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Long-Term Outcomes of an Antimicrobial Stewardship Program Implemented in a Hospital with Low Baseline Antibiotic Use

Timothy C. Jenkins, MD^{1,2,7,8}, Bryan C. Knepper, MPH, MSc³, Katherine Shihadeh, PharmD⁴, Michelle K. Haas, MD^{1,2,7,8}, Allison L. Sabel, MD, PhD, MPH^{3,9}, Andrew W. Steele, MD, MPH^{1,5,7}, Michael L. Wilson, MD⁶, Connie S. Price, MD^{1,2,7,8}, William J. Burman, MD^{1,2,7,8}, and Philip S. Mehler, MD^{1,2,3,7,8}

¹Department of Medicine, Denver Health, Denver, CO

²Division of Infectious Diseases, Denver Health, Denver, CO

³Department of Patient Safety and Quality, Denver Health, Denver, CO

⁴Department of Pharmacy, Denver Health, Denver, CO

⁵eHealth Services, Denver Health, Denver, CO

⁶Department of Pathology and Laboratory Services, Denver Health, Denver, CO

⁷Department of Medicine, University of Colorado School of Medicine, Aurora, CO

⁸Division of Infectious Diseases, University of Colorado School of Medicine, Aurora, CO

⁹Department of Biostatistics and Informatics, Colorado School of Public Health, Aurora, CO

Abstract

Objective—To evaluate the long-term outcomes of an antimicrobial stewardship program (ASP) implemented in a hospital with low baseline antibiotic use

Design—Quasi-experimental, interrupted-time series study

Setting—525-bed public safety-net hospital

Intervention—Implementation of a formal ASP in July 2008

Methods—We conducted a time-series analysis to evaluate the impact of the ASP over a 6.25-year period (July 1, 2008 – September 30, 2014) while controlling for trends during a 3-year preintervention period (July 1, 2005 – June 30, 2008). The primary outcome measures were total antibacterial and antipseudomonal use in days of therapy (DOT) per 1000 patient-days (PD). Secondary outcomes included antimicrobial costs and resistance, hospital-onset *C. difficile* infection, and other patient-centered measures.

Results—During the preintervention period, total antibacterial and antipseudomonal use were declining (−9.2 and −5.5 DOT/1000 PD per quarter, respectively). During the stewardship period,

Correspondence: Timothy C. Jenkins, MD, 660 Bannock Street, Denver, Colorado 80204, Office: 303-602-5041, Fax: 303-602-5055, timothy.jenkins@dhha.org.

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both continued to decline, although at lower rates (−3.7 and −2.2 DOT/1000 PD, respectively), resulting in a slope change of 5.5 DOT/1000 PD per quarter for total antibacterial use ($P = .10$) and 3.3 DOT/100 PD per quarter for antipseudomonal use ($P = .01$). Antibiotic expenditures declined markedly during the stewardship period (−\$295.42/1000PD per quarter, $p=.002$). There were variable changes in antimicrobial resistance and few apparent changes in *C. difficile* infection and other patient-centered outcomes.

Conclusion—In a hospital with low baseline antibiotic use, implementation of an ASP was associated with sustained reductions in total antibacterial and antipseudomonal use and declining antibiotic expenditures; however, this study highlights limitations of commonly used stewardship outcome measures.

Keywords

Antimicrobial stewardship; antimicrobial stewardship program; antimicrobial resistance; *Clostridium difficile* infection; safety-net hospital

Introduction

Combating the increasing global prevalence of antibiotic-resistant bacteria has become a national focus.^{1–3} Antimicrobial stewardship programs (ASPs) play a key role in limiting the emergence of antimicrobial resistance through improving antibiotic use in hospitals.^{2,3} Approximately half to two-thirds of hospitalized patients are exposed to antibiotics,^{4,5} and a significant amount of hospital antibiotic use is suboptimal.⁶ Infectious Diseases societies and the Centers for Disease Control and Prevention (CDC) therefore advocate for ASPs in all hospitals.^{1,7} Recent studies suggest that over half of hospitals have a formal ASP or are developing a program,^{8,9} and many more are engaged in some form of antimicrobial stewardship activities.^{8,10} Adoption of a stewardship program may ultimately be mandated as a condition of participation in Medicare and Medicaid.²

In light of these national efforts to scale up antimicrobial stewardship, it is essential to understand how ASPs affect outcomes in a wide spectrum of hospitals. One factor that could be an important determinant of the success of a stewardship program, as well as the decision to implement a program, is a hospital's baseline antibiotic use. That is, in hospitals where benchmarking data reveal low antibiotic use relative to other institutions, it is uncertain whether a stewardship program is necessary or adds benefit. Furthermore, a better understanding of the potential impact of stewardship programs on a breadth of outcomes is necessary to further inform policy considerations.

At Denver Health Medical Center, a public safety-net hospital, antibiotic use in 2006 ranked as being the second-lowest among 35 academic medical centers.¹¹ Yet, an informal audit of hospital antibiotic use revealed opportunities to improve prescribing; therefore, in July, 2008, Denver Health implemented a formal ASP. Our experience therefore offers a unique opportunity to assess the impact of a stewardship program in a hospital with low baseline antibiotic use. The objectives of this programmatic evaluation were to evaluate changes in antimicrobial use and costs, antimicrobial resistance, and clinical outcomes after implementation of the program.

Methods

Study setting

Denver Health is a vertically-integrated public safety-net healthcare system.¹² The 525-bed teaching hospital and Level 1 trauma center include medical, surgical, pediatric, and neonatal intensive care units as well as obstetric, correctional care, acute rehabilitation, medical, surgical, and pediatric wards. Neither cardiac surgeries nor organ transplantations are performed. With the exception of housestaff, providers are employed by Denver Health.

Antimicrobial stewardship program

A formal ASP was implemented in July 2008, staffed by an Infectious Diseases (ID) physician (0.5 full-time equivalent) and an ID pharmacist (1.0 full-time equivalent) with support from hospital leadership, ID physicians, data management and information technology specialists, and an Infection Prevention program. Prior to implementation of the ASP, stewardship-related activities consisted of formulary restriction, automatic intravenous to oral transitions, and once-weekly presence of an ID attending and ID pharmacist at multidisciplinary surgical intensive care unit rounds. After implementation of the ASP, stewardship activities were coordinated and broadened (Table 1) with a focus in three areas: (1) pre-authorization requirement for select broad-spectrum, toxic, or costly antibiotics; (2) post-prescription review with real-time feedback to prescribers; and (3) development and implementation of local guidelines for common infections. In general, interventions were designed to reduce use of broad-spectrum antibiotics, in particular, agents with activity against *Pseudomonas aeruginosa* (hereafter referred to as antipseudomonal agents), and to promote the shortest effective duration of therapy. Throughout the program, interventions were developed and implemented through the engagement of relevant stakeholders (physician champions).

Antimicrobial use and cost surveillance

Prior to the ASP, antimicrobial use and costs were not systematically monitored. At the outset of the program, we developed a surveillance tool to track quarterly hospital antimicrobial use and costs using patient-level pharmacy and census data from the enterprise data repository (Siemens Decision Support Solutions) (Online Supplemental Table 1). These data were available retrospectively dating back to the third quarter of 2005.

Study design and outcomes

We performed a quasi-experimental study with interrupted-time series design to evaluate the effects of the ASP on hospital antimicrobial use and costs, antimicrobial resistance, and patient-centered outcomes. The preintervention period consisted of 3 years immediately prior to implementation of the ASP (July 1, 2005 – June 30, 2008), while the stewardship period included the 6.25 years after inception of the program (July 1, 2008 – September 30, 2014). The primary outcomes were total antibacterial and antipseudomonal (imipenem-cilastatin, piperacillin-tazobactam, ticarcillin-clavulanate, fluoroquinolones, cefepime, or aminoglycosides) use expressed in quarterly days of therapy (DOT) per 1000 patient-days (PD).¹³ Secondary outcomes included antimicrobial expenditures, antimicrobial resistance

rates for key gram-negative and gram-positive pathogens, hospital-onset *Clostridium difficile* infection (CDI), and, for patients exposed to an antimicrobial during the hospitalization, length of hospital stay, in-hospital mortality, and 30-day hospital readmissions. Antimicrobial expenditures were calculated using patient-level data and expressed as acquisition costs to the hospital per 1000 PD. Hospital-wide antibiogram data were aggregated to determine the proportion of *P. aeruginosa*, *Escherichia coli*, enterococcal species, and *Staphylococcus aureus* isolates resistant to select antibiotics before (2005 – 2007) and after (2009 – 2013) implementation of the program. Hospital-onset CDI was defined as microbiological confirmation of *C. difficile* toxin production greater than 48 hours after hospital admission.¹⁴ Case-mix index was used to evaluate for changes in severity of illness in the population over time.¹⁵ This protocol was reviewed by the Colorado Multiple Institutional Review Board and deemed to represent quality assurance work.

Statistical analysis

Time-series analysis was used to estimate changes in antimicrobial use and expenditures, hospital-onset CDI, length of stay, in-hospital mortality, and 30-day hospital readmissions after implementation of the ASP, controlling for preintervention trends and other autocorrelation.^{16–19} The models generated by SAS's PROC AUTOREG included a constant, a baseline slope term to control for secular trends, and terms estimating changes in the level and slope of outcome rates. As secondary analyses, mean antimicrobial use and costs during the two periods were compared using Student's *t* test.^{16,20} Antimicrobial resistance during the two periods was compared using the Chi-Square test of proportions. A *P* value of <.05 (two-sided) was considered significant. All analyses were performed with SAS Version 9.3 (SAS Institute, Cary, NC).

Results

Antimicrobial utilization

During the preintervention period, total antibacterial and antipseudomonal use were declining (–9.2 and –5.5 DOT/1000 PD per quarter, respectively) (Table 2, Figure 1). During the stewardship period, both continued to decline, although at lower rates (–3.7 and –2.2 DOT/1000 PD, respectively), resulting in a slope change of 5.5 DOT/1000 PD per quarter for total antibacterial use (*P* = .10) and 3.3 DOT/1000 PD per quarter for antipseudomonals (*P* = .01). Use of agents with activity against resistant gram-positive organisms declined in both periods, but there was no significant change in slope after implementation of the ASP (–1.2 DOT/1000 PD per quarter; *P*=0.28; Table 2, Figure 2). Total antifungal use declined during the preintervention period, and this trend did not significantly change during the intervention period (slope change, 0.4 DOT/1000 PD per quarter; *P*=0.22; Table 2).

Regarding individual antipseudomals, there was a significant decrease in use of imipenem-cilastatin immediately after implementation of the stewardship program (–10.4 DOT/1000 PD, *P*<.001) (Figure 3). Over the course of the stewardship period, there were significant reductions in use of imipenem-cilastatin, β -lactam/ β -lactamase inhibitor combinations, fluoroquinolones, and aminoglycosides, while use of cefepime significantly increased, by design (Table 2, Figure 3).

In secondary analyses, mean quarterly antibacterial use decreased 14.2% from the baseline to stewardship period (533.1 vs. 457.5 DOT/1000 PD, $P<.001$) (Online Supplemental Table 2). Total use of antipseudomonals, resistant gram-positive agents, and antifungals decreased 30.0% (203.9 to 142.8 DOT/1000 PD, $p<.001$), 7.3% (102.9 to 95.4 DOT/1000 PD, $P = .10$), and 22.3% (22.0 to 17.1 DOT/1000 PD, $P<.001$), respectively.

Antimicrobial expenditures

Prior to the ASP, total antimicrobial expenditures increased at a rate of \$13.67/1000 PD per quarter. However, during the ASP period, expenditures decreased by \$260.44/1000 PD per quarter. Thus, there was a significant decline of $-\$295.42/1000$ PD per quarter after the intervention ($P = 0.002$; Table 2, Figure 1). In a secondary analysis, mean quarterly antimicrobial expenditures decreased 27.9% from a baseline of \$10,024/1000 PD to \$7,224/1000 PD during the stewardship period ($P<.001$) (Online Supplemental Table 3). This was largely a result of declining antipseudomonal expenditures (\$4,063/1000PD to \$2,756/1000PD, $P = .002$).

Antimicrobial resistance

Between the preintervention and stewardship periods, there was a significant decrease in the proportion of *P. aeruginosa* isolates resistant to imipenem-cilastatin (21.2% vs. 13.1%, $P<.001$) and levofloxacin (30.5% vs. 21.4%, $P<.001$) (Table 3). There were small but statistically significant increases in levofloxacin and ceftriaxone resistance among *E. coli* isolates and a significant decrease in methicillin resistance among *S. aureus* isolates.

Patient-centered outcomes

By time series analysis, there were no significant differences in the preintervention and stewardship period trends in hospital-onset CDI, length of stay, in-hospital mortality, or 30-day hospital readmission rates (Figure 4). Average severity of illness, as measured by case mix index, was higher during the stewardship period (1.71 vs. 1.87, $P<.001$).

Discussion

We describe the implementation of an ASP in an academic hospital with low baseline antibiotic use and report a wide spectrum of outcomes. Although total antibacterial and antipseudomonal use were declining prior to the start of the ASP, sustained declines were observed over the more than 6 years since the program's inception. Antimicrobial expenditures declined markedly during the stewardship period. The program was associated with variable changes in antimicrobial resistance and few apparent changes in clinical outcomes.

Denver Health's experience is unique in that the hospital had nearly the lowest unadjusted antibiotic use out of 35 hospitals prior to implementation of the ASP.¹¹ Our findings suggest that a hospital's absolute measure of antibiotic use does not necessarily correlate with the degree of opportunity to reduce use. Risk-adjusted facility benchmarks may better reflect such opportunity;²¹ however, during 2009, shortly after the inception of our program, Denver Health had the lowest risk-adjusted antibiotic use among 70 hospitals.⁵ Despite the

low risk-adjusted use, substantial reductions in total and broad-spectrum antimicrobial use were subsequently achieved. We therefore caution that the measure of opportunity for a stewardship program should not be singularly based on either absolute or risk-adjusted benchmarking. Rather, our experience suggests that opportunity to improve antibiotic use likely exists in all hospitals, including those with low baseline use, and supports recent calls for a mandate for stewardship programs in all hospitals.^{2,7}

There have been a number of reports of long-term outcomes of stewardship programs.^{17–20,22} Although the most appropriate outcomes have not yet been established, they have been the subject of considerable discussion in the field recently.^{21,23,24} The present study adds to the literature by providing one of the broadest assessments of potential stewardship outcomes to date. Our findings are instructive in that they demonstrate a number of complexities of proposed outcome measures.

One such complexity is that total antibacterial and antipseudomonal use were declining prior to the start of the ASP leading to difficulty in assessing the impact of the program. We believe the high antimicrobial use in the early part of the preintervention period (Figures 1 – 3) was in large part the result of an outbreak of multi-drug resistant *Acinetobacter baumannii* that resulted in heavy use of broad-spectrum antibiotics.²⁵ The overall declining trends in antimicrobial use during the remainder of the preintervention period likely reflected “normalization” of prescribing patterns after the outbreak was stopped. We cannot rule out that these declines were due to stewardship-related activities prior to implementation of the ASP, reductions in healthcare-associated infections due to infection prevention interventions, or other unknown factors. The declines observed during the stewardship period therefore could have been the result of those same factors; however, we think this is unlikely for several reasons. First, after the ASP was implemented, we observed clear changes in prescribing patterns including expected decreases in use of broad-spectrum antibiotics targeted for reduction (e.g., carbapenems and β -lactam/ β -lactamase inhibitors) and increases in other antibiotics that were promoted for empiric therapy (e.g., cefepime, ceftriaxone plus metronidazole). Second, detailed cohort studies of patients with skin and soft tissue infections²⁶ and community-acquired pneumonia (unpublished data) demonstrated that specific interventions during the stewardship period reduced use of broad-spectrum antibiotics and shortened durations of therapy. These findings strongly suggest that the stewardship program impacted prescribing irrespective of the declining preintervention trends.

Another complexity of antimicrobial measurement is that there is likely a minimum amount of antimicrobial use necessary to maintain optimal clinical outcomes. This notion of a “floor” that use should not fall below, even with perfect prescribing, may be particularly relevant for hospitals such as ours that have low antimicrobial use prior to starting a stewardship program. It therefore stands to reason that programs should not expect to see indefinite declines in antimicrobial use. This has both statistical implications, since time series analysis is a comparison of slopes of antimicrobial use, and practical implications for evaluating the success of a program. Our data on imipenem-cilastatin (Figure 3) represents an interesting example of this issue: since use of this agent approached zero during the stewardship period, a further decline over time would neither be expected nor feasible.

It is notable that long-term declines in the use of imipenem-cilastatin and levofloxacin were associated with reductions in resistance to these agents in *P. aeruginosa*. Such an association with fluoroquinolone use has been reported previously.²⁷ Importantly, factors besides hospital antimicrobial use can affect resistance such as transmission of resistant organisms,²⁸ infection control interventions,²⁹ community antibiotic use,³⁰ and pathogen-specific factors.³¹ Furthermore, changes in Clinical and Laboratory Standards Institute breakpoints may affect resistance trends. Aside from the changes in antimicrobial use, we are not aware of any changes at our institution that would have substantially affected *P. aeruginosa* resistance rates. It should also be noted that both inpatient and outpatient isolates were included in this analysis of antibiogram data. This likely had an effect on the results of common outpatient pathogens such as *E. coli* and *S. aureus*. Furthermore, since the incidence of hospital-onset methicillin-resistant *S. aureus* infections (MRSA) has declined nationally,^{32,33} it is possible that the observed reduction in use of vancomycin during the stewardship period was a result of fewer MRSA infections rather than the converse. Thus, determining the true impact of antimicrobial stewardship on antimicrobial resistance poses challenges.

Several studies have demonstrated declines in CDI associated with antimicrobial stewardship,^{17,18,34} and the CDC estimated a 30% reduction in broad-spectrum antibiotic use would result in a 26% reduction in CDI.⁶ Interestingly, we observed a 30% reduction in the use of antipseudomonal agents but did not observe a decrement in our CDI rate. This could be due to several reasons. First, our CDI rate is low compared with other Colorado hospitals (unpublished data) which may indicate less opportunity to prevent cases. Second, the relative stability of our rate during a national epidemic³⁵ may in fact reflect a benefit of the ASP. Finally, in late 2009, our diagnostic test was changed from a toxin assay to a combined antigen plus toxin assay with PCR testing for equivocal tests. The increased sensitivity of this diagnostic approach³⁶ likely increased case detection during the stewardship period which may have offset any decrease in CDI cases due to reduced antimicrobial use. Similar to antimicrobial resistance and CDI, other patient-centered outcomes are impacted by a number of factors other than antimicrobial use. Without adjustment for such potential confounders, such data have significant limitations. Despite the limitations of the outcomes we report, the relatively consistent trends in favor of the stewardship period were reassuring.

Even though benchmarking data suggested antibiotic use in our hospital was low,^{5,11} we observed a substantial reduction in antimicrobial expenditures after implementation of the stewardship program. These cost savings were due to both an overall decrease in antimicrobial use and use of less expensive agents (e.g., cephalosporins) in place of more expensive agents (e.g., piperacillin/tazobactam, imipenem, nafcillin) in appropriate clinical settings. Our cost data were not adjusted for changes in antimicrobial costs, inflation, nor the addition of new expensive antibiotics (e.g., daptomycin, liposomal amphotericin B) to the formulary over time. Furthermore, stewardship team member salaries and potential cost savings from averted antimicrobial-resistant infections³⁷ or cases of CDI^{38,39} were not taken into account. Without a more robust economic analysis, the true financial impact of the stewardship program is not known; however, the substantial decline in antimicrobial expenditures we observed suggests there may be opportunity for hospitals even with low

baseline antibiotic use to realize additional cost savings through antimicrobial stewardship. This may also have relevance for other safety-net hospitals as a means to control health care costs, helping to maintain their financial viability.

This study has additional limitations that warrant further consideration. First, it reflects the experience of a single institution with low baseline antibiotic use which limits its generalizability. Second, because of the ecological study design, our findings do not prove that the stewardship program itself led to any of the described changes in outcomes. Third, our study does not address whether there were changes in the appropriateness of antimicrobial use. This would be a more meaningful outcome than overall changes in antimicrobial use; unfortunately, standardized measures of appropriateness do not presently exist.⁴⁰ For this reason, we assessed a number of clinical outcomes potentially related to antimicrobial use as discussed above. Fourth, we made multiple comparisons without formal statistical adjustment. Given this work represents a broad programmatic evaluation, this is unlikely to have affected the overall conclusions. Fifth, it is not known which interventions had the greatest impact on antimicrobial use. We believe the observed changes represent the sum of numerous interventions that have begun to change prescribing norms at our institution.

In summary, implementation of the ASP was associated with sustained declines in total and broad-spectrum antimicrobial use, a marked reduction in antimicrobial expenditures, variable changes in antimicrobial resistance, and few apparent effects on clinical outcomes. Our experience suggests that even hospitals with low baseline antibiotic use may still have substantial opportunity to reduce unnecessary antibiotic use and costs. These findings have relevance to national efforts aimed at scaling up antimicrobial stewardship and considerations of a mandate for stewardship programs in all hospitals. The numerous potential pitfalls of common stewardship outcomes measures that we encountered highlight the need for improved methods to measure the impact of antimicrobial stewardship.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Total antibacterial use (top panel), total antipseudomonal use (middle panel), and total antimicrobial expenditures (bottom panel) before (closed markers) and after (open markers) implementation of the antimicrobial stewardship program.

Figure 2.

Use of antibiotics with activity against resistant gram-positive pathogens before (closed markers) and after (open markers) implementation of the antimicrobial stewardship program. Top panel: Total vancomycin, daptomycin, and linezolid. Middle panel: Vancomycin. Bottom panel: Daptomycin plus linezolid. Data presented in days of therapy per 1000 patient-days.

Figure 3.

Use of agents with activity against *Pseudomonas aeruginosa* before (closed markers) and after (open markers) implementation of the antimicrobial stewardship program. Clockwise from top left: carbapenems, β -lactam/ β -lactamase inhibitor combinations, aminoglycosides, cefepime, fluoroquinolones. Data presented in days of therapy per 1000 patient-days. Total antipseudomonal use is displayed in Figure 1.

Figure 4.

Patient-centered outcomes before (closed markers) and after (open markers) implementation of the antimicrobial stewardship program. Analyses limited to patients who received at least one antimicrobial agent during the hospitalization. Clockwise from top left: Hospital-onset *C. difficile* infection, length of hospital stay, 30-day hospital readmissions, and in-hospital mortality. For each outcome, *P* value for change in slope = 0.20.

Table 1

Description of main antimicrobial stewardship program interventions.

Intervention	Description
Pre-authorization requirement for select antibiotics	Use of carbapenems, aminoglycosides, aztreonam, tigecycline, colistin, daptomycin, linezolid, and all antifungals except fluconazole required prior authorization via a centralized pager. During evenings or overnight, the first dose could be given without approval.
Post-prescription review with feedback	Prospective case review by ID pharmacist or ID physician with real-time prescribing recommendations. Cases identified through reports of the following: restricted antibiotics, positive blood cultures, 3 or more antibiotics, >7 consecutive days of antibiotic therapy, piperacillin-tazobactam, levofloxacin, vancomycin
Local guidelines for common infections	Development and implementation of hospital guidelines for the management of skin and soft tissue infections, community-acquired pneumonia, catheter-associated urinary tract infection, complicated intra-abdominal infection, diabetic foot infection, febrile neutropenia, <i>C. difficile</i> infection, necrotizing pancreatitis, and invasive candidal infection as well as empiric antibiotic selection in the medical intensive care unit
Antimicrobial stewardship program website	Development of a hospital intranet site containing links to local guidelines, hospital antibiogram, antimicrobial formulary, antimicrobial use surveillance data, and relevant stewardship literature
Antimicrobial stewardship pager	A centralized contact number for prescribing questions not requiring formal ID consultation and approval of antibiotics requiring prior authorization
Vancomycin pharmacy-to-dose	Decentralized pharmacists review indication for vancomycin daily and order dose, frequency, and drug levels based on nomogram
Cost-effective antibiotic substitution initiatives	Examples include use of ceftriaxone plus metronidazole in place of piperacillin-tazobactam for select intra-abdominal infections and cefazolin in place of nafcillin or penicillin G for select <i>S. aureus</i> and streptococcal infections
Intensive care unit collaborations	ID physician presence at multi-disciplinary critical care rounds in surgical and medical intensive care units
Emergency department collaboration	Development and implementation of prescribing guidance for emergency department patients being hospitalized or discharged
Provider and pharmacist education	Didactic teaching sessions on the importance of judicious antibiotic use and methods to improve antibiotic prescribing
Engagement of physician champions	Physician champions from relevant clinical services involved in the development and implementation of local guidelines and other interventions

Table 2

Trends in antimicrobial use before and after implementation of the stewardship program by time series analysis.

	Days of Therapy / 1000 Patient-Days per quarter (95% Confidence Interval)			
	Preintervention period slope	Stewardship period slope	Change in slope ^a	P
All antibacterials	-9.2 (-15.5, -2.92)	-3.7 (-5.9, -1.6)	5.5 (-1.4, 12.4)	.1
Antipseudomonal agents	-5.5 (-7.8, -3.3)	-2.2 (-3.0, -1.5)	3.3 (0.8, 5.8)	.01
Imipenem-cilastatin	-1.3 (-1.6, -0.9)	-0.2 (-0.3, -0.1)	1.1 (0.7, 1.5)	<.001
β-lactamase inhibitor combinations	-0.5 (-2.1, 1.2)	-1.7 (-2.2, -1.1)	-1.2 (-3.0, 0.6)	.17
Fluoroquinolones	-2.8 (-3.6, -2.0)	-0.6 (-0.9, -0.3)	2.2 (1.4, 3.1)	<.001
Cefepime	0.2 (-0.7, 1.1)	1 (0.7, 1.3)	0.8 (-0.1, 1.7)	.07
Aminoglycosides	-0.6 (-1.5, 0.3)	-0.5 (-0.8, -0.2)	0.07 (-1.0, 1.1)	.88
Resistant gram-positive agents	-0.3 (-2.3, 1.6)	-1.5 (-2.2, -0.8)	-1.2 (-3.2, 1)	.28
Vancomycin	-0.7 (-2.9, 1.4)	-1.6 (-2.4, -0.8)	-0.9 (-3.2, 1.5)	.46
Linezolid	0.2 (-0.03, 0.5)	0 (-0.1, 0.1)	-0.2 (-0.5, 0.04)	.09
Daptomycin	0.2 (-0.04, 0.4)	0.1 (0.1, 0.2)	-0.1 (-0.3, 0.2)	.59
Other common antibacterials				
Ceftriaxone	1.2 (-0.2, 2.5)	0.6 (0.1, 1.1)	-0.6 (-2.1, 0.9)	.43
Cefazolin	-2.6 (-3.9, -1.3)	-0.9 (-1.3, -0.4)	1.7 (0.3, 3.1)	.02
Nafcillin	-0.9 (-1.5, -0.2)	-0.2 (-0.4, 0.04)	0.7 (-0.01, 1.4)	.05
Ampicillin-sulbactam	-0.3 (-0.9, 0.3)	0.1 (-0.2, 0.3)	0.4 (-0.3, 1.0)	.27
Azithromycin	0.6 (-0.4, 1.5)	0.1 (-0.2, 0.4)	-0.5 (-1.5, 0.5)	.33
Clindamycin	-1.2 (-1.7, -0.8)	-0.2 (-0.3, -0.02)	1.1 (0.6, 1.5)	<.001
Metronidazole	-0.4 (-1.2, 0.3)	0.7 (0.4, 0.9)	1.1 (0.3, 1.9)	.006
Ceftriaxone plus metronidazole ^a	0.2 (-0.2, 0.6)	0.5 (0.3, 0.6)	0.3 (-0.2, 0.7)	.23
Antifungals	-0.5 (-1.1, 0.2)	-0.1 (-0.3, 0.2)	0.4 (-0.3, 1.1)	.22
Fluconazole	-0.5 (-0.9, -0.05)	0 (-0.1, 0.1)	0.5 (0.03, 1.0)	.03
Echinocandins	-0.1 (-0.3, 0.2)	-0.1 (-0.1, 0.01)	-0.02 (-0.3, 0.2)	.87
Total antimicrobial expenditures	\$13.67 (-\$161.14, \$188.49)	-\$281.74 (-\$337.02, -\$226.47)	-\$295.42 (-\$476.62, -\$114.21)	.002

^aDifference between the preintervention and stewardship period slopes.

Table 3

Aggregate antimicrobial resistance rates for key pathogens before (2005 – 2007) and after (2009 – 2013) implementation of the antimicrobial stewardship program^{a, b}

Organism-antibiotic combination	Isolates resistant in preintervention period n (%)	Isolates resistant in stewardship period n (%)	P
<i>Pseudomonas aeruginosa</i>			
Imipenem-cilastatin	99/466 (21.2)	104/796 (13.1)	<.001
Piperacillin-tazobactam	52/466 (11.2)	94/796 (11.8)	0.73
Cefepime	97/466 (20.8)	142/796 (17.8)	0.19
Levofloxacin	142/466 (30.5)	170/796 (21.4)	<.001
Amikacin	22/466 (4.7)	30/796 (3.8)	0.41
Enterococcus species			
Vancomycin	147/824 (17.8)	256/1388 (18.4)	0.72
<i>Escherichia coli</i>			
Levofloxacin	780/7087 (11.0)	2023/14598 (13.9)	<.001
Ceftriaxone	71/7047 (1.0)	379/14601 (2.6)	<.001
<i>Staphylococcus aureus</i>			
Methicillin	1922/3915 (49.1)	2203/5618 (39.2)	<.001

^aData from 2008 were not included since the stewardship program was initiated in the middle of the year and the resistance data were only available in aggregate for the year.

^bData include isolates from inpatient and outpatient sites