American Journal of Infection Control 47 (2019) 869–875

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major Article

Impact of syndrome-specific antimicrobial stewardship interventions on use of and resistance to fluoroquinolones: An interrupted time series analysis

Michelle T. Hecker MD [a,b], Andrea H. Son PharmD [c], Nina Naeger Murphy PharmD [c], Ajay K. Sethi PhD [d], Brigid M. Wilson PhD [e], Richard R. Watkins MD [f], Curtis J. Donskey MD [b,e,*]

[a] Division of Infectious Diseases, MetroHealth Medical Center, Cleveland, OH
[b] Department of Medicine, Case Western Reserve University School of Medicine, Cleveland, OH
[c] Department of Pharmacy, MetroHealth Medical Center, Cleveland, OH
[d] Department of Population Health Sciences, University of Wisconsin School of Medicine and Public Health, Madison, WI
[e] Geriatric Research, Education, and Clinical Center, Louis Stokes Cleveland Veterans Affairs Medical Center, Cleveland, OH
[f] Department of Medicine, Akron General Medical Center, Akron, OH

Key Words:
Pseudomonas aeruginosa
Clostridioides difficile
Urinary tract infection
Asymptomatic bacteriuria

Background: Fluoroquinolones are often prescribed unnecessarily and are an important risk factor for infection with fluoroquinolone-resistant gram-negative bacilli and *Clostridioides difficile*.

Methods: We conducted a quasi-experimental study to determine the impact of sequential syndrome-specific stewardship interventions on use of and resistance to fluoroquinolones in a tertiary care hospital. An initial 2-year intervention focused on reducing treatment of asymptomatic bacteriuria and ensuring concordance of urinary tract infection treatment with guidelines. A second 5-year intervention focused on limiting overuse of fluoroquinolones for health care–associated pneumonia in conjunction with a formal stewardship program. The primary outcomes were fluoroquinolone use and changes in use over time analyzed by segmented regression analysis.

Results: The asymptomatic bacteriuria and urinary tract infection intervention resulted in a significant reduction in fluoroquinolone use, with a significant change from an increasing to a decreasing rate of use (change in slope of quarterly defined daily doses/1,000 patient days −15.3, $P < .01$). The health care–associated pneumonia intervention resulted in a continued significant reduction in fluoroquinolone use (rate ratio = 0.68, $P < .01$). During the interventions, fluoroquinolone susceptibility increased significantly in *Pseudomonas aeruginosa*, but not in *Escherichia coli*, *Klebsiella* spp., or *C difficile*.

Conclusions: Antimicrobial stewardship interventions focused on specific syndromes may be effective in reducing fluoroquinolone use. In our hospital, reduction in fluoroquinolone use resulted in increased fluoroquinolone susceptibility in *P aeruginosa*, but not other Enterobacteriaceae or *C difficile*.

Inappropriate use of antimicrobials is a common and serious public health concern. Fluoroquinolones are an attractive target for stewardship interventions because they are often prescribed unnecessarily and they are associated with colonization and infection with multidrug-resistant pathogens and *Clostridioides difficile*.[1-2] Previous studies suggest that fluoroquinolone restriction may be effective in improving gram-negative fluoroquinolone susceptibility rates.[3] Moreover, recent reports suggest that fluoroquinolone restriction may be effective as a control measure for *C difficile* infection (CDI), in part through reduction in infections due to fluoroquinolone-resistant *C difficile* strains.[3-10] In many of these studies, fluoroquinolone use was reduced through formulary restrictions or revised fluoroquinolone use guidelines, often over relatively short time periods and with resultant increases in use of other antibiotic classes.

* Address correspondence to Curtis J. Donskey, MD, Geriatric Research, Education, and Clinical Center, Louis Stokes Cleveland Veterans Affairs Medical Center, 10701 East Blvd, Cleveland, OH 44106.
E-mail address: Curtis.Donskey@va.gov (C.J. Donskey).

Funding/support: This work was supported by a grant from the Centers for Disease Control and Prevention (R01 CI000614-01 to C.J.D.) and by the Department of Veterans Affairs.

Conflicts of interest: C.J.D has received research grants from Pfizer, GOJO, Clorox, Professional Disposables Internationa, Boehringer Laboratories, and Avery Dennison. All other authors report no conflicts of interest relevant to this article.

https://doi.org/10.1016/j.ajic.2019.01.026

Recent guidelines recommend that antimicrobial stewardship programs implement syndrome-specific interventions to improve antibiotic use and clinical outcomes.[11,12] Urinary tract infections (UTI) and respiratory tract infections, particularly health care–associated pneumonia (HCAP), are common syndromes that offer a great opportunity to address the problem of inappropriate fluoroquinolone use.[13-14] Fluoroquinolone are often prescribed for these syndromes when alternative antibiotics may be more appropriate.[15-19] Moreover, many fluoroquinolone regimens prescribed for presumed UTIs are unnecessary because they are prescribed for asymptomatic bacteriuria (ASB) that does not require treatment.[20-26] The fluoroquinolone component of "triple antibiotic therapy" regimens for presumed HCAP is also often unnecessary because the diagnosis of pneumonia is incorrect or the diagnosis of pneumonia is incorrectly classified as HCAP based on the 2005 American Thoracic Society and Infectious Diseases Society of America guidelines[27] (authors' unpublished data). In addition, many patients defined as having HCAP based on the wide range of health care contact criteria listed in the 2005 guidelines may not be at high risk for multidrug-resistant pathogens that would require such broad empiric triple antibiotic therapy.[28-29] Finally, the duration of therapy prescribed for UTIs is often longer than necessary[17,19] and the duration of the fluoroquinolone component of "triple antibiotic therapy" regimens for HCAP is often longer than necessary owing to failures to de-escalate therapy at 48-72 hours.[30]

Here, we report the impact of an initial intervention to reduce treatment of ASB and ensure concordance of UTI treatment with guidelines followed by a formal stewardship intervention that included a focus on reducing use of fluoroquinolones for treatment of HCAP. The primary outcome was the impact of the interventions on fluoroquinolone use. A secondary outcome was susceptibility of select gram-negative bacilli and *C difficile* to fluoroquinolones.

METHODS

Study design and setting

We conducted a quasi-experimental study of antibiotic use and susceptibility from 2008 through 2016 at a 700-bed academic urban level 1 trauma center. From January 2008 through December 2009, baseline data were collected on antibiotic use as well as appropriateness of laboratory testing and antibiotic use for UTI syndromes. An initial 2-year intervention focused primarily on reducing treatment of ASB and ensuring concordance of UTI treatment (appropriate antimicrobial choice and duration) with guidelines.[31-33] All provider documented UTI syndromes were targeted for stewardship intervention including cystitis, pyelonephritis, complicated UTI, and ASB. For the purpose of making treatment recommendations, cystitis and pyelonephritis were defined based on proposed classification systems in the literature,[34,35] whereas complicated UTI and ASB were defined based on guideline definitions.[31,33] A second 5-year intervention focused on reducing use of fluoroquinolones for treatment of provider documented cases of HCAP in conjunction with a formal antimicrobial stewardship program. Recommendations for therapy were based on the 2005 guideline definition of HCAP and on local and emerging data regarding individual patient risk for multidrug-resistant organisms.[27-29] Both ciprofloxacin (antipseudomonal fluoroquinolone) and moxifloxacin (fluoroquinolone without significant antipseudomonal activity) were on formulary. Infection prevention interventions were monitored during the study. The study protocol was approved by the hospital's institutional review board.

ASB and UTI-focused stewardship intervention (intervention 1)

From January 2010 through December 2011, an intervention was conducted that included education, modifications of the electronic medical record (EMR), and audit and feedback. Grand rounds and small group educational sessions were provided to staff physicians, nurse practitioners, medical residents, and medical students in all departments of the medical center. Educational sessions included data collected from the baseline evaluation as well as information on diagnosis and treatment of UTI, ASB, and appropriate use of urinary catheters.

EMR interventions included changing urine culture orders such that previous urine culture results and links to ASB, uncomplicated UTI, and complicated UTI guidelines were displayed within the order.[31-33] Order sets on management of UTIs were created for the emergency department (ED) and for other services. The ED implemented a financial incentive for use of the ED UTI order set. Finally, an order for placement of indwelling urinary catheters was created that required selection of an indication based on a list of appropriate indications. A daily alert was also created that required providers to document continued need for the catheter.

Audit and feedback interventions were implemented in 4 areas that had frequent nonadherence to guidelines. From July to August 2010, urine cultures ordered in internal medicine, family medicine, and rehabilitation inpatient units were reviewed and feedback was provided on the appropriateness of lab testing, UTI therapy, and urinary catheter use. From December 2010 through March 2011, all fluoroquinolone prescriptions and urine cultures ordered in the medical intensive care and medical step-down units were reviewed and feedback was provided regarding appropriateness of fluoroquinolone use and avoidance of antibiotic therapy for ASB. From June through July 2011, urine cultures ordered in the outpatient setting were reviewed and feedback was provided regarding appropriateness of urine cultures and treatment. From November 2011 through January 2012, charts of female patients seen in the ED with a UTI diagnosis code were reviewed and feedback was provided on appropriateness of urine cultures and treatment.[19]

HCAP intervention in conjunction with a formal antimicrobial stewardship program (intervention 2)

From January 2012 through December 2016, a formal antimicrobial stewardship program was implemented. Audit and feedback and education were the primary strategies used by the stewardship team. One goal of the stewardship team was to limit overuse of fluoroquinolones, primarily for HCAP. Approximately 80% of recommendations related to fluoroquinolone use during this intervention period were to stop the fluoroquinolone component of triple antibiotic therapy prescribed for HCAP. The formal stewardship program also focused on ensuring appropriate therapy for gram-positive bacteremia and CDI, and limiting overuse of carbapenems, especially antipseudomonal carbapenems, and antibiotics with activity against methicillin-resistant *Staphylococcus aureus*.

Outcomes

The primary outcome measure was inpatient fluoroquinolone use and changes in fluoroquinolone use over time in the baseline versus intervention periods. Secondary outcomes included fluoroquinolone susceptibility in select gram-negative bacilli (*Pseudomonas aeruginosa*, *Escherichia coli,* and *Klebsiella* spp) and *C difficile*, trends in total inpatient antibiotic use (ie, all intravenous and oral antibacterials excluding topical agents) and trends in use of other antibiotics including some commonly used alternatives to fluoroquinolones (piperacillin-tazobactam, ceftriaxone, trimethoprim-sulfamethoxazole, nitrofurantoin, intravenous vancomycin, and carbapenems), and the incidence of health care facility-onset CDI.[36]

Microbiology

Antibiotic susceptibility data for the gram-negative bacilli were obtained from the hospital's yearly antibiogram that included both inpatient and outpatient isolates from any source. Only the first isolate per patient per year was included. Susceptibility testing was determined with the VITEK 2 system (bioMérieux, Marcy-l'Étoile, France). Intermediately susceptible isolates were considered resistant. For *C difficile*, 20 to 30 consecutive stool specimens that tested positive for toxigenic *C difficile* in the clinical microbiology laboratory were collected at multiple time points during the study. The stool specimens were cultured for toxigenic *C difficile* and isolates recovered were tested for binary toxin, *tcd*C deletion, and fluoroquinolone susceptibility as previously described.[37]

Data analysis

Data on patient charges for antibiotic use (except for carbapenems and total antibiotics) were available from quarter 1, 2008 through quarter 4, 2011. Antibiotic days of therapy per 1,000 patient days from the EMR (including carbapenems and total antibiotics) were available from quarter 2, 2009 through quarter 4, 2016. To provide a sufficient number of baseline time points for interrupted time series analyses, we used data on patient charges for antibiotic use, converted to defined daily doses per 1,000 patient days, for the comparison of baseline and ASB/UTI intervention periods. Antibiotic days of therapy per 1,000 patient days from the EMR were used for the comparison of ASB/UTI versus HCAP intervention periods.

The primary outcomes of fluoroquinolone use and changes in fluoroquinolone use over time were analyzed using the Poisson tests of rates and segmented regression analysis, respectively. The 4 tests of the primary endpoints were adjusted using a Bonferroni correction. The χ^2 tests, with simulated *P* values in instances of small cell counts, were used to assess differences in the rate of fluoroquinolone susceptibility across periods (baseline, intervention 1, intervention 2). Changes in fluoroquinolone susceptibility were assessed separately for *P aeruginosa*, *E coli, Klebsiella* spp, and *C difficile*. Spearman rank correlations were used to assess associations between yearly inpatient fluoroquinolone use and yearly susceptibility rates in these organisms from 2009 to 2016, and between quarterly inpatient fluoroquinolone use and quarterly incidence of CDI. Changes in use of additional inpatient antibiotics over time were examined across the intervention periods and analyzed using segmented regression analysis. All *P* values from analyses of secondary endpoints are presented without adjustment. All analyses were performed using R software 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Figure 1 shows the impact of the ASB and UTI intervention on use of fluoroquinolones, ceftriaxone, piperacillin/tazobactam, and intravenous vancomycin. The intervention resulted in a significant reduction in total inpatient fluoroquinolone use (rate ratio = 0.91; adjusted $P < .01$) with a significant change from an increasing to a decreasing rate of use (change in slope of quarterly defined daily doses/1,000 patient days = −21.3; adjusted $P < .01$). The reduction was mainly attributable to reduced ciprofloxacin use (Fig 1A). The ASB and UTI intervention was also associated with a significant change from an increasing to a decreasing rate of piperacillin/tazobactam use (change in slope of quarterly charge defined daily doses/1,000 patient days = −22.7; $P < .01$) and nitrofurantoin use (change in slope of quarterly charge defined daily doses/1,000 patient days = −1.53; $P < .05$). There were no significant changes in the slopes of use of ceftriaxone, intravenous vancomycin, or trimethoprim/sulfamethoxazole. Data for trimethoprim/sulfamethoxazole and nitrofurantoin are not shown as numbers were small.

Figure 2 shows the impact of the HCAP intervention in conjunction with implementation of a formal stewardship program on antibiotic use. The intervention resulted in a continued significant reduction in fluoroquinolone use (rate ratio = 0.68; adjusted $P < .01$), despite a significant slowing in the rate of decrease of fluoroquinolone use (change in slope of quarterly EMR days of therapy/1,000 patient days = 1.87; adjusted $P < .05$) (Fig 2A). There were no significant changes in the slopes of use for piperacillin/tazobactam, ceftriaxone, carbapenems, intravenous vancomycin, trimethoprim/sulfamethoxazole, or nitrofurantoin. Total antibiotic use decreased during the interventions (rate ratio = 0.88; $P < .01$, but there was no statistically significant change in slope of use between interventions 1 and 2) (Fig 2B).

A total of 5,397 isolates of *P aeruginosa*, 36,533 isolates of *E coli*, and 9,031 isolates of *Klebsiella* spp were included in the antibiogram data during the study. Figure 3 shows the fluoroquinolone susceptibility of selected gram-negative bacilli during the study. We observed a significant negative correlation between inpatient fluoroquinolone use and fluoroquinolone susceptibility in *P aeruginosa* (Spearman's rho = −0.98; $P < .01$), but not in other analyzed gram-negative bacilli (*E coli* and *Klebsiella* spp). The fluoroquinolone susceptibility rate in *P aeruginosa* differed across periods ($P < .01$), with a marked increase from 75% and 76% in the baseline and intervention 1 periods, respectively, to 84% during intervention 2. There was no change in fluoroquinolone susceptibility in *E coli* (84% baseline vs 85% after the interventions). In *Klebsiella* spp, the fluoroquinolone susceptibility rate differed across periods ($P < .01$) with the lowest susceptibility rate observed during intervention 1.

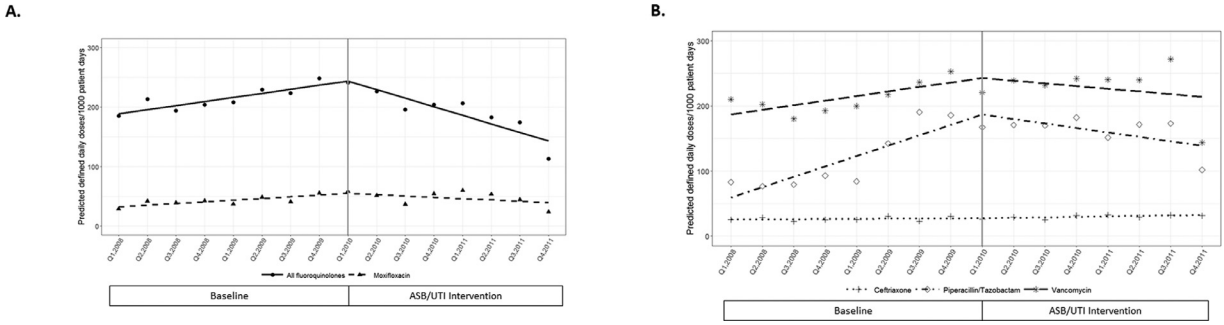

Fig 1. Changes in inpatient use of fluoroquinolones (A) and ceftriaxone, piperacillin/tazobactam, and intravenous vancomycin (B) associated with a 2-year intervention focused on reducing treatment of ASB and ensuring concordance of UTI treatment with guidelines. Fluoroquinolones included ciprofloxacin and moxifloxacin. Data on patient charges for antibiotic use were used to calculate predicted defined daily doses per 1,000 patient days for the baseline and intervention periods. *ASB*, asymptomatic bacteriuria; *UTI*, urinary tract infection.

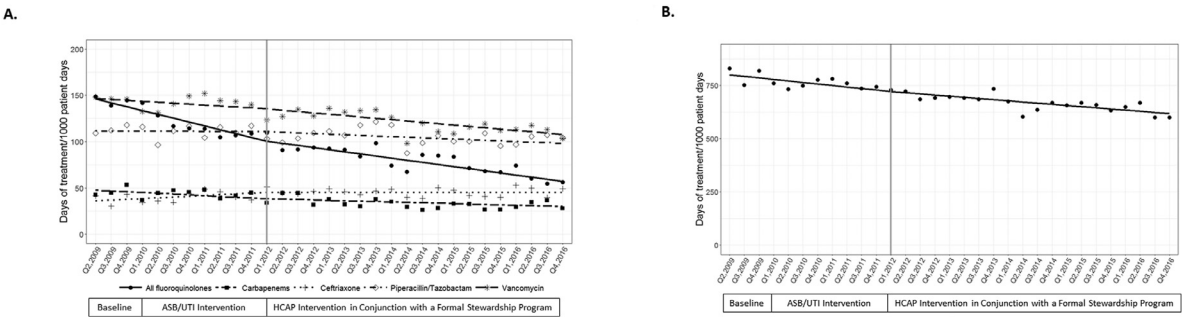

Fig 2. Changes in use of fluoroquinolones, carbapenems, ceftriaxone, piperacillin/tazobactam, and intravenous vancomycin (A) and in total antibiotic use (B) associated with a 5-year intervention focused on reducing inappropriate use of fluoroquinolones for treatment of HCAP in conjunction with implementation of a formal antimicrobial stewardship program. Carbapenems on formulary included imipenem-cilastatin, meropenem, and ertapenem. *ASB*, asymptomatic bacteriuria; *HCAP*, health care–associated pneumonia; *UTI*, urinary tract infection.

As shown in Figure 4, there was no significant decrease in the incidence of health care facility-onset CDI during the intervention periods ($P > .5$). A total of 143 *C difficile* isolates were tested for strain type and fluoroquinolone susceptibility during the study. There was no observed change in the percentages of *C difficile* isolates that were epidemic NAP1/027/BI strains, nor in fluoroquinolone susceptibility of *C difficile* (53% baseline vs 44% after the interventions). All NAP1/027/BI strains were resistant to moxifloxacin, whereas none of the non-NAP1/027/BI strains were resistant to moxifloxacin. Infection prevention interventions during the study included a hand hygiene intervention in 2010 that was associated with improved compliance with use of alcohol hand sanitizer and an environmental disinfection intervention beginning in November 2013, that resulted in improved thoroughness of cleaning and reduced recovery of *C difficile* from CDI rooms after cleaning.[38]

DISCUSSION

We found that a stewardship intervention focused on reducing treatment of ASB and ensuring concordance of UTI treatment with guidelines resulted in a significant reduction in use of fluoroquinolones. A further reduction was achieved with a stewardship intervention focused on reducing inappropriate use of fluoroquinolones for HCAP in conjunction with a formal antimicrobial stewardship program. The magnitude of the reduction in fluoroquinolone use is consistent with our previous report that 39% of all days of fluoroquinolone therapy in our facility were unnecessary.[18] The reduction in inpatient fluoroquinolone use was associated with an increase in fluoroquinolone susceptibility in *P aeruginosa*, but not in other gram-negative bacilli or *C difficile* and was not associated

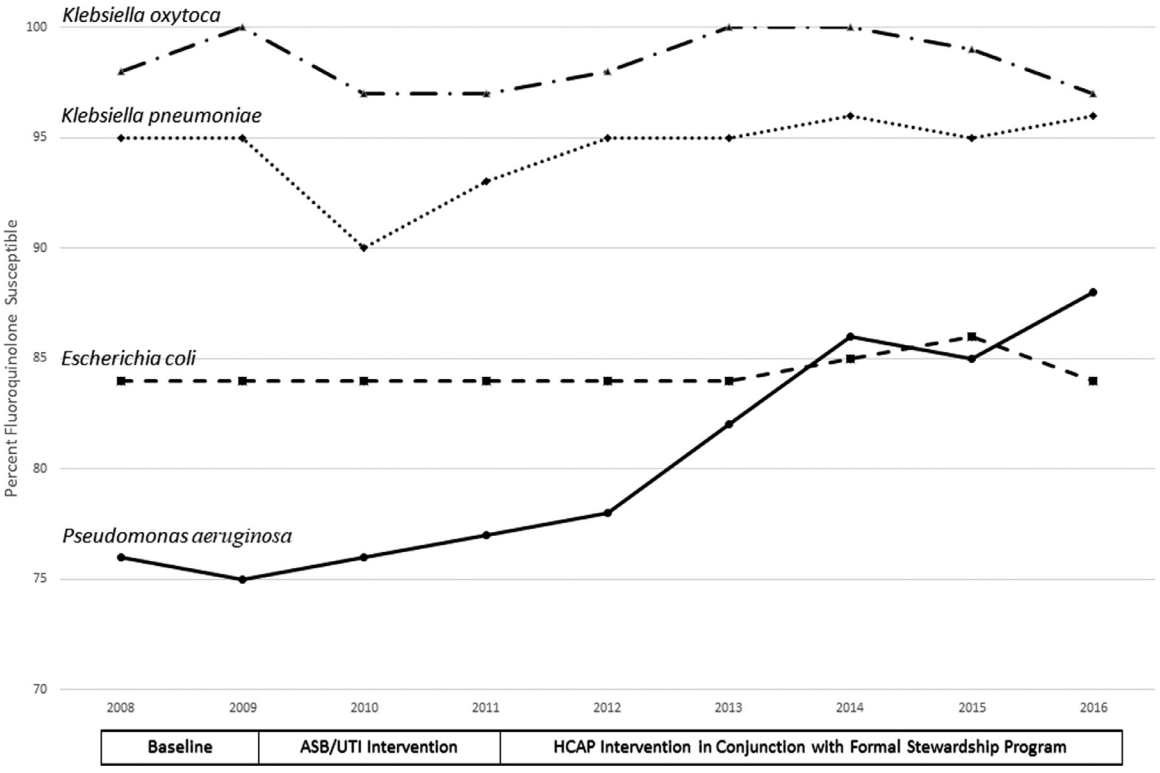

Fig 3. Fluoroquinolone susceptibility of selected gram-negative bacilli during sequential interventions to reduce unnecessary use of fluoroquinolones. The first 2-year intervention focused on reducing unnecessary use of fluoroquinolones for treatment of UTIs and ASB. The second 5-year intervention focused on reducing unnecessary use of fluoroquinolones for treatment of HCAP in conjunction with a formal antimicrobial stewardship program. *ASB*, asymptomatic bacteriuria; *HCAP*, health care–associated pneumonia; *UTI*, urinary tract infection.

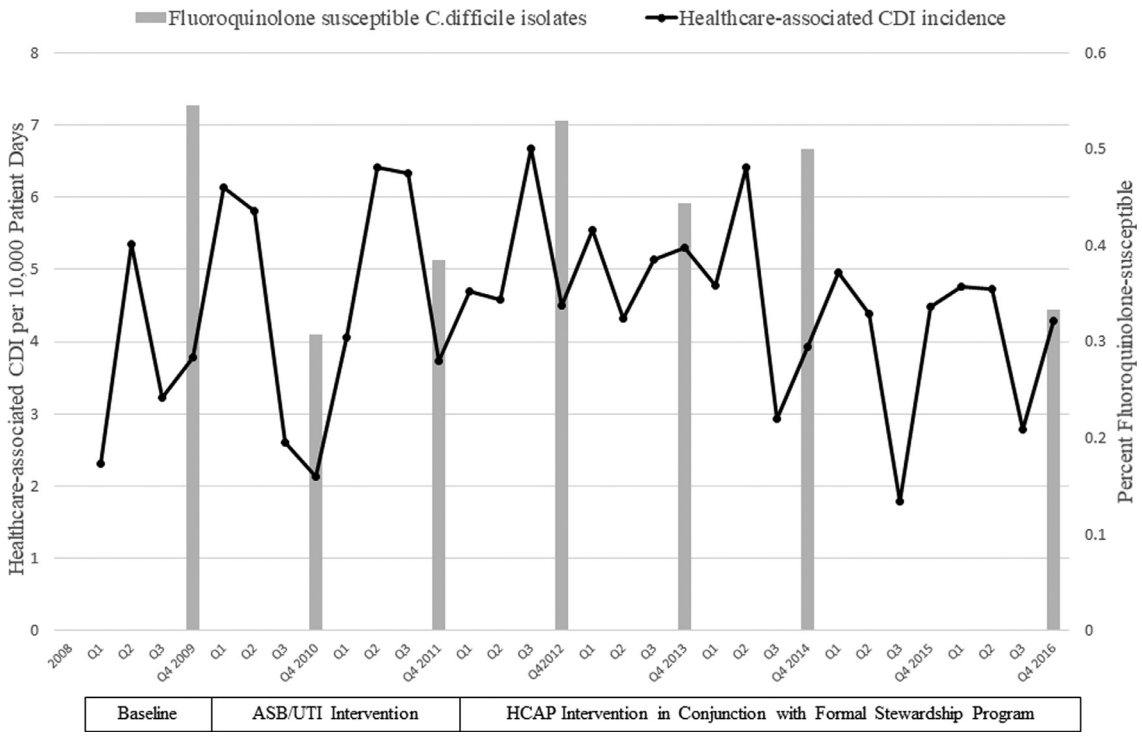

Fig 4. Changes in the incidence of health care facility-onset CDI and in the percentage of *C difficile* isolates susceptible to fluoroquinolones during sequential interventions to reduce unnecessary use of fluoroquinolones. The first 2-year intervention focused on reducing unnecessary use of fluoroquinolones for treatment of UTI and ASB. The second 5-year intervention focused on reducing unnecessary use of fluoroquinolones for treatment of HCAP in conjunction with a formal antimicrobial stewardship program. *ASB*, asymptomatic bacteriuria; *CDI*, *Clostridioides difficile* infection; *HCAP*, health care–associated pneumonia; *UTI*, urinary tract infection.

with a decrease in the incidence of health care facility-associated CDI.

Our findings demonstrate that interventions focused on specific syndromes can have a substantial impact in reducing overuse of fluoroquinolone and may contribute to reductions in total antibiotic therapy. Although one goal of the ASB and UTI intervention was to substitute alternative agents for fluoroquinolones for treatment of symptomatic UTI in accordance with current guidelines (eg, use of nitrofurantoin rather than ciprofloxacin for uncomplicated cystitis), the major goal of the intervention was to reduce unnecessary fluoroquinolone use by stopping treatment of ASB and preventing longer than recommended durations of therapy for symptomatic UTI. This was based on our previous finding that a substantial percentage of unnecessary antibiotic use was owing to longer than necessary treatment durations and treatment of colonizing or contaminating microorganisms,[18,23] and was demonstrated in one of our ASB and UTI-focused initiatives.[19] The subsequent intervention also focused on stopping unnecessary fluoroquinolone therapy, mostly for patients with presumed HCAP. Thus, during both intervention periods, we sought to avoid the "squeezing the balloon" phenomenon, in which reductions in use of a targeted antibiotic class result in increases in use of alternative antibiotic classes.[39] In fact, changes in use over time for the additional antibiotics analyzed either remained flat or decreased, possibly related to providers' general acceptance of antimicrobial stewardship principles for other syndromes as well.

Our results are consistent with previous studies that demonstrated increased fluoroquinolone susceptibility in clinical isolates of *P aeruginosa* with reductions in fluoroquinolone use.[3] In contrast to several previous studies, we did not demonstrate the same improvements in fluoroquinolone susceptibility in *E coli* and *Klebsiella* spp. Whether and how quickly rates of resistance to a particular antibiotic can be reversed in a particular organism when use of that antibiotic is reduced is complex.[40] It has been suggested that the least naturally sensitive species acquire higher levels of resistance more rapidly and may become susceptible more rapidly with antibiotic restriction.[41] Thus, it is plausible that *P aeruginosa* might exhibit more rapid improvements in fluoroquinolone susceptibility after reduction in fluoroquinolone use because of reduced intrinsic susceptibility to fluoroquinolones in comparison to Enterobacteriaceae such as *E coli* or *Klebsiella* spp. The degree to which preferentially decreasing antipseudomonal fluoroquinolones as well as antipseudomonal carbapenems contributed to the different results observed for *P aeruginosa* as compared to *E coli* and *Klebsiella* spp is unclear.

Improvements in susceptibility may also be more likely when the microorganisms evaluated are collected in the same ecologic setting in which the antibiotic of interest is decreased. In many of the previous studies, isolates were obtained from the same ecologic setting (eg, hospital unit or geographic region) in which the reduction in fluoroquinolone use occurred. Our interventions primarily targeted inpatient fluoroquinolone use, but measured fluoroquinolone susceptibility from our yearly hospital antibiogram that included isolates from both the inpatient and outpatient setting. We did not have access to separate inpatient and outpatient antibiogram data during the entire study; however, based on data from the last 2 study years, 62% of *P aeruginosa,* but only 30% of *E coli*, isolates represented in the antibiogram were collected in the inpatient setting. Thus, for *P aeruginosa,* but not for *E coli*, the isolates tested for susceptibility were mostly from the same ecologic setting (inpatient setting), in which the greatest reduction in fluoroquinolone use occurred. In addition, fluoroquinolone susceptibility rates at the beginning of the study were higher for *E coli* and *Klebsiella* spp as compared to *P aeruginosa*, leaving less room for significant improvement.

The incidence of health care facility-onset CDI did not decrease significantly during the study nor was there a significant decrease in the proportion of isolates that were moxifloxacin-resistant BI/NAP1/027 epidemic strains. This is in contrast to findings from several

recent studies that have suggested fluoroquinolone restriction may be a useful CDI control measure, particularly in settings with a high proportion of infections due to fluoroquinolone-resistant strains of *C difficile*.[4-10] One potential explanation for this discrepancy might be that the United Kingdom intervention occurred nationwide. It is plausible that single hospital interventions might be less effective than regional or national efforts because of frequent inter-facility sharing of patients. In addition, many of the previous reports of reductions in CDI with fluoroquinolone restriction occurred in outbreak settings, whereas our intervention was implemented in a nonoutbreak setting with relatively low baseline rates of CDI.

Our study has some limitations. The intervention was conducted in 1 hospital and was quasi-experimental in design. Thus, we cannot exclude the possibility that factors other than the interventions reduced fluoroquinolone prescribing during the period of the study. Future studies are needed in other settings and with other hospitals as controls. Antibiotic susceptibility data were obtained from the medical center's antibiogram data, representing only the first isolate per patient per year, rather than all clinical isolates. This was the only consistent source of susceptibility data over the entire course of the study. It is also a practical measure of antibiotic susceptibility for stewardship programs. We used intermittent point-prevalence surveys to assess fluoroquinolone susceptibility of *C difficile* isolates and the percentage of infecting isolates that were BI/027/NAP1 strains. Thus, we cannot exclude the possibility that results would have differed if more intensive surveillance had been conducted. There is a need for randomized trials to evaluate fluoroquinolone restriction as a control measure for CDI.

CONCLUSIONS

Our study adds to the existing antimicrobial stewardship literature by demonstrating that interventions focused on specific syndromes including ASB/UTI and HCAP can result in significant reductions in fluoroquinolone use. The reduction in inpatient fluoroquinolone use was associated with an increase in fluoroquinolone susceptibility in *P aeruginosa*, but not other Enterobacteriaceae or *C difficile*.

Acknowledgments

The authors would like to thank members of the STOMP UTI (Strategies to Optimize Management and Prevention of UTI) Study Group and the clinical and administrative staff of the study hospital.

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