

# Impact of a Prospective-Audit-With-Feedback Antimicrobial Stewardship Program at a Children's Hospital

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**Background.** The emergence of antibiotic-resistant organisms and the lack of development of new antimicrobials have made it imperative that additional strategies be developed to maintain the effectiveness of these existing antibiotics. The objective of this study was to describe the impact of a prospective-audit-with-feedback antimicrobial stewardship program (ASP) on antibiotic use in a children's hospital.

**Method.** A quasi-experimental study design with a control group was performed to assess the impact of a prospective-audit-with-feedback ASP. The control group was the combined antibiotic use at 25 similar children's hospitals that are members of the Child Health Corporation of America.

**Results.** The ASP reviewed 10 460 broad-spectrum or select antibiotics in 8765 patients in the 30 months following the intervention. The most common select antibiotics reviewed were ceftriaxone/cefotaxime (43%), vancomycin (18%), ceftazidime (12%), and meropenem (7%). A total of 2378 recommendations were made in 1703 (19%) patients; the most common recommendation was to stop antibiotics (41%). Clinicians were compliant with agreed-upon ASP recommendations in 92% of patients. When comparing our antibiotic use with that of the control group, a monthly decline in all antibiotics of 7% ( $P = .045$ ) and 8% ( $P = .045$ ) was observed for days of therapy (DoT) and length of therapy (LoT) per 1000 patient-days, respectively. An even greater effect was observed in the select antibiotics as the monthly DoT per 1000 patient-days declined 17% ( $P < .001$ ) and the monthly LoT per 1000 patient-days declined 18% ( $P < .001$ ).

**Conclusions.** A prospective-audit-with-feedback ASP can have a significant impact on decreasing antibiotic use at a children's hospital.

**Key words.** Antimicrobial Stewardship; Children's Hospitals; Prospective Audit; Time Series

(See the Editorial Commentary by Ambroggio et al, on pages 187–9.)

Antimicrobials are commonly prescribed therapeutic agents in healthcare. In 2007, antimicrobials were the third most common drug purchased by nonfederal hospitals, costing in excess of 3 billion dollars [1]. Data from pediatric studies have shown that

30%–67% of children will receive at least one antimicrobial during their hospital stay [2, 3]. Furthermore, up to 35% of inpatient antibiotic prescriptions are either unnecessary or inappropriate [4–6].

Several studies have firmly established that increased use of antimicrobials results in the development of antimicrobial resistance [7, 8]. Unfortunately, pharmaceutical companies have not produced new antimicrobial agents while antimicrobial resistance has continued to increase [9]. Furthermore, the emergence of resistant bacteria such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and extended-spectrum  $\beta$ -lactamase producing gram-negative bacteria, makes it paramount that we develop additional strategies to preserve our antibiotic armamentarium.

Implementing an antimicrobial stewardship program (ASP) is one strategy to help curb the inappropriate use of antimicrobials and, in turn, decrease resistance associated with misuse. In 2007, a national guideline on the development of institutionally based ASPs was published by the Infectious Diseases Society of America [10]. The guideline describes two core strategies for effective stewardship: prospective-audit-with-feedback and preauthorization. Additionally, the guideline specifically states that research is needed to determine whether these programs are beneficial in pediatrics [10].

Data have been published in pediatrics showing the positive impact that ASPs can have on antimicrobial use [11–15]. However, none of these studies has investigated the effectiveness of the recommended core strategy, prospective-audit-with-feedback, in reducing the days of antibiotic therapy in a children’s hospital. Additionally, none of these studies has compared their antibiotic use with a group of similar hospitals. The primary objective of this study was to demonstrate the impact of a prospective-audit-with-feedback ASP on antimicrobial use at a children’s hospital.

METHODS

Study Design

A quasi-experimental study with a control group was conducted from January 1, 2004 to December 31, 2010 to determine the impact of an ASP—implemented March 3, 2008—on all antibiotic and broad-spectrum (select) antibiotic use. The combined antibiotic use from 25 member children’s hospitals within Child Health Corporation of America (CHCA) served as the control group. This study was approved by the institutional review board at Children’s Mercy Hospitals & Clinics.

Setting

The study was conducted at a 317-bed tertiary care children’s hospital. The hospital contains a 68-bed

neonatal intensive care unit and a 27-bed pediatric intensive care unit. Approximately 15 000 admissions occur each year and include children with malignancy, complex congenital heart disease, and those requiring liver, kidney, and bone marrow transplants. The medical staff comprises approximately 600 staff physicians. Additionally, the hospital trains 100 residents and 65 fellows annually.

Antimicrobial Stewardship Program (ASP)

After obtaining support from the hospital administration and medical staff, a prospective-audit-with-feedback ASP was implemented on March 3, 2008. The core members of the ASP team were: clinical pharmacist (1 full-time equivalent [FTE]), infectious diseases physician (0.3 FTE), and a data analyst (0.5 FTE). Additionally, the ASP worked closely with infection control, information systems, and clinical microbiology. The ASP monitored a group of broad-spectrum, or “select,” antibiotics (Table 1) 2 calendar days after they were initiated by the clinician. Patients to be reviewed by the ASP were identified through the electronic health record system. A clinical pharmacist reviewed the medical record of a patient receiving one or more select antibiotics for pertinent history and physical findings necessitating initiation of antibiotics, including culture data, radiographic findings, and significant laboratory values, as well as dosing and intended duration. Additional antibiotics prescribed to an individual receiving a select antibiotic were also reviewed. Recommendations were then communicated

Table 1. Select Antibiotics Monitored by the Antimicrobial Stewardship Program

Select Antibiotic	Number (N = 10 459) (%)
Ceftriaxone/cefotaxime	4475 (43)
Vancomycin	2068 (18)
Ceftazidime	1229 (12)
Meropenem	741 (17)
Cefepime	643 (6)
$\beta$ -Lactam/ $\beta$ -lactamase inhibitor <sup>a</sup>	489 (5)
Ciprofloxacin	332 (3)
Tobramycin	201 (2)
Linezolid	192 (2)
Levofloxacin	35
Aztreonam	30
Amikacin	20
Imipenem	1
Daptomycin	1
Moxifloxacin	0

<sup>a</sup>Ampicillin/sulbactam, amoxicillin/clavulanate, piperacillin/tazobactam, ticarcillin/clavulanate.

to the clinician caring for the child. Interventions were categorized by type of recommendation and included the following: discontinue the antibiotic; narrow or broaden antimicrobial therapy based on culture and susceptibility data; convert the administration method from parenteral to oral route; narrow or broaden empirically; increase or decrease the dose; shorten or lengthen the planned duration of therapy, consolidate to fewer antimicrobials, or obtain an infectious diseases consult. Infectious diseases consultation was reserved for cases with multiple complex issues and/or where the diagnosis met criteria for infectious diseases consultation in our institution.

### Data Collection

Data collected on each patient review included the following: clinical service; antibiotic(s) prescribed; dose of antibiotic(s); clinical indication; length of therapy; recommendations made by the ASP; and agreement and compliance with recommendations.

In cases where the clinician outlined a plan in the medical record that was in agreement with that formulated by the ASP staff, no further intervention occurred. In cases where a program intervention was recommended, clinical provider responses to the recommendations were categorized based on whether agreement was achieved. Data were collected on a per-patient basis even if multiple recommendations were made. After an agreement was reached between the clinician and ASP staff, compliance was determined by returning to the medical record at a later date to observe whether the agreement or plan had been followed. In cases where the clinician did not agree with the ASP plan, further discussion may have led to a compromise recommendation. In such cases, the medical record was also reviewed to ensure compliance with the compromise plan. Compliance was only determined if there was an agreement between the clinician and the ASP.

### PHIS Data

In order to understand the secular trends of antibiotic use, the Pediatric Health Information Systems (PHIS) database, an administrative database maintained by the Child Health Corporation of America (CHCA), was utilized. The PHIS database contains patient-level demographic, diagnostic, procedural, and resource utilization data from CHCA member hospitals. Data quality and reliability are ensured through a joint effort between CHCA, Thomson Healthcare, and contributing hospitals. Hospitals were excluded from our study if they did not contribute complete antimicrobial

utilization data for the entire study period. Additionally, we used the PHIS database to assess the monthly readmission rate, mortality rate, and percentage of patients with an infection, as defined by ICD-9 codes for bacterial, viral, or fungal infections.

### Statistical Analysis

Descriptive statistics were calculated for all antibiotics administered to the patients being reviewed by ASP staff. A  $\chi^2$  test for trend was performed to assess trends in recommendations and compliance on a monthly basis over the time period analyzed. Poisson regression analysis was used to assess changes in antibiotic use between the pre- and postintervention period. This analysis was performed using SAS version 9.2 (SAS Institute). Results were considered significant if  $P < .05$ .

Antibiotic utilization was expressed as days of therapy (DoT) per 1000 patient-days and length of therapy (LoT) per 1000 patient-days and was calculated on a monthly basis [16]. DoT for a patient accounts for all antibiotics that a patient is receiving over a specific time frame. Therefore, if a patient is receiving 2 antibiotics for 5 days, the DoT is 10. LoT for a patient only counts the days of therapy irrespective of how many antibiotics the patient is receiving on a given day. For example, if a patient is receiving 2 antibiotics for 5 days, the LoT is 5. The denominator, 1000 patient-days, includes all hospital days for patients admitted during the study period. Three categories of antibiotics were analyzed: all-antibiotics; select antibiotics; and nonselect antibiotics. The first category included all antibiotics administered to inpatients by the oral or intravenous route. The second category was composed of only the subset of select antibiotics monitored by the ASP (Table 1). The final category is the nonselect antibiotics that were not monitored by the program; recommendations could have been made on these drugs if they were reviewed by the program in a patient who was also receiving a select antibiotic.

An interrupted time series design with a control group [17] was applied to this study using ARIMAX intervention analysis (AutoRegressive, Integrated, and Moving Averages with Independent variables-X) [18]. Because antibiotic usage rates are reported monthly, ARIMAX modeling was performed to control for autocorrelations, variance nonstationarity, seasonality, and trends [18, 19]. In order to model percentage changes in antibiotic use, the original antibiotic use variables of LoT and DoT were transformed to natural logarithms. Separate time series were

performed for all antibiotics, select antibiotics, and nonselect antibiotics. Additionally, these analyses were done controlling for the monthly case mix index (CMI) [2]. The CMI is a numerical value representing the severity of each patient based upon the All Patient Refined Diagnosis-Related Groups severity levels. Each patient's severity of illness is classified as minor, moderate, major, or extreme. This analysis was performed by dividing the DoT or LoT by the average CMI for that month. These analyses were also performed using the combined antibiotic use at 25 CHCA hospitals. As an internal control, time series was performed on the combined use of the following antivirals: acyclovir, valacyclovir, ganciclovir, valganciclovir, cidofovir, and foscarnet. Finally, time series was done for the monthly readmission rate, mortality rate, and infection rate for Children's Mercy Hospitals and Clinics (CMH). Analysis was completed using version 8 of the Regression Analysis of Times Series statistical software (Version 8.0, Estima, 2010) and then verified using SPSS version 19 (IBM, 2011).

RESULTS

Description of the ASP

The ASP reviewed 8765 patients who were receiving 10 460 select antibiotics from March 3, 2008 to December 31, 2010. The median age of patients reviewed was 2.5 years (interquartile range 68 days–10 years) and 48% were female. The most common select antibiotics reviewed included ceftriaxone/cefotaxime, vancomycin, and ceftazidime (Table 1), and the primary indications for using these antibiotics included suspected sepsis (28%), fever and neutropenia (12%), and intra-abdominal infections (9%) (Supplementary Table 1). The clinical services most commonly interacting with the ASP were general pediatric/resident service (20%), hematology/oncology (17%), and hospitalist (17%) (Supplementary Table 2).

Overall, 2380 recommendations were made in 19% (1704/8765) of patients; 75% of the recommendations were made on a select antibiotic. In analyzing the percent of recommendations by month, we observed a significant decrease over time, from 37% at the beginning of the program to 13% at the end of the observation (*P* for trend <.001). The type of recommendations and their frequencies are represented in Table 2.

Agreement with initial recommendations occurred in 80% (1352/1704) of patients who had a recommendation made. We identified that the overall

Table 2. Type of Recommendations Made by the Antimicrobial Stewardship Program

Type of Recommendation	Number (N = 2380) (%)
Stop	1051 (44)
No indication for antibiotic	863 (36)
Eliminate redundant therapy	73 (3)
Consolidating to fewer agents	59 (2)
Virus identified	38 (2)
Change to an agent with lower frequency	18 (1)
ID consult	287 (12)
Narrow based on culture and susceptibility	259 (11)
IV to PO conversion	139 (6)
Narrow empirically	127 (5)
Increase dose	114 (5)
Shorten duration	85 (4)
Other	83 (3)
Broaden empirically	61 (3)
Lengthen duration	47 (2)
Decrease frequency of antibiotic	42 (2)
Broaden based on culture and susceptibility	34 (1)
Change antibiotic based on culture and susceptibility	32 (1)
Decrease dose	15 (1)
Change due to drug interaction	4 (0.2)

Abbreviations: ID, infectious diseases; IV, intravenous; PO, by mouth.

compliance with agreed-upon recommendations made by the ASP was 92% (1220/1325). Over time the monthly compliance rate ranged from 83% to 100% but did not significantly change (*P* for trend = .34).

Antibiotic Use

At our institution, all antibiotic use decreased from 883 DoT per 1000 patient-days prior to the implementation of the ASP to 787 DoT per 1000 patient-days postimplementation (*P* <.001). Select antibiotics demonstrated similar trends, dropping from 353 DoT per 1000 patient-days to 311 DoT per 1000 patient-days (*P* <.001). Comparable decreases were seen for LoT. All antibiotic use decreased from 567 LoT per 1000 patient-days preintervention to 523 LoT per 1000 patient-days with the ASP in place (*P* <.001). Select antibiotic use similarly decreased from 294 LoT per 1000 patient-days to 256 LoT per 1000 patient-days (*P* <.001).

In order to better control for seasonality and other confounding influences on antibiotic utilization, time series was used to model preintervention and postintervention DoT and LoT. Following the implementation of the ASP, the overall antibiotic monthly usage was 6% less for both DoT (*P* <.001) and LoT (*P*

Table 3. ARIMAX-Intervention Impacts on Antibiotic Usage Without/With Case Mix Index

Days of Therapy	Pre <sup>a</sup> Means <sup>c</sup>	Post <sup>b</sup> Means <sup>c</sup>	Effect <sup>d</sup>	W/O CMI %Decline	t-Value	P-Value	W/CMI %Decline	t-Value <sup>e</sup>	P-Value
Select	5.114	4.928	AP	-11.73%	-5.000	3.4E-06	-17.94%	-4.869	5.54E-06
All	6.144	6.034	AP	-6.30%	-2.489	0.01529	-10.44%	-5.615	2.60E-07
Length of therapy									
Select	4.928	4.733	AP	12.76%	-5.912	8.0E-08	-18.95%	-4.983	3.55E-06
All	6.330	5.625	AP	-5.64%	-2.789	0.00687	-7.12%	-3.828	2.51E-04

Abbreviations: AP, abrupt permanent impacts; ARIMAX, AutoRegressive, Integrated, and Moving Averages with Independent variables-X; CMI, case mix index.

<sup>a</sup>Preintervention values through February 2008 (n = 50).

<sup>b</sup>Postintervention from March 2008 through December 2010 (n = 34).

<sup>c</sup>Means of natural logarithmic values of each variable, original metric =  $e^{\text{Mean}}$ .

<sup>d</sup>Based on parsimony, all intervention effects were abrupt permanent impacts.

<sup>e</sup>T-values equal to  $\pm 1.96$  are equal to a P-value of 0.05, and larger t-values are associated with more significant P-values.

<.001) per 1000 patient-days (Table 3). A greater effect was seen with select antibiotics usage with monthly decrease of 12% and 13% for DoT ( $P < .001$ ) and LoT ( $P < .001$ ) per 1000 patient-days, respectively (Table 3). Further analysis was performed controlling for severity of illness by utilizing monthly CMI. After controlling for CMI, the postintervention decrease in select antibiotic use was more pronounced, with an average monthly decrease of 19% for both LoT ( $P < .001$ ) and DoT ( $P < .001$ ) per 1000 patient-days (Table 3). No significant increase or decrease was noted in the time series analyses of nonselect antibiotic use.

To ensure that events other than the ASP did not reduce antibiotic use, antiviral usage was used as an internal control for noninterventions effects. The post-intervention antiviral DoT and LoT increased by 9%. Thus, ARIMAX intervention modeling did not show there to be a decrease in antiviral usage during the time period that antibiotic use was declining further, confirming the impact of the ASP on antibiotic use.

Finally, it was important to analyze our data in respect to the trends in antibiotic use occurring at similar tertiary-care freestanding children's hospitals. When we controlled for the combined antibiotic use at 25 similar children's hospitals, the monthly decline of DoT and LoT per 1000 patient-days for all antibiotics was 7% ( $P = .045$ ) and 8% ( $P = .045$ ), respectively. A more notable and significant decrease was seen for select antibiotics, with the monthly decline being 18% for DoT per 1000 patient-days ( $P < .001$ ) and 17% for LoT per 1000 patient-days ( $P < .001$ ) (Fig. 1).

To ensure that the decrease in antibiotic use was not due to a decrease in infections, pre- and post- ASP rates of infections were studied. Of the total 109 483

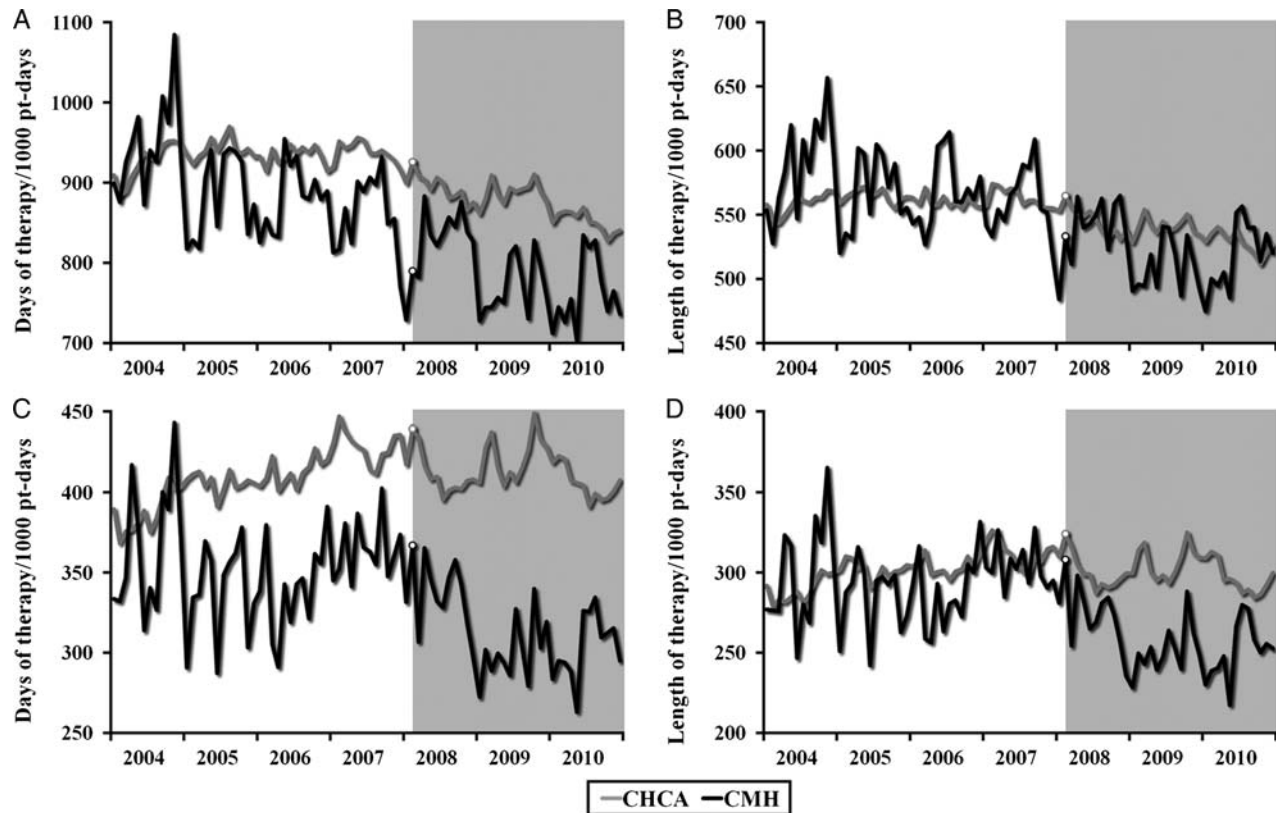
patients hospitalized at CMH from 2004 to 2010, 53 514 (49%) had infections designated by the PHIS infection flag; 37 439 (60%) of 62 290 patients on any antibiotic and 23 720 (72%) of 33 074 patients on select antibiotics had infections. Time series was performed on monthly infection rates pre- and postintervention; no statistically significant changes were observed ( $P = .65$ ).

In order to assess potential negative consequences of decreased antibiotic use, time series were performed on monthly mortality and readmission rates during the study period. In both instances, no increases were seen after the implementation of the ASP ( $P = .40$ ,  $P = .35$ , respectively).

## DISCUSSION

To our knowledge, this is the first study in pediatrics evaluating a prospective-audit-with-feedback antimicrobial stewardship program utilizing time series with the common antibiotic use metric of days of therapy and a control group that consisted of other similar children's hospitals. We demonstrate that this type of ASP can successfully decrease the broad-spectrum antibiotic use that the program was monitoring and in turn lead to an overall decrease in antibiotic use. Furthermore, the study provides insight into the antibiotics, medical services, types of indications, and recommendations that a prospective-audit-with-feedback program in a tertiary care children's hospital will encounter.

Data on the impact of pediatric ASPs has been limited to only a few studies [11–13, 15]. Recently, Di Pentima and colleagues demonstrated that a



**Figure 1.** Trends from 2004 to 2010 for all antibiotics and select antibiotic use at Child Health Corporation of America and Children's Mercy Hospitals and Clinics. Shaded area represents the postintervention period. Abbreviations: CHCA, Child Health Corporation of America; CMH, Children's Mercy Hospitals and Clinics.

prospective-audit-with-feedback program led to an overall dose reduction of 21%, but no data were provided in terms of DoT or LoT [14]. Our study demonstrates that a pediatric prospective-audit-with-feedback ASP can significantly decrease the DoT and LoT of all antibiotics and, more importantly, the broad-spectrum antibiotics that the Centers for Disease Control and Prevention have recommended avoiding to prevent resistance in hospitalized children [20].

The potential impact for other children's hospitals can be estimated from data published by Gerber and colleagues, which showed that the adjusted rate of antibiotic use per 1000 patient-days for children's hospitals was as high as 601 DoT per 1000 patient-days. With a 6% monthly decline for all antibiotics, as much as 36 DoT per 1000 patient-days could be saved per month, resulting in greater than 432 DoT per 1000 patient-days being saved per year per hospital. Our study shows an even greater impact with the select or broad-spectrum antibiotics, as up to 19% monthly reduction was observed. In comparison with adult institutions, the magnitude of the impact is similar [21–23].

This study provides insight into the potential benefit of using a prospective-audit-with-feedback over other strategies such as prior approval or preauthorization. Patel et al. demonstrated that the most common area where inappropriate antibiotic use occurred in the neonatal intensive care unit was not on the empiric selection but 72 hours after the initiation of the antibiotic, suggesting that a prospective-audit-with-feedback is a more beneficial strategy [6]. Interestingly, our program's most common recommendation was to stop antibiotics, comprising over 40% of all recommendations. Conversely, a pediatric study evaluating a prior-approval program observed that only 4% of their recommendations were to stop antibiotics [15]. While it is unknown which program leads to the greater reduction in antibiotic use, these data suggest it might occur more frequently with a prospective-audit-with-feedback ASP where more information is available at the time the ASP is intervening, allowing for the stop recommendation to be made more often.

Pediatric infectious diseases physicians have reported that taking away physician autonomy is a potential barrier to the development of ASPs [24]. Our study

revealed that compliance was high, demonstrating that possible concerns about autonomy may not actually prevent physicians from following ASP recommendations. Metjian and colleagues also reported compliance rates of approximately 90%, further confirming that this fear should not prevent the development of ASPs [15].

Another unique aspect of this study is the use of DoT and LoT to describe antibiotic use. Weight-based dosing in children makes defined daily dose—a common antibiotic use metric in adults—inappropriate to assess usage trends. Days of therapy has been suggested as a universal metric as it can be used in both pediatric and adult studies. Recently, Polk and colleagues introduced LoT to help better understand the true lengths of therapy that are being utilized in hospitals for adults [16]. Since DoT accounts for all antibiotics being used, examining DoT alone does not provide the complete story of how antibiotics are used. For example, in a given condition DoT could be reduced by half by eliminating one antibiotic in an institution that generally uses 2 drugs. However, this institution could have excessively long LoTs that would be unnoticed without looking at the LoT metric at the same time. By using both metrics, hospitals are able to obtain the best understanding of the number of antibiotics used and the true lengths of therapy being delivered, thus identifying all areas where improvement can be made. This study is the first to utilize both of these metrics and to demonstrate that both LoT and DoT were decreased.

An important strength of this study is the use of time series with a control group. Time series accounts for trends, seasonality, and autocorrelation. A recent review of time series suggests that this analysis is most effective when approximately 50 time points of data are available [25]. Our study includes 50 months of preintervention data and 34 months of postintervention. This significant amount of data allowed us to account for the seasonality and autocorrelation that could be present in the data and further confirms that our ASP intervention had a significant impact on antibiotic use. The most recent pediatric ASP study showed a reduction in doses administered utilizing segmented regression analysis, which is a robust design but lacks the ability to control for seasonality and autocorrelation [14]. Other pediatric ASP studies showed significant declines in antibiotic use by simple 2 group, pre–post intervention analysis as well as  $\chi^2$  trend analysis that does not account for the dependence that might be present in these data [11, 12]. Finally, our analysis was further strengthened by the

incorporation of a control group that consisted of the antibiotic use occurring at other similar children's hospitals. While we observed an overall decrease in antibiotic use, we demonstrated an even greater decrease after the implementation of our ASP. Furthermore, the utilization of the broad-spectrum or select antibiotics was unchanged in the control group while our institution's biggest decline occurred in these antibiotics. On the basis of this finding, we are able to determine that the decreased utilization at our hospital is not due to secular trends.

Limitations exist in this study. First, infection control initiatives such as efforts to prevent central-line-associated bloodstream infections and surgical site infection could result in a decrease in antibiotic use. Additionally, the implementation of a new evidence-based guideline for community-acquired pneumonia in July of 2008 led to the reduction of ceftriaxone use and an increase in ampicillin use. Both the guideline and ASP were found to independently cause a significant change in both of these antibiotics [26]. Finally, this study does not address the program's impact on clinical outcomes or bacterial resistance.

The results of this study confirm that a prospective-audit-with-feedback ASP can lead to a significant reduction in both all and broad-spectrum antibiotic use in a children's hospital. The most common type of recommendation from this type of ASP was to stop antibiotics, and the compliance with these recommendations was high. Furthermore, these types of programs can educate clinicians on the appropriate use of antibiotics. Future work is needed in pediatrics to demonstrate that ASPs not only limit antibiotic use but also improve the quality of care and patient outcomes.

### Supplementary Data

Supplementary materials are available at the *Journal of the Pediatric Infectious Diseases Society* online (<http://jpid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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