

Original Article

Acceptability and effectiveness of antimicrobial stewardship implementation strategies on fluoroquinolone prescribing

Katie J. Suda PharmD, MS, FCCP^{1,2}, Gosia S. Clore MPH^{3,4}, Charlesnika T. Evans PhD, MPH^{5,6}, Heather Schacht Reisinger PhD^{3,4}, Ibuola Kale MPH⁵, Kelly Echevarria PharmD⁷, Stacey Hockett Sherlock MAA^{3,4}, Eli N. Perencevich MD^{3,4} and Matthew Bidwell Goetz MD^{8,9} for the VA-CDC Practice-Based Research Network

¹Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania, ²University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, ³Department of Medicine, Carver College of Medicine, University of Iowa, Iowa City, Iowa, ⁴Center for Access and Delivery Research and Evaluation, Iowa City Veterans' Affairs (VA) Health Care System, Iowa City, Iowa, ⁵Center of Innovation for Complex Chronic Healthcare, Edward Hines VA Hospital, Hines, Illinois, ⁶Northwestern University Feinberg School of Medicine, Department of Preventive Medicine; Center for Health Services and Outcomes Research, Chicago, Illinois, ⁷Pharmacy Benefits Management, Department of Veterans' Affairs, San Antonio, Texas, ⁸Department of Infectious Diseases, VA Greater Los Angeles Healthcare System, Los Angeles, California and ⁹Department of Medicine, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, California

Abstract

Objective: To assess the effectiveness and acceptability of antimicrobial stewardship-focused implementation strategies on inpatient fluoroquinolones.

Methods: Stewardship champions at 15 hospitals were surveyed regarding the use and acceptability of strategies to improve fluoroquinolone prescribing. Antibiotic days of therapy (DOT) per 1,000 days present (DP) for sites with and without prospective audit and feedback (PAF) and/or prior approval were compared.

Results: Among all of the sites, 60% had PAF or prior approval implemented for fluoroquinolones. Compared to sites using neither strategy (64.2 ± 34.4 DOT/DP), fluoroquinolone prescribing rates were lower for sites that employed PAF and/or prior approval (35.5 ± 9.8 ; $P = .03$) and decreased from 2017 to 2018 ($P < .001$). This decrease occurred without an increase in advanced-generation cephalosporins. Total antibiotic rates were 13% lower for sites with PAF and/or prior approval, but this difference did not reach statistical significance ($P = .20$). Sites reporting that PAF and/or prior approval were “completely” accepted had lower fluoroquinolone rates than sites where it was “moderately” accepted (34.2 ± 5.7 vs 48.7 ± 4.5 ; $P < .01$). Sites reported that clinical pathways and/or local guidelines (93%), prior approval (93%), and order forms (80%) “would” or “may” be effective in improving fluoroquinolone use. Although most sites (73%) indicated that requiring infectious disease consults would or may be effective in improving fluoroquinolones, 87% perceived implementation to be difficult.

Conclusions: PAF and prior approval implementation strategies focused on fluoroquinolones were associated with significantly lower fluoroquinolone prescribing rates and nonsignificant decreases in total antibiotic use, suggesting limited evidence for class substitution. The association of acceptability of strategies with lower rates highlights the importance of culture. These results may indicate increased acceptability of implementation strategies and/or sensitivity to FDA warnings.

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The US Food and Drug Administration (FDA) has issued multiple safety communications on the fluoroquinolone class. These statements recommend use of alternative antibiotics for common infections because adverse events associated with the fluoroquinolone class outweigh potential benefits in some situations.¹ FDA safety warnings for the fluoroquinolones include aortic dissection, central nervous system effects, glucose homeostasis disturbances,

QT prolongation and disabling side effects involving tendons, muscles, joints, nerves, and the central nervous system. These side effects can occur hours to weeks after exposure to fluoroquinolones and may potentially be permanent.^{1–7} An FDA advisory panel recommended avoidance of fluoroquinolones unless suitable alternatives were not available for acute bacterial sinusitis, acute chronic obstructive pulmonary disease exacerbations, and uncomplicated urinary tract infections.⁸ Despite these FDA warnings, fluoroquinolones continue to be prescribed and remain a high priority for stewardship.

Moreover, fluoroquinolone use has been associated with bacterial resistance and *Clostridioides difficile* infection (CDI).^{9–13} The most modifiable risk factor to decrease resistance and CDI is

Author for correspondence: Dr Katie J. Suda, E-mail: ksuda@pitt.edu. Or Dr Matthew B. Goetz, E-mail: matthew.goetz@va.gov

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antibiotic use. A meta-analysis found that stewardship interventions directed at reducing the use of fluoroquinolones and cephalosporins had a protective effect against the development of CDI (pooled risk ratio, 0.48; 95% CI, 0.38–0.62).¹⁴ Prospective audit with intervention and feedback (PAF) and prior approval are core antibiotic stewardship implementation strategies. These stewardship strategies have been shown to be effective in decreasing antibiotic prescribing and are recommended by the Centers for Disease Control and Prevention (CDC), the Infectious Diseases Society of America (IDSA), and the Society for Healthcare Epidemiology of America (SHEA).^{15–18} Implementation of such policies has been associated with decreased rates of CDI, extended-spectrum β -lactamase (ESBL)-producing bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA), and antimicrobial costs without adversely affecting hospital length of stay and survival.^{18–24}

Despite these successes, prior approval is not often implemented due to concerns about loss of prescriber autonomy, potential delays in treatment, adverse effects on professional culture, and the consequences of replacing the use of one antibiotic or antibiotic class with another.^{18,25,26} Furthermore, the effectiveness of prior approval depends on the manner of enforcement, expertise of the approver, enforcement policies during evenings and weekends, and permitting providers to self-approve the use of formulary restricted antimicrobials if specified criteria are satisfied (eg, multidrug resistance).²⁰ These concerns have led many facilities to instead implement prospective audit and feedback (PAF) programs, under which antibiotics can be freely initiated but in which there is a postprescriptive review within 24–72 hours of prescribing. During postprescriptive review, alternative recommendations for antimicrobials are issued; compliance with such recommendations is voluntary.¹⁸ PAF programs have been shown to improve outcomes in general medical-surgical units and intensive care units without adversely affecting patient outcomes.¹⁸ The disadvantages of PAF include the following: (1) implementation is labor intensive, (2) providers may be reluctant to change therapy, (3) specialized technology support may be needed, and (4) success is dependent on the presence of dedicated personnel and the method used to communicate recommendations to prescribers.^{18,27}

Few studies have explicitly assessed the impact of prior approval and PAF implementation strategies on antibiotic prescribing. In light of the FDA safety warnings and recommendations, evidence is needed for implementation strategies to guide prescribing of fluoroquinolones when suitable alternatives are available. Thus, we evaluated the implementation, perception, and effectiveness of prior approval and PAF to impact fluoroquinolone and total antibiotic prescribing in a Practice-Based Research Network (PBRN) of Veterans' Affairs (VA) acute-care facilities.

Methods

Study design, setting, and study population

A cross-sectional survey was conducted with antimicrobial stewardship champions at 15 acute-care facilities in April 2018. Study data were collected and managed using REDCap electronic data capture tools. The sample included VA medical centers enrolled in a Practice-Based Research Network (PBRN) jointly supported by the CDC and the VA. The sampling strategy included all VA PBRN facilities to ensure that we captured the diversity of perceptions and implemented practices. The antimicrobial stewardship leader was defined as the facility personnel designated to direct antimicrobial stewardship. The survey focused on the

local implementation and acceptability of different strategies to improve fluoroquinolone prescribing.

Survey Development

Questions were closed-ended in the form of a survey (Supplementary Table 1 online). Development of the survey was focused on topic areas in the Consolidated Framework for Implementation Research (CFIR) domains: inner setting (organizational context) including current practices and procedures (ie, existing guidelines and/or formularies), characteristics of individuals (ie, knowledge, attitudes, beliefs) and outer setting (ie, awareness of external policies and incentives). The purpose of the survey and accompanying questions were (1) to determine which antimicrobial stewardship strategies were implemented, (2) to assess the perception of the potential effectiveness of antimicrobial stewardship strategies, and (3) to identify the perceived acceptability of antimicrobial stewardship strategies. Questions in the survey were developed based on stakeholder input, current work (AHRQ no. R01HS025175 with primary investigator Samore and NIA no. P30AG022849 with primary investigator Hughes), and the American Society for Health-Systems Pharmacists best practice statement on formulary management.^{28–31} Study team members included operational partners, clinicians, and researchers with expertise in the design of surveys to capture provider behavior and strategies to improve prescribing. All study team members reviewed and provided feedback at each stage of questionnaire development. The survey was pilot-tested and feedback was provided by 1 antimicrobial stewardship physician and 1 antimicrobial stewardship pharmacist champion.

Antibiotic prescribing and facility characteristics data collection

Facility characteristics and antibiotic administration data were collected from national VA data sets, including the Veterans' Health Administration (VHA) Corporate Data Warehouse (CDW) for 2017–2018. These data sets were also used to gather information on mean bed days of care, facility complexity, specialty services available, and antibiotic exposure. Facility complexity is a standardized classification system across the VHA. Complexity is based on patient characteristics, clinical programs, and teaching programs. Facilities with complexity levels of 1a–c were classified as high-complexity facilities and levels 2–3 were classified as low-complexity facilities. Specialty services were categorized into presence of bone-marrow or stem-cell transplant unit, spinal cord injury center, and long-term care facility. Antibiotic exposure was reported overall (all systemic antibacterial classes combined), for fluoroquinolones, and for advanced-generation cephalosporins. Advanced-generation cephalosporins were defined as the third- and fourth-generation cephalosporins. For each facility, antibiotic exposure was reported as mean days of therapy and total days of therapy per 1,000 acute-care days present.

Statistical analysis

Facilities with audit and feedback (PAF) and/or prior approval were compared with sites without these strategies implemented. PAF was defined as a one-on-one interaction between an antimicrobial steward and a prescriber regarding antibiotic use in a specific case that is conducted within 1 business day after a restricted antibiotic is prescribed. Prior approval was defined as the medication cannot be used without review of the specific patient case and indication (includes instances where first dose is allowed but subsequent doses require approval). Independent *t* tests and

Table 1. Facility Characteristics and Fluoroquinolone PAF and/or Prior Approval Implementation Strategies

| Facility Characteristics | With PAF and/or Prior Approval | Without PAF and/or Prior Approval | P Value |
|---|--------------------------------|-----------------------------------|---------|
| No. of facilities | 9 | 6 | ... |
| Bone-marrow or stem-cell transplant unit, no. (%) | 3 (33.3) | 2 (33.3) | 1 |
| Long-term care, no. (%) | 6 (66.7) | 4 (66.7) | 1 |
| SCI specialty care center, no. (%) | 9 (100.0) | 6 (100.0) | 1 |
| Region, no. (%) | | | |
| Northeast | 1 (11.1) | 0 | 1 |
| Midwest | 4 (44.4) | 2 (33.3) | 1 |
| South | 2 (22.2) | 3 (50.0) | .3287 |
| West | 2 (22.2) | 1 (16.7) | 1 |
| Facility complexity^a no. (%) | | | |
| 1a | 5 (55.6) | 5 (83.3) | .5804 |
| 1b | 3 (33.3) | 1 (16.7) | .6044 |
| 1c | 1 (11.1) | 0 | 1 |
| Other facility characteristics (mean±SD) | | | |
| Authorized beds | 157.67 (±69.5) | 196.33 (±76.4) | .3283 |
| Daily census 2017 | 104.98 (±51.4) | 118.74 (±45.0) | .6033 |
| Admissions 2017 | 6,685.56 (±1,867.8) | 8,154.00 (±2,172.4) | .185 |
| Admissions 2018 | 6,758.56 (±1,957.9) | 8,264.50 (±2,021.3) | .1732 |
| Bed days of care 2017 | 36,333.33 (±14,440.8) | 47,938.83 (±22,742.3) | .2452 |
| Bed days of care 2018 | 34,744.33 (±13,148.8) | 43,105.83 (±15,590.0) | .2821 |

Note. SCI, spinal cord injury.

^aBased on levels of patient volume and risk, teaching, and research.

contingency tables were used to determine the differences in continuous and nominal data, respectively. Simple linear regression was applied to test differences in antibiotic prescribing over time. All data and statistical analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, NC). A *P* value <.05 was considered statistically significant. The VA Greater Los Angeles Healthcare System Institutional Review Board approved this study through expedited review.

Results

All PBRN acute-care facilities (N = 15; 87% antimicrobial stewardship physician; 13% antimicrobial stewardship pharmacist responders) completed the survey for a 100% response rate. Overall, 9 antimicrobial stewardship champions (60%) identified their site as having fluoroquinolone implementation strategies, 2 of 9 (22%) used PAF, 4 of 9 (44%) used prior approval, and 3 of 9 (33%) used both PAF and prior approval. At sites without PAF or prior approval implementation strategies, 20% (N = 3) had criteria for use and 13% (N = 2) had specific prescriber or care area restrictions in place for fluoroquinolones. Most facilities were of high complexity (10 of 15, 67%), and all were urban sites. Most of the facilities were regionally located in the Midwestern (6 of 15, 40%) and Southern (5 of 15, 33%) US geographic regions. Table 1 describes characteristics of facilities with either PAF or prior approval and without these strategies implemented. There was no significant difference in facility characteristics by group, including presence of specialty services and bed days of care.

No differences in total days of therapy at the facility level for 2017 or 2018 were detected for the the presence or absence of

implementation strategies. Figure 1 illustrates the total antibiotic (Fig. 1a), fluoroquinolone (Fig. 1b), and advanced-generation cephalosporin (Fig. 1c) prescribing rates for facilities with PAF and/or prior approval implemented for fluoroquinolones compared to facilities without PAF and/or prior approval in place for 2017 and 2018. Even though the total antibiotic rates (Fig. 1a) did not differ by group, fluoroquinolone days of therapy rates (Fig. 1b) were significantly lower in facilities with PAF and/or prior approval. Interestingly, the decrease in fluoroquinolones was achieved in the absence of increased prescribing of advanced-generation cephalosporins (Fig. 1c).

Figures 2a and 2b illustrate fluoroquinolone prescribing rates over time for facilities. The fluoroquinolone days of therapy rates were much lower in facilities with fluoroquinolone PAF and/or prior approval implementation strategies than at sites without fluoroquinolone implementation strategies. However, both groups experienced significant decreases in the fluoroquinolone days of therapy rate over the 2-year period (*P* = .0001) (Fig. 2a and 2b). Interestingly, in facilities with fluoroquinolone PAF and/or prior approval implementation strategies there was no change in advanced-generation cephalosporin days of therapy rate (*P* = .10) (Fig. 2a), but we detected a significant increase in cephalosporin rates in the facilities without fluoroquinolone PAF and/or prior approval (*P* = .001) (Fig. 2b). No temporal decrease in total antibiotic days of therapy rate was detected for either group (*P* ≥ .20) (Fig. 2a and 2b).

Table 2 illustrates antimicrobial stewardship leaders' perception of the level of provider acceptance for current fluoroquinolone PAF and/or prior approval strategies implemented at their facility (N = 8). (One additional site with implementation strategies did

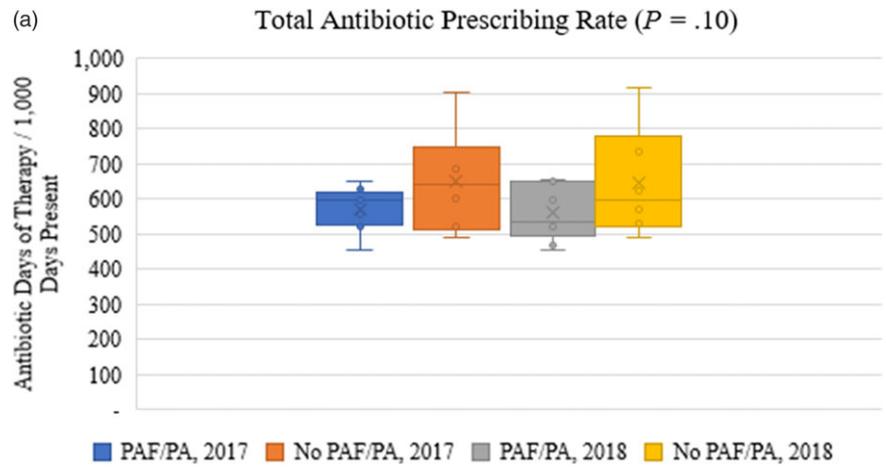


Fig. 1a. Comparison of overall antibiotic prescribing rates stratified by implementation strategies
Note. PAF, audit and feedback; PA, prior approval, the bar above and below each box represents the range.

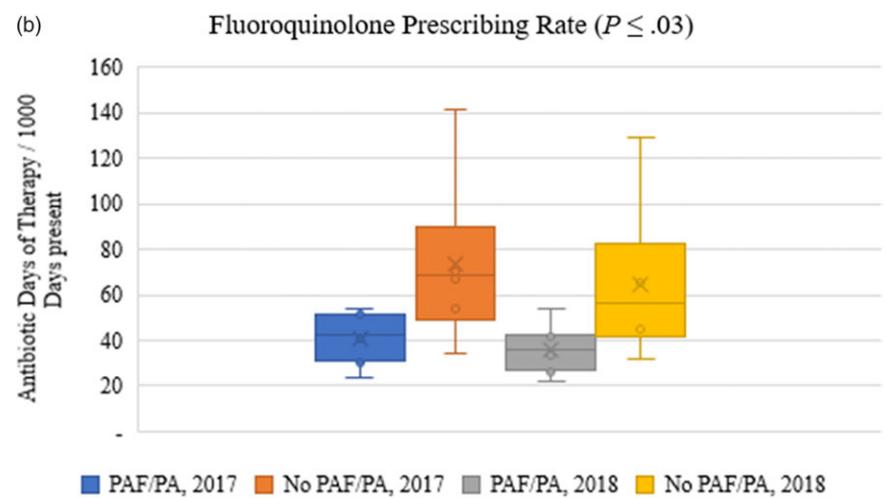


Fig. 1b. Comparison of fluoroquinolone prescribing rates stratified by implementation strategies

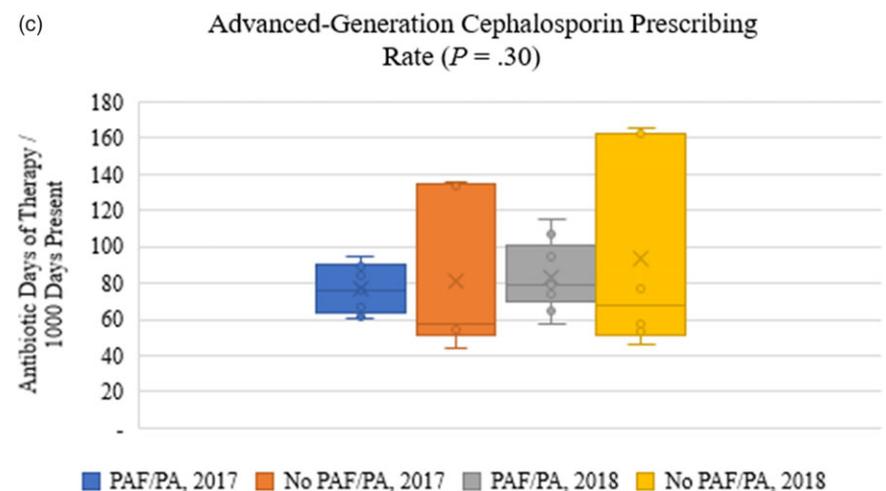


Fig. 1c. Comparison of advanced-generation cephalosporin prescribing rates stratified by implementation strategies.

not complete this section of the survey and was excluded from the acceptability analysis.) Of the sites with either PAF or prior approval implemented, 5 of 8 (62.5%) perceived that PAF and/or prior approval were completely accepted and 3 of 8 (37.5%) were moderately accepted, respectively. Facilities that perceived fluoroquinolone PAF and/or prior approval strategies were “completely” accepted by providers had lower fluoroquinolone days of therapy

rates than sites where formulary restrictions were “moderately” accepted ($P < .04$) (Table 2).

Antimicrobial stewardship leaders at all study sites ($N = 15$ sites) were asked to rate their perceived effectiveness of potential stewardship strategies. These included mandatory infectious disease (ID) consults for certain conditions, clinical pathways and/or local guidelines, antimicrobial order forms, and prior approval

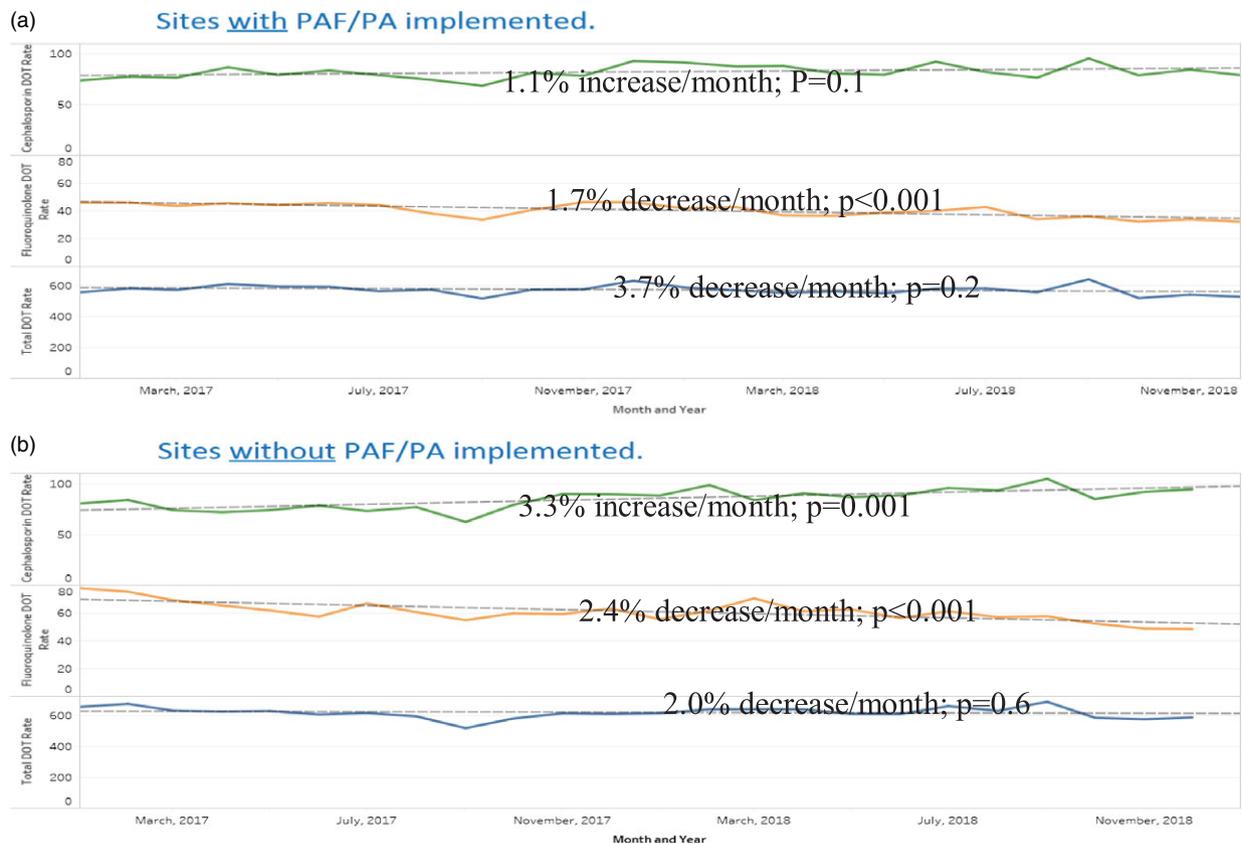


Fig. 2. Trends in advanced-generation cephalosporin (green), fluoroquinolone (orange) and total (blue) prescribing, 2017–2018. (a) Sites with PAF/prior approval implemented. (b) Sites without PAF/prior approval implemented.

on fluoroquinolone prescribing. With the exception of mandatory ID consults, most stewards perceived that clinical pathways and/or local guidelines, antimicrobial order forms, and prior approval would be effective or had already been implemented to improve fluoroquinolone prescribing (Fig. 3). For prior approval and clinical pathways, only 1 site either did not already have this strategy implemented for fluoroquinolones or did not believe that it would be effective in reducing fluoroquinolone use. Most antimicrobial stewardship leaders (13 of 15, 87%) perceived that implementation of mandatory ID consultations would be difficult.

Discussion

Implementation strategies to improve fluoroquinolone prescribing varied across the PBRN acute-care sites. Those facilities that implemented fluoroquinolone PAF and/or prior approval implementation strategies had decreased quinolone prescribing over the study period without a corresponding increase in advanced-generation cephalosporin prescribing, a common alternative. Conversely, in facilities without implementation strategies decreased fluoroquinolone use was accompanied by increased use of advanced-generation cephalosporins. Neither group had decreases in total antibiotic prescribing by year or overall. Although stewards are frequently concerned that implementing strategies focused on the fluoroquinolones will lead to increases in other antibiotics with a high risk of CDI (ie, advanced-generation cephalosporins), facilities without fluoroquinolone PAF or prior approval experienced increases in advanced-generation cephalosporin use. The literature on the impact of stewardship strategies to shift

use from fluoroquinolones to advanced-generation cephalosporins is scarce. However, many facilities with PAF and/or prior approval implemented for quinolones also had strategies in place for cephalosporins.

PAF and prior approval implementation strategies have been associated with a 50% reduction in acute-care fluoroquinolone prescribing.¹⁴ A quasi-experimental, crossover trial found that PAF had a greater effect on decreasing antimicrobial use than prior approval.³³ In contrast, a 2013 Cochrane review of 52 studies found that although outcomes at 12–24 months were similar, restrictive prior approval had a more rapid, salutary effect on antimicrobial use than did persuasive, PAF programs.¹⁷ Similarly, a meta-analysis found prior approval to be more effective than persuasive PAF strategies in reducing CDI¹⁴; this difference was not found in a second analysis that compared a broader range of restrictive and persuasive policies.²⁵ A study in Scotland found that prior approval of amoxicillin/clavulanate, clindamycin, fluoroquinolones, and third-generation cephalosporins was associated with reductions in CDI and methicillin-resistant *Staphylococcus aureus* (MRSA) infections despite a reciprocal doubling of alternative antibiotic use.^{22,24} A systematic review found that prior approval strategies targeting the fluoroquinolone class were associated with decreases in MRSA, CDI and quinolone-resistant *P. aeruginosa*, *A. baumannii*, and *E. coli*.³⁴ PAF strategies focused on fluoroquinolones similarly observed decreases in MRSA, CDI, extended-spectrum β -lactamase-producing organisms, and quinolone-resistant *P. aeruginosa*.³⁴

This study has several limitations. The sample of acute-care hospitals participated in a Practice-Based Research Network

Table 2. Perceived Acceptability of Fluoroquinolone PAF and Prior Approval Strategies Implemented and Facility Demographics

| Facility Characteristics | Moderately | Completely | P Value |
|---|----------------------|-----------------------|---------|
| No. of facilities | 3 | 5 | ... |
| Bone marrow or stem cell transplant unit, no. (%) | 1 (33.3) | 2 (40.0) | 1 |
| Long-term care, no. (%) | 3 (100.0) | 4 (80.0) | 1 |
| Spinal cord injury (SCI) specialty care center, no. (%) | 3 (100.0) | 5 (100.0) | 1 |
| Region, no. (%) | | | |
| Northeast | 0 | 1 (20.0) | 1 |
| Midwest | 1 (33.3) | 2 (40.0) | 1 |
| South | 1 (33.3) | 1 (20.0) | 1 |
| West | 1 (33.3) | 1 (20.0) | 1 |
| Complexity, no. (%) | | | |
| 1a | 3 (100.0%) | 3 (60.0) | 0.4643 |
| 1b | 0 | 2 (40.0) | 0.4643 |
| 1c | 0 | 0 | 0.4643 |
| Other facility characteristics (mean±SD) | | | |
| Authorized beds | 195.33 (±46.7) | 202.40 (±85.6) | 0.9014 |
| Daily census 2017 | 109.51 (±69.4) | 97.59 (±25.9) | 0.7309 |
| Admissions 2017 | 8,793.67 (±1,544.6) | 7,712.20 (±1,821.0) | 0.4258 |
| Admissions 2018 | 8,765.33 (±1,157.6) | 7,655.40 (±1,787.2) | 0.3802 |
| Bed days of care 2017 | 49,011.33 (±6,995.7) | 51,682.20 (±22,864.2) | 0.8545 |
| Bed days of care 2018 | 48,472.33 (±8,170.4) | 44,470.00 (±14,817.0) | 0.6877 |
| Antibiotic prescribing (mean±SD) | | | |
| Total antibiotic days, 2017 | 28,344.0 (±1,535.5) | 28,912.2 (±9,997.5) | 0.9276 |
| Total antibiotic days, 2018 | 26,545.7 (±1,242.7) | 25,209.4 (±7,444.7) | 0.7751 |
| Fluoroquinolone, ^a 2017 | 57.4 (±8.3) | 40.1 (±9.0) | 0.0363 |
| Fluoroquinolone, ^a 2018 | 48.7 (±4.5) | 34.2 (±5.7) | 0.0097 |
| Advanced-generation cephalosporin, ^{a,b} 2017 | 64.28 (±27.3) | 74.20 (±14.1) | 0.5128 |
| Advanced-generation, ^{a,b} cephalosporin 2018 | 64.53 (±26.3) | 80.29 (±17.6) | 0.3416 |

^aDays of therapy per 1,000 days present.

^bAdvanced-generation cephalosporin = third- and fourth-generation cephalosporins combined.

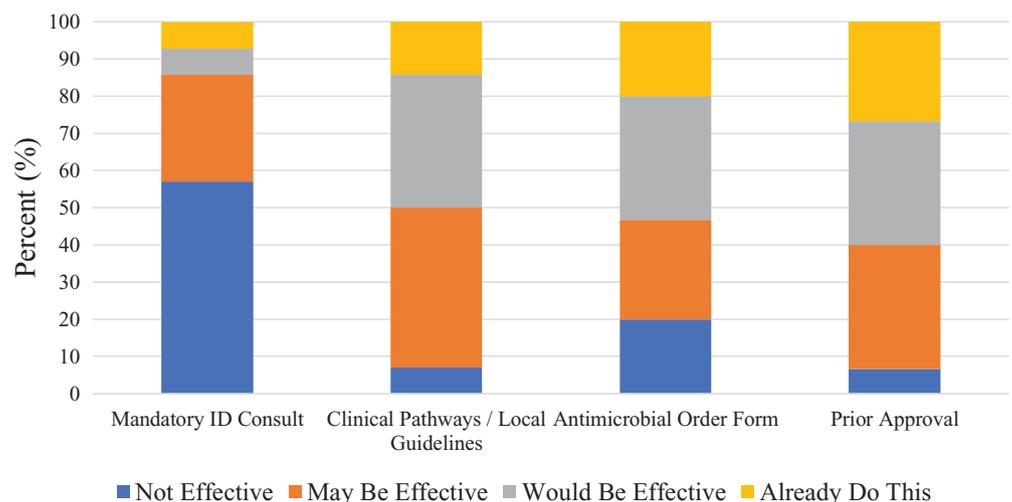


Fig. 3. Perceived effectiveness of implementation strategies on fluoroquinolone prescribing.

and, thus, may have been more supportive of evidence-based stewardship practices than other VA or non-VA facilities. Also, whereas 8 of the 9 facilities that implemented PAF and/or prior approval for fluoroquinolones implemented similar strategies for cefepime, ceftazidime, or ceftriaxone/cefotaxime, only 1 of the 5 facilities without such fluoroquinolone policies had similar strategies implemented for the use of these cephalosporins. Pharmacist time directly engaged in antimicrobial stewardship may also have influenced our results. At our PBRN sites, pharmacists spent 100% of their time on antimicrobial stewardship activities at 46.7% of facilities, 75% time at 20% of facilities, and 50% time at 33.3% of facilities. The survey was composed of closed-ended questions and allowed for little depth in material obtained. Only 1 person responded per facility to the survey. Thus, the responses may not reflect overall attitudes at their facility and may have introduced ecologic fallacy. The survey was administered in April 2018 and may not reflect current practices or perceptions after the multiple warnings issued on the fluoroquinolone class by the Food and Drug Administration in 2018.

Regardless, our study informs the effectiveness and acceptability of implementation strategies to improve fluoroquinolone prescribing. Furthermore, we demonstrate the feasibility of decreasing fluoroquinolone use without increasing the use of other drugs associated with increased rates of *C. difficile* infection, namely third- and fourth-generation cephalosporins. Facilities are motivated and perceive an opportunity to reduce fluoroquinolone use with a variety of implementation strategies. Although clinical pathways and/or local guidelines, antimicrobial order forms, and prior approval were perceived to be effective in improving fluoroquinolone prescribing, mandatory ID consultations were perceived to be difficult to implement. Therefore, external facilitation should be provided to sites to encourage interventions targeting fluoroquinolones. Although sites may perceive a high workload with the fluoroquinolone class, data on all new acute-care orders should be assessed for appropriateness and potential for alternative treatment. Our work has demonstrated that the volume of new orders is lower than that perceived. Therefore, antimicrobial stewardship programs should be involved in all policies that use persuasive or restrictive strategies on antimicrobials to assess acceptability and feasible implementation. The antimicrobial stewardship program should also determine effectiveness, especially class substitution (a reduction in prescribing of a particular class with a corresponding increase in another class). For the fluoroquinolone class, a common substitution are the advanced-generation cephalosporins. This is concerning due to similar risk of CDI as the fluoroquinolone class.³⁵ Our results demonstrate that facilities with PAF and/or prior approval implemented were effective in decreasing fluoroquinolone prescribing without a corresponding increase in advanced-generation cephalosporins. Although we detected a decrease in fluoroquinolone prescribing over time in facilities without PAF and/or prior approval implemented, this was achieved with an increase in advanced-generation cephalosporins.

Additional research should be conducted to provide further insight as to facilitators and barriers to implementing persuasive and restrictive strategies on the use of fluoroquinolones. In addition, appropriate antibiotic substitutes for these agents should be identified based on safety, local sensitivities, and as recommended in treatment guidelines. Finally, factors influencing the decision making regarding antimicrobial selection and feasibility and acceptability of implementation of PAF and prior approval by non-stewards should be assessed.

In conclusion, PAF and prior approval implementation strategies focused on fluoroquinolones were associated with lower fluoroquinolone prescribing rates in acute care. With a trend toward lower total antibiotic use, there was also no evidence of significant class substitution. Fluoroquinolone prescribing rates decreased in the PAF and/or prior approval sites without a corresponding increase in advanced-generation cephalosporins. This finding may indicate increased acceptability of implementation strategies and/or sensitivity to the FDA warnings. The acute-care PBRN sites perceived most formulary restrictions to be effective in improving fluoroquinolone use. Acceptability of antibiotic stewardship strategies which focus on medication restrictions may lower antibiotic prescribing rates and improve implementation.

Supplementary material. To view supplementary material for this article, please visit <https://doi.org/10.1017/ice.2021.10>

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Conflicts of Interest. All authors report no conflicts of interest relevant to this article.

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