatment of pneumonia, bronchitis, and sinusitis [20].

Research into the positive impacts of outpatient antimicrobial stewardship has become increasingly apparent and gained enough traction for the Centers for Disease Control and Prevention (CDC) to release 4 core elements in 2016 as a framework for effective outpatient antimicrobial stewardship: commitment, action for policy and practice, tracking and reporting, and education and expertise [21]. The CDC guidance comes after multiple studies and systematic reviews concluded that targeted interventions were successful in reducing inappropriate antimicrobial use in the ambulatory setting without negative clinical outcomes. However, the current evidence does not point toward any single intervention as more effective than another, but rather highlights that a combination of interventions aimed at multiple points in the clinical decision process is more effective than 1 intervention alone. The success of the

multimodal approach is likely due to the differences between health care institutions, EMRs, workflows, prescribing habits, and provider readiness to change [21, 22]. Arnold et al. evaluated 39 studies assessing various stewardship efforts at PCCs including active and passive (eg, printed educational materials) education for providers and patients, delayed prescriptions, audit and feedback, physician reminders via EMR clinical decision support tools, and multifaceted interventions. In this study, the authors found that the effectiveness of an intervention depends largely on the particular prescribing behaviors and barriers to change for the specific groups being targeted. Their conclusion centered on the notion that no single intervention is effective and that multifaceted interventions where education occurs at multiple levels (eg, provider and patient) may be the only means of potentially reducing inappropriate antibiotic prescribing and the incidence of antibiotic-resistant bacteria [23]. Similarly, multiple systematic reviews have come to the conclusion that broad-based multifaceted strategies with active clinician education at their core are the most effective means of reducing antibiotic prescribing without worsening patient outcomes [24–26]. These studies illustrate that any stewardship strategy can improve outpatient usage of antibiotics; however, targeting specific barriers from an institutional level to the patient level, coupled with continued active provider education, may provide the most benefit.

Our study evaluated the effectiveness of several interventions in outpatient antimicrobial stewardship targeting fluoroquinolone utilization, an area that is not well elucidated yet given the limited available data, which have shown mixed results. Dobson et al. recommended implementing multifaceted approaches to improve outpatient antibiotic utilization, and such interventions can include additional testing to aid in diagnostic certainty, audit and feedback, clinical decision support systems, delayed prescribing strategies, evidence-based guidelines, patient and/or prescriber education, and provider pledge to practice antibiotic stewardship [27]. In this study, 4 unique stewardship interventions were performed at several different time points. Because many interventions were done over a course of time, it is challenging to assess the impact of each intervention independently. Moreover, the selection of patients from 1 specific month each year may not be representative of general trends in use across the institution. The same month was used in each

year, though, to account for potential seasonal differences in prescribing. Furthermore, the public release of multiple FDA warnings against fluoroquinolone use during the study period may also have contributed to these results outside of the education provided by the stewardship team. Other explanations to account for differences between settings may be due to leadership willingness to embrace stewardship practices. For example, it was noted that the ED physician champion was more engaged and proactive with reinforcing stewardship principles and practices, which may have accounted for the more apparent decrease in inappropriate prescribing compared with the UCCs and PCCs. Also, more frequent provider turnover in the UCCs may have played a role in the slower onset of decreased inappropriate prescribing. Though we grouped the PCCs together, there are 10 different PCCs serving geographically distinct populations within the city and the surrounding suburbs, which presents another set of challenges with attempting to standardize practice and stewardship decisions.

The limitations of our data precluded an investigation into whether the decrease in fluoroquinolone use was a result of the prescription of alternative agents for cystitis or more appropriate identification of true infection vs asymptomatic bacteriuria. It is interesting that the first intervention period (October 2016 to October 2017) provided less robust shifts in fluoroquinolone prescribing than the time period with fewer interventions (October 2017 to October 2018). This may be attributed to the Diffusion of Innovation Theory, which explains how new ideas or behaviors (ie, prescribing nonfluoroquinolone antibiotics for cystitis) are adopted among a population (ie, prescribers) [28]. New ideas are adopted by only a minority of people initially, and only over time does the majority of the intended audience subscribe to the changes being recommended. Furthermore, as outpatient prescribing of antibiotics is largely empiric, with decisions having to be made before culture result availability, providers may prefer to initially prescribe more broad-spectrum drugs, though conscious decisions to balance antimicrobial stewardship and appropriate treatment are very complex. Perceptions of the importance of antibiotic resistance, negative anecdotal experience with withholding antibiotics or deviating from the norm, external pressure to reduce prescribing, and potential conflicts with patients can all influence a provider's clinical decision-making.

Additional areas for research include the effect of these interventions on the patient and microbiological and safety outcomes such as recurrence of infections, rates of hospitalization, antimicrobial susceptibility patterns, and antibiotic-related adverse events including *C. difficile* infections.

## CONCLUSIONS

A multimodal stewardship initiative effectively reduced the total number and proportion of inappropriate fluoroquinolone prescriptions written in 3 different outpatient settings.

Continued efforts to support the positive effects of these interventions are likely necessary to sustain or improve the rates of appropriate fluoroquinolone use in the outpatient setting.

## Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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