

The Impact of Hospital Antimicrobial Stewardship Programs
on Antibiotic Resistance and Prescribing

Mackenzie S Fuller

A thesis
submitted in partial fulfillment of the
requirements for the degree of

Master of Public Health

University of Washington

2017

Committee:

Gary Goldbaum, Chair

Joseph Delaney

Peter Rabinowitz

Program Authorized to Offer Degree:

Epidemiology

© Copyright 2017
Mackenzie S Fuller

University of Washington

Abstract

The Impact of Hospital Antimicrobial Stewardship Programs
on Antibiotic Resistance and Prescribing

Mackenzie S Fuller

Chair of the Supervisory Committee:
Associate Professor Emeritus Gary Goldbaum
Epidemiology

Abstract

Background: The spread of antibiotic resistance has spurred the development of hospital antimicrobial stewardship programs (ASPs). In this observational study, the effects of hospital ASPs on antibiotic isolate susceptibility and antibiotic days of therapy (DOT) were assessed amongst inpatients at two hospitals in Seattle, WA: one children's hospital and one general acute care hospital.

Methods: A retrospective analysis was conducted of hospital laboratory and pharmacy databases containing antibiotic susceptibility testing records of clinical isolates and antibiotic prescribing records. Using linear regression, a changepoint analysis was performed to test for slope changes in the percentage of antibiotic nonsusceptible isolates and change points and slope changes in antibiotic DOT per 10,000 patient days at each hospital.

Results: A 0.45 (95% CI: -0.80, -0.10) decrease per quarter in the percent change in *Pseudomonas aeruginosa* isolates that were multidrug resistant was observed after ASP implementation compared to pre-ASP implementation at the children's hospital. At the general acute care hospital, a 0.54 (95% CI: -1.02, -0.07) decrease per quarter in the percent change in *Staphylococcus aureus* isolates that were methicillin-resistant (MRSA) was observed after ASP implementation compared to pre-ASP implementation. ASP implementation was associated with significant decreases in glycopeptide DOT and monobactam DOT at both hospitals, decreases in β -lactam/ β -lactamase inhibitor combination, fluoroquinolone, macrolide, and oxazolidinone DOT at the general acute care hospital, and decreases in carbapenem and rifampin DOT at the children's hospital. ASP implementation was associated with an increase in overall cephalosporin DOT at the children's hospital, but not the general acute care hospital.

Conclusion: ASPs may decrease antibiotic prescribing, MDR *P. aeruginosa* within children's hospitals, and MRSA within general acute care hospitals. However, the limited linkage between prescribing and susceptibility outcomes suggests that other factors may be influencing susceptibility, and the generally limited impact overall suggests that additional strategies may be needed.

TABLE OF CONTENTS

LIST OF FIGURES	ii
LIST OF TABLES	iii
INTRODUCTION	1
METHODS	3
Study design	3
Data sources	4
Interventions.....	4
Antibiotic susceptibility outcomes	7
Antibiotic prescribing outcomes	10
Analysis.....	11
Antibiotic susceptibility.....	11
Antibiotic DOT	13
Statistical analysis.....	15
RESULTS	16
Antibiotic susceptibility	16
Antibiotic DOT	19
DISCUSSION.....	25
BIBLIOGRAPHY.....	29

LIST OF FIGURES

Figure 1. Flow-chart of susceptibility test record inclusion.	9
Figure 2. Flow-chart of pharmacy record inclusion.....	11
Figure 3. Antibiotic DOT calculation method at the general acute care hospital.....	14
Figure 4. Percent of <i>P. aeruginosa</i> isolates that were MDR (nonsusceptible to at least one antibiotic in at least three antimicrobial categories) over time at a children’s hospital. ASP implementation took place at quarter zero.....	18
Figure 5. Percent of <i>S. aureus</i> isolates that were MRSA (nonsusceptible to oxacillin) over time at a general acute care hospital. ASP implementation took place at quarter zero	18
Figure 6. Forest plot of the change in DOT per 10,000 patient days at the quarter of ASP implementation with 95% CI for antibiotic classes at a children’s hospital from October 2010 to December 2015 (ASP implemented January 2013) and at a general acute care hospital from April 2005 to December 2015 (ASP implemented August 2007).....	22
Figure 7. Forest plot of differences in the change in DOT per 10,000 patient days per quarter after ASP implementation compared to pre-ASP implementation with 95% CI for antibiotic classes at a children’s hospital from October 2010 to December 2015 (ASP implemented January 2013) and at a general acute care hospital from April 2005 to December 2015 (ASP implemented August 2007).....	23
Figure 8. DOT per 10,000 patient days over time for glycopeptides and monobactams at a children’s and a general acute care hospital. ASP implementation occurred at quarter zero.	24

LIST OF TABLES

Table 1. Quarter of first implementation of each ASP component, based on the CDC Checklist for Core Elements of Hospital Antimicrobial Stewardship Programs, relative to overall ASP implementation. Quarter values are negative before ASP implementation quarter, zero at ASP implementation quarter, and positive after ASP implementation quarter. None indicates that the facility had not implemented the ASP component as of survey completion in June 2017.....	5
Table 2. Total number of susceptibility test results (n) and difference in the percent change of nonsusceptible isolates per quarter after ASP implementation compared to pre-ASP implementation with 95% confidence intervals (CI) for MRSA, clindamycin-nonsusceptible <i>S. pneumoniae</i> , erythromycin-nonsusceptible <i>S. pneumoniae</i> , and MDR <i>P. aeruginosa</i> at a children’s hospital and a general acute care hospital.....	17
Table 3. Number of pharmacy observations and DOT per 10,000 patient days per antibiotic class and antibiotic at a children’s hospital from October 2010 to December 2015 and at a general acute care hospital from January 2005 to December 2015.....	20

ACKNOWLEDGEMENTS

This study could not have been completed without the support of many mentors and collaborators. I would like to thank Gary Goldbaum for his sound advice, eagerness to help, and enthusiasm throughout the project as my Committee Chair – I learned quickly that my early trepidation before our meetings was misplaced, as I always left our meetings encouraged to continue on no matter the hurdle. I would also like to thank Chris Delaney for his tireless methods guidance throughout the project, manifested in many hours of meetings, and Peter Rabinowitz and the Center for One Health Research for their assistance with study design, theory, data acquisition, and data management. I am extremely grateful to Scott Weissman, Paul Pottinger, Rupali Jain, and Andrew Bryan for their support, both through enlightening conversations and data acquisition at their institutions. In addition, I am deeply grateful to Robin Nance for her extensive assistance with Stata programming and spending so many hours running code with me. I have benefited from the advice and encouragement of Marisa d'Angeli and Kelly Kauber from the very early stages of this project and am very grateful to them. Finally, I would like to thank my friends and family for their support throughout this project, as they both understood when I was less available with my days centered around thesis work and eagerly joined me when I needed to take breaks and get outside.

INTRODUCTION

At least two million people are infected by antibiotic resistant organisms each year in the United States, with 23,000 people dying as a result.¹ Human contributions to the spread of antibiotic resistance are well-established,² including antibiotic use in both humans and animals that asserts selective pressure spurring the spread of antibiotic resistant organisms and genes as antibiotic susceptible organisms are out-competed. Transmission of antibiotic resistant organisms occurs between individuals within both hospitals and the community, including international transmission through humans and animals.³

One intervention point for the emergence of antibiotic resistance is hospital antimicrobial stewardship programs (ASPs). The Centers for Disease Control and Prevention (CDC), the Infectious Diseases Society of America (IDSA), the Society for Healthcare Epidemiology of America, and the Pediatric Infectious Diseases Society, amongst other organizations, have all called for ASPs throughout health care.⁴⁻⁶ The goals of these programs are to optimize clinical outcomes while minimizing adverse effects of antimicrobial use, including toxicity, selection of pathogenic organisms, and emergence of resistance, through appropriate selection, dosing, route, and duration of antimicrobial therapy.^{4,6} The IDSA 2007 ASP guidelines specify that ASPs should include an antimicrobial stewardship team constituted of at least an infectious disease physician and a clinical pharmacist with infectious disease training, and that this team should collaborate with hospital infection control, pharmacy, administration, medical staff leadership, and local providers. ASPs leverage a range of strategies, such as prospective antimicrobial use audit and feedback to the prescriber, formulary restriction and preauthorization, education,

guidelines and clinical pathways, antimicrobial order forms, streamlining or de-escalation of therapy, dose optimization, and parenteral to oral conversion.⁶

While these programs may not halt transmission of resistant organisms outside the hospital, e.g., in the community or internationally, they have been found to sometimes diminish antibiotic resistance within hospitals. Several systematic reviews have characterized the effect of hospital ASPs on antibiotic prescribing⁷⁻⁹ and resistance.⁷⁻¹⁰ Evidence of the impact of hospital ASPs on antibiotic resistance shows a mixed direction of effects depending on organism.⁷⁻¹⁰ One systematic review did not specify study organisms,⁹ but all three that specified study organisms demonstrated a decrease in methicillin resistant *Staphylococcus aureus* (MRSA).^{7, 8, 10} The effects on antibiotic resistant *Pseudomonas aeruginosa* varied by antibiotic and by study,^{7, 10} as did the effect on *Klebsiella pneumoniae*,^{7, 10} vancomycin-resistant enterococci (VRE), and *Acinetobacter baumannii*.^{8, 10} In evaluations of the impact of ASPs on resistance amongst gram-negative bacteria as a group, some studies found significant decreases in resistance while others found no statistically significant effect, with variation by antibiotic.^{8, 10} No statistically significant association with ASPs was found for extended-spectrum beta-lactamase (ESBL) producing *Escherichia coli*,⁷ gram-positive bacteria as a group,¹⁰ and multi-drug resistant Enterobacteriaceae as a group.¹⁰

All three systematic reviews that examined prescribing outcomes largely found decreases in antibiotic use,⁷⁻⁹ and Karanika et al. (2016) found significant decreases in broad-spectrum carbapenems and broad-spectrum glycopeptides, specifically.⁷ However, one review highlighted that some studies found ASPs to decrease prescribing of restricted antibiotics, while increasing prescribing of non-restricted antibiotics.⁹

The studies in these systematic reviews collapse a variety of ASP components as the exposure of interest, which can lead to uncertainty about which components of ASPs have an impact on antibiotic resistance and prescribing.⁷⁻¹⁰ In addition, Davey et al. (2013) noted that 77% of their studies took place at single hospitals and that some studies had short time frames pre-ASP intervention.⁸ Karanika et al. (2016) noted that the time range of their studies included pre- and post-ASP implementation periods of six months to three years.⁷

This study fills gaps in the literature by evaluating both a children's and a general acute care hospital serving the same region and by utilizing extended pre- and post-ASP implementation time periods to evaluate the long-term effects of ASPs on antibiotic resistance and prescribing amongst inpatient populations for a range of organisms and antibiotics. In addition, by including a measure of antibiotic prescribing, we can assess the predicted causal pathway of ASPs impacting antibiotic resistance via antibiotic prescribing.

METHODS

The institutional review board at the University of Washington approved all study activities. Informed consent was not required of patients whose antibiotic and susceptibility test result records were included.

Study design

A retrospective observational study was conducted to assess the impact of hospital ASP implementation on antibiotic resistance and prescribing at two Seattle, WA hospitals: one children's hospital and one general acute care hospital. Changes in the percentage of organisms

nonsusceptible to antibiotics and in antibiotic days of therapy (DOT) per 10,000 patient days were compared before and after ASP implementation.

Data sources

Susceptibility test results were collected from the microbiology administrative databases at each hospital for date ranges of July 2010 – December 2015 for the children’s hospital and January 2003 – December 2015 for the general acute care hospital. Antibiotic prescription data was collected from administrative databases at the children’s hospital (October 2010 – December 2015) and the general acute care hospital (January 2005 – December 2015).

Hospital patient-days were collected from administrative databases at each hospital to enable standardization of DOT to the size of the hospital inpatient population per quarter.

A RedCap web survey was administered to the physician and pharmacist leaders of each hospital’s ASP to characterize each hospital’s ASP. The survey included questions about whether the hospital had implemented each of the ASP components listed in the CDC Checklist for Core Elements of Hospital Antimicrobial Stewardship Programs,⁵ during which calendar year quarter each ASP component had been implemented, and what degree of confidence the ASP leader had in the quarter reported.

Interventions

The children’s hospital implemented its ASP in January 2013, while the general acute care hospital implemented its ASP in August 2007. ASP overall implementation quarter was defined as the quarter that ASP leaders specified in response to the survey questions, “When did

the facility first implement its hospital antimicrobial stewardship program?”. Stewardship leaders at both hospitals qualitatively identified prospective audit and feedback as a key component of the beginning of their ASPs.

In addition to prospective audit and feedback, in the quarter of ASP overall implementation, both hospitals began monitoring compliance with stewardship interventions; one lead or a rotating set of stewardship pharmacists began stewardship activities; and clinician, epidemiology, and microbiology laboratory personnel began working with the stewardship leaders to improve antibiotic use (Table 1). Rather than having one pharmacist responsible for stewardship, the children’s hospital has multiple stewardship pharmacists who rotate stewardship responsibilities to total one full time position. The general acute care hospital implemented multiple other ASP components in the quarter of overall ASP implementation, and both hospitals implemented some ASP components before or after the overall ASP implementation quarter.

Table 1. Quarter of first implementation of each ASP component, based on the CDC Checklist for Core Elements of Hospital Antimicrobial Stewardship Programs, relative to overall ASP implementation. Quarter values are negative before ASP implementation quarter, zero at ASP implementation quarter, and positive after ASP implementation quarter. None indicates that the facility had not implemented the ASP component as of survey completion in June 2017.

ASP component	Children’s hospital quarter	General acute care hospital quarter
Overall ASP implementation (survey question “When did the facility first implement its hospital antimicrobial stewardship program?”)	0	0
Prospective audit and feedback	0	0
Formal, written statement of support from leadership for antibiotic stewardship	>11	0
Budgeted financial stewardship support	-5	0
Physician leader responsible for ASP outcomes	-5	0

One lead or rotating stewardship pharmacists responsible for improving antibiotic use	0	0
Monitoring compliance with stewardship interventions	0	0
The following staff work with stewardship leaders to improve antibiotic use:		
Clinician	0	0
Infection prevention and healthcare epidemiology	0	0
Quality improvement	6	0
Microbiology laboratory	0	0
Information technology	8	0
Nursing	>11	0
Policy requiring prescribers to document in medical record or during order entry a dose, duration, and indication for all antibiotic prescriptions	None	None
Facility-specific treatment recommendations, based on national guidelines and local susceptibility, to assist with antibiotic selection for common clinical conditions	-11	4
Formal procedure for all clinicians to review the appropriateness of all antibiotics 48 hours after the initial orders (e.g. antibiotic time out)	None	None
Pre-authorization of specific antibiotics	<-36	0
Automatic changes from intravenous to oral antibiotic therapy in appropriate situations	None	<-14
Dose adjustments in cases of organ dysfunction	<-36	<-14
Dose optimization to optimize the treatment of organisms with reduce susceptibility	-22	<-14
Automatic alerts in situations where therapy might be unnecessarily duplicative	None	14
Specific interventions in place to ensure optimal use of antibiotics to treat the following common infections:		
Community-acquired pneumonia	-2	1
Urinary tract infection	-11	1
Skin and soft tissue infections	2	1
Surgical prophylaxis	-2	<-14

Empiric treatment of MRSA	2	1
Non-C. difficile infection antibiotics in new cases of C. difficile infection	None	1
Culture-proven invasive infections	0	1
Monitor adherence to a documentation policy	None	None
Monitor adherence to facility-specific treatment recommendations	-11	1
Monitor compliance with ≥ 1 specific interventions in place	0	0
Track rates of C. difficile infection	-20	<-14
Produce an antibiogram	<-36	<-14
Monitoring of antibiotic DOT at the unit and/or facility level	>11	0
Monitoring of antibiotic defined daily dose	None	None
Monitoring of antibiotic purchasing costs	-7	<-14
Share facility-specific reports on antibiotic use with prescribers	None	None
Current antibiograms distributed to prescribers at the facility	<-36	<-14
Prescribers receive direct, personalized communication about how they can improve their antibiotic prescribing	None	0
Providing education to clinicians and other relevant staff on improving antibiotic prescribing	4	0

Antibiotic susceptibility outcomes

To assess changes in the percent of isolates nonsusceptible to antibiotics, susceptibility test results were gathered for the following twelve organisms at both hospitals: *Acinetobacter baumannii*, *Campylobacter jejuni*, *Enterobacter spp.*, *Enterococcus faecium*, *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, non-typhoidal

Salmonella spp., *Shigella spp.*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*. These organisms were selected based on public health importance in the United States, as determined by being major causes of hospital infections (ESKAPE organisms)^{11, 12} or being serious or urgent threats identified by the CDC.¹ All ESKAPE organisms were included. All CDC serious or urgent threats were included except fungal organisms (*Candida spp.*), organisms that are not generally cultured (*Clostridium difficile*), organisms that are not generally treated on an inpatient basis (*Neisseria gonorrhoeae*), rarely seen organisms in Washington State (*Salmonella typhi*), and tuberculosis, as drug-resistant tuberculosis is treated differently than other antibiotic-resistant infections.

As can be seen in Figure 1, 70,969 susceptibility test records at the children's hospital and 179,301 susceptibility test records at the general acute care hospital were assessed for eligibility. At both hospitals, records were excluded if patient type was not inpatient or observation, if the record was for an organism other than one of the twelve study organisms, or if the result was for a neonatal intensive care unit (NICU) patient. NICU patients were excluded because this setting is optional to report in the National Healthcare Safety Network (NHSN) Antimicrobial Use and Resistance (AUR) Module July 2015 for antimicrobial use, leading to NICU patient exclusion from the collected antibiotic prescribing records. Thus, NICU patients were also excluded from the antibiotic susceptibility records in order to maintain a comparable patient population for the antibiotic susceptibility and antibiotic prescribing outcomes.

To account for testing of multiple isolates from the same patient for a single infection, only the first colony tested of each organism per patient per year (twelve-month period) was included. At the general acute care hospital, each record pertained to one type of test (e.g., disk diffusion, broth microdilution on plates, E-test test strips, and automated systems like Vitek) for

one colony, while each record for the children's hospital pertained to one colony's test results (collapsing results from different test types). E-tests use individual testing strips for individual antibiotics, testing one antibiotic at a time rather than a panel of antibiotics. Results yielded from E-test at the general acute care hospital were excluded because if E-test was the first test result for a patient-organism combination in a one-year period and thus the only test included, this would yield test results for only one antibiotic for that organism rather than multiple antibiotics, shrinking the number of results eligible for analysis. E-test results were included at the children's hospital because E-test results were merged with other testing types. In total, 6,227 susceptibility test records were eligible for analysis at the children's hospital and 13,475 at the general acute care hospital.

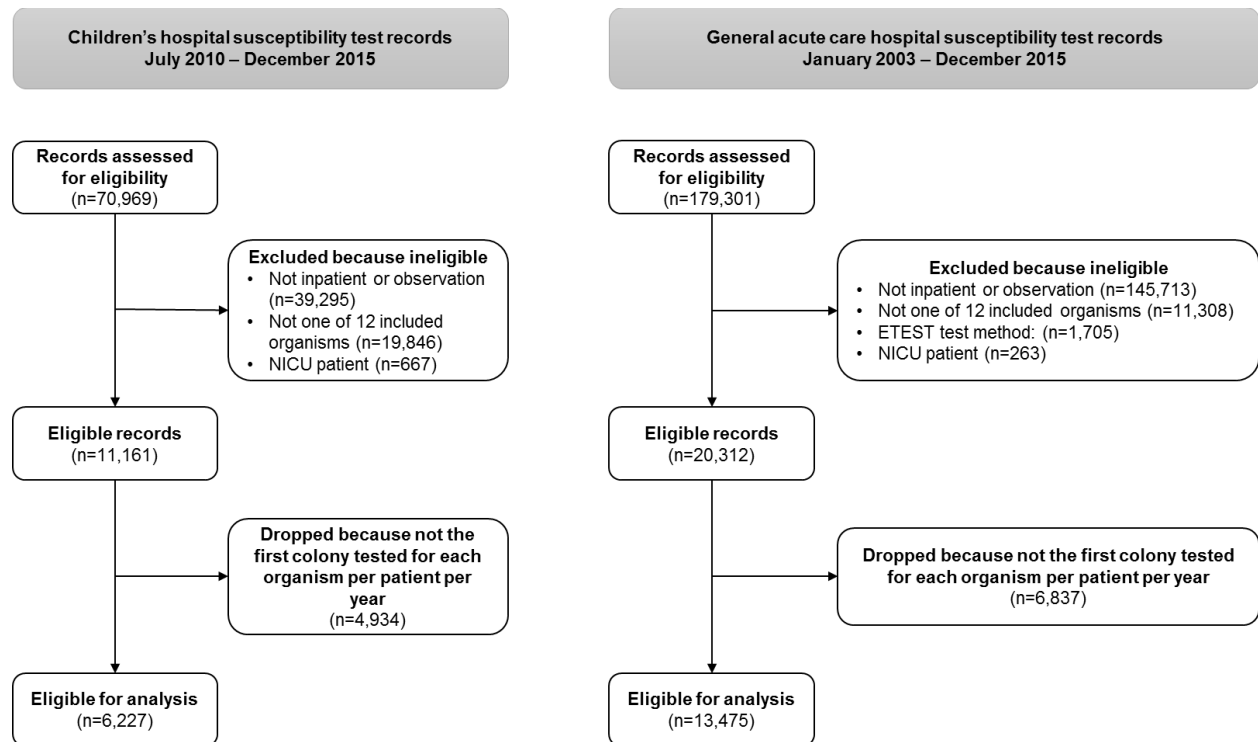


Figure 1. Flow-chart of susceptibility test record inclusion.

Antibiotic prescribing outcomes

Days of therapy (DOT) for the following 38 antibiotics were calculated for both hospitals: amikacin, amoxicillin, amoxicillin clavulanate, ampicillin, ampicillin sulbactam, azithromycin, aztreonam, cefazolin, cefepime, cefotaxime, ceftazidime, ceftazidime, ceftriaxone, cefuroxime, ciprofloxacin, clarithromycin, clindamycin, daptomycin, doxycycline, ertapenem, erythromycin, gentamicin, imipenem cilastatin, levofloxacin, linezolid, meropenem, minocycline, moxifloxacin, nafcillin, nitrofurantoin, penicillin g, penicillin v, piperacillin tazobactam, rifampin, sulfamethoxazole trimethoprim, tobramycin, trimethoprim, and vancomycin. These antibiotics were selected because they were (1) listed as reportable susceptibility test results on the NHSN AUR Module July 2015 Appendix A for at least one of the nine major included organisms (excluding non-typhoidal *Salmonella spp.*, *C. jejuni*, and *Shigella spp.* because of their low susceptibility test counts and because they are not part of the AUR module), (2) approved by the Food and Drug Administration (FDA) before 2005, (3) not discontinued as of the FDA Orange Book 2017, and (4) in use at both hospitals. Bead, microsphere, intraventricular or intrathecal, topical, ophthalmology, and NICU formulations were excluded during data pull queries because these are not collected by NHSN per the AUR Module, and study patient records were excluded during data pull queries because patients with antibiotics prescribed as part of studies would not be representative of hospital prescribing practices. Records for patients classified as inpatient or observation were included for each hospital.

As can be seen in Figure 2, 544,507 pharmacy records at the children's hospital and 764,179 records at the general acute care hospital were assessed for eligibility. Records were excluded if the patient was neither inpatient nor observation, if the patient was in the NICU, if

the administration route was antibiotic lock, if the prescription start date occurred on or after January 1, 2016, if the antibiotic stop date had an impossible value, if DOT were less than zero, if the start date occurred one day after the stop date (indicating a likely canceled order), or if DOT was not calculable. At the general acute care hospital, records missing medical record number (MRN) were dropped because MRN was the only complete unique patient identifier in the dataset. This yielded 67,617 pharmacy records eligible for analysis at the children's hospital and 415,310 at the general acute care hospital.

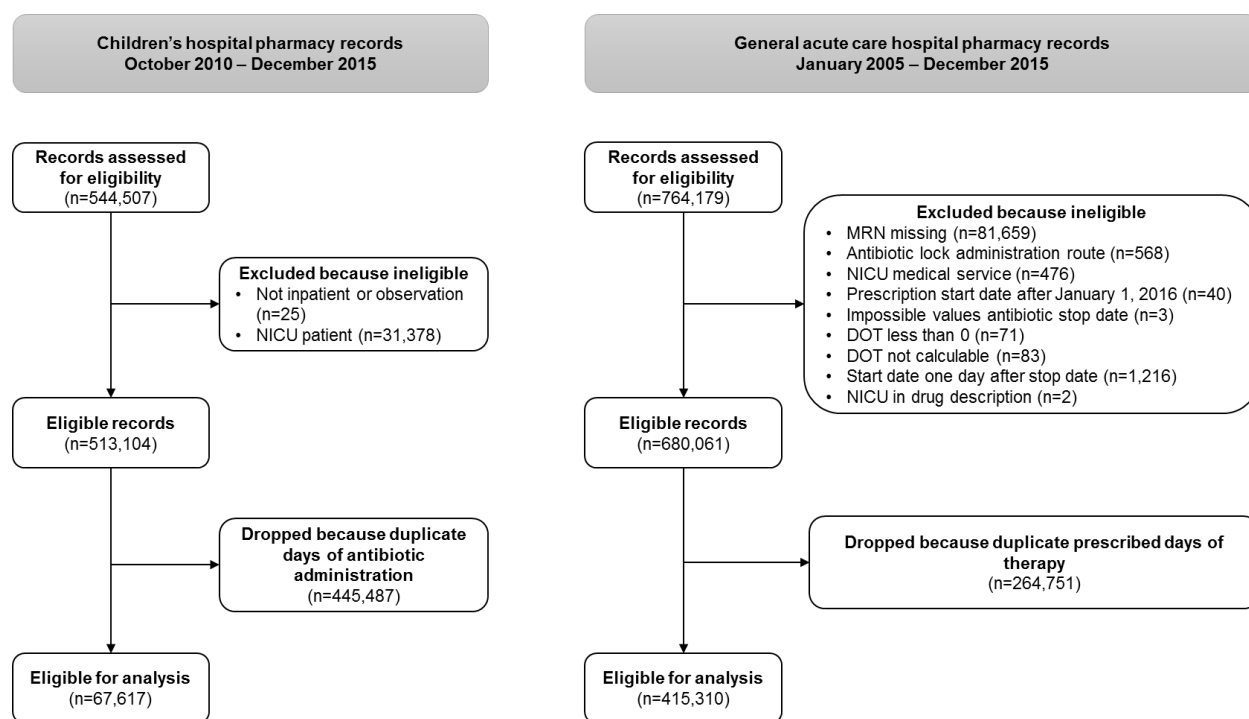


Figure 2. Flow-chart of pharmacy record inclusion.

Analysis

Antibiotic susceptibility

The susceptibility interpretations at the time of susceptibility testing, as defined by the Clinical and Laboratory Standards Institute, were used to categorize organisms as susceptible or nonsusceptible (resistant, intermediate, or susceptible dose-dependent) to various antibiotics, enabling analyses of the percentage of nonsusceptible organism-antibiotic combinations at each hospital.

A subgroup of serious and urgent threats described by the CDC¹ were selected for analysis based on having sufficient data at least eight quarters pre- and post-ASP at both hospitals: MRSA, clindamycin-resistant *S. pneumoniae*, erythromycin-resistant *S. pneumoniae*, and multidrug resistant (MDR) *P. aeruginosa*. MRSA was defined as oxacillin-nonsusceptible *S. aureus*. MDR *P. aeruginosa* was defined as *P. aeruginosa* nonsusceptible to at least one antibiotic in at least three antimicrobial categories, in concordance with the standard definition proposed by international experts.¹³ The antimicrobial categories for which *P. aeruginosa* was tested at both hospitals are aminoglycosides (gentamicin, tobramycin, and amikacin), antipseudomonal carbapenems (imipenem and meropenem), antipseudomonal cephalosporins (ceftazidime and cefepime), antipseudomonal fluoroquinolones (ciprofloxacin and levofloxacin), antipseudomonal penicillins and β -lactamase inhibitors (ticarcillin-clavulanic acid and piperacillin-tazobactam), monobactams (aztreonam), phosphonic acids (fosfomicin), and polymyxins (colistin).

The percent clindamycin-nonsusceptible *S. pneumoniae* and erythromycin-nonsusceptible *S. pneumoniae* were assessed quarterly from July 2010 – December 2015 at the children's hospital and from January 2003 – December 2012 at the general acute care hospital. The percent oxacillin-nonsusceptible *S. aureus* and multidrug-nonsusceptible *P. aeruginosa* were assessed

quarterly from July 2010 – December 2015 at the children’s hospital and from January 2003 – December 2015 at the general acute care hospital.

Antibiotic DOT

Due to the type of data available from each hospital, administered DOT were calculated for the children’s hospital and prescribed DOT for the general acute care hospital. DOT is the total number of days that an antibiotic is administered or prescribed to a patient per quarter.

At the children’s hospital, antibiotic administration date was complete in the dataset. For observations with the same patient, antibiotic, and start date, administration dates were stitched together to form a single continuous observation of DOT.

At the general acute care hospital, prescribed DOT was calculated as described in Figure 3. While antibiotic start date was complete in the dataset, stop date, frequency, doses, and discharge date were not. If the number of doses was less than zero, doses was set to missing. For antibiotics received with a frequency of at least once per day, DOT for each antibiotic prescription to a patient was calculated as the number of days between the start date and study stop date. Study stop date equaled the stop date if stop date was present for the observation, start date plus calculated duration of therapy (doses divided by frequency) if frequency and doses were present and stop date missing for the observation, and discharge date if stop date and the combination of frequency and doses were missing and discharge date present. For antibiotics received with a frequency of less than once per day, DOT for each antibiotic prescription to a patient was calculated as the number of doses, assuming one dose per day on the days in which therapy was received. If multiple observations existed for the same patient, antibiotic, and start date combination, we used a hierarchy of evidence to estimate DOT: if at least one of the

observations calculated study stop date from either stop date or the combination of doses and frequency, observations calculating study stop date from discharge date were dropped because discharge date was considered to be less reliable than the other two methods of calculating study stop date. Observations for the same patient, antibiotic, and start date were stitched together to form a single observation of DOT for each antibiotic prescription episode. Winsorization was applied to outliers at the upper 1% of DOT, setting any DOT greater than 17 to equal 17 to prevent large outliers from overly influencing the statistical inference.¹⁴

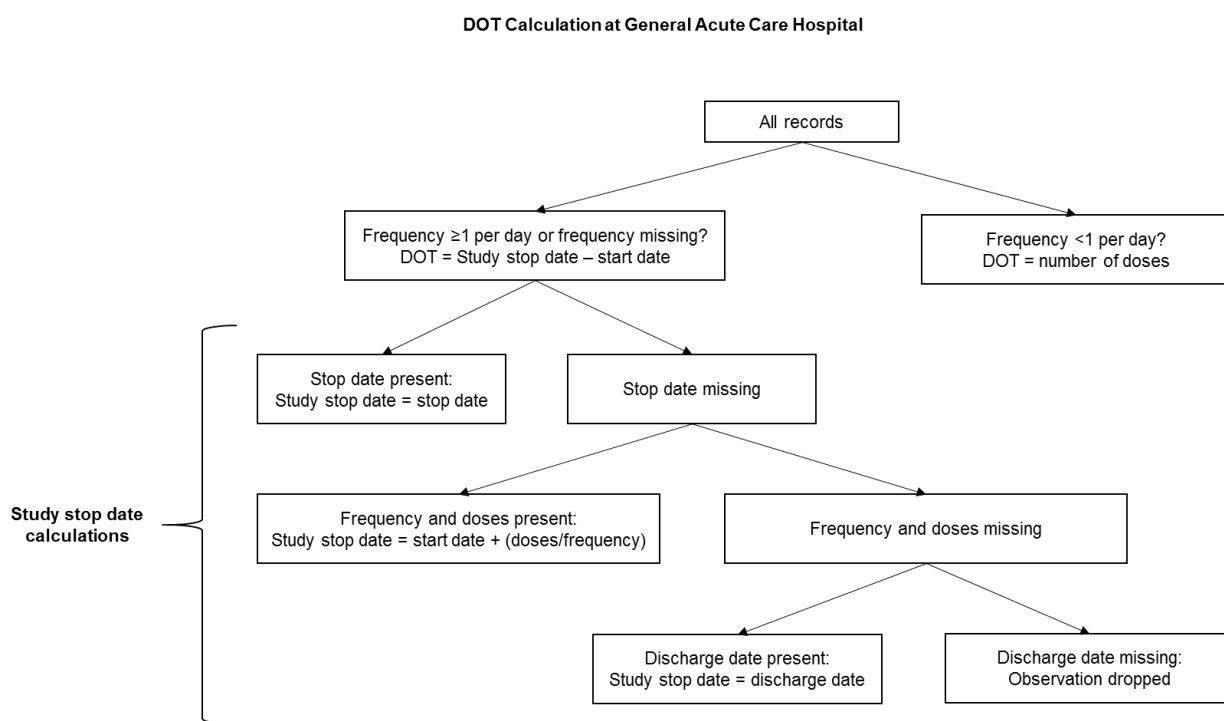


Figure 3. Antibiotic DOT calculation method at the general acute care hospital.

DOT per 10,000 patient days per quarter were totaled by antibiotic class in each hospital. The following classes were considered: aminoglycosides (amikacin, tobramycin, gentamicin), β -lactam/ β -lactamase inhibitor combinations (amoxicillin clavulanate, ampicillin sulbactam, piperacillin tazobactam), carbapenems (ertapenem, imipenem cilastatin, meropenem), cephalosporins (cefazolin, cefepime, cefotaxime, ceftazidime, ceftazidime, ceftriaxone,

cefuroxime), fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin), folate pathway inhibitors (sulfamethoxazole trimethoprim, trimethoprim), glycopeptides (vancomycin), lincosamides (clindamycin), lipopeptides (daptomycin), macrolides (azithromycin, clarithromycin, erythromycin), monobactams (aztreonam), nitrofurans (nitrofurantoin), oxazolidinones (linezolid), penicillins (amoxicillin, ampicillin, nafcillin, penicillin g, penicillin v), rifampin, and tetracyclines (doxycycline, minocycline). Third and fourth generation cephalosporins (cefepime, cefotaxime, ceftazidime, ceftriaxone) and first and second generation cephalosporins (cefazolin, cefoxitin, ceftriaxone) were also evaluated separately.

Statistical analysis

Changepoint analyses were conducted using linear regression to test for slope changes in the percentage of antibiotic nonsusceptible isolates (1) and change points and slope changes in antibiotic DOT per 10,000 patient days after ASP implementation (2) at each hospital.

$$Y = \beta_0 + \beta_1 x_{resist} + \beta_2 x_{time} + \beta_3 x_{inter} \quad (1)$$

$$Y = \beta_0 + \beta_1 x_{dot} + \beta_2 x_{asp} + \beta_3 x_{time} + \beta_4 x_{asp} x_{time} \quad (2)$$

For each of the four antibiotic susceptibility outcomes, model 1 included percent nonsusceptible (β_1); calendar year quarter centered on the quarter of ASP implementation, with quarter set to negative values prior to ASP implementation, zero during the quarter of ASP implementation, and positive values after ASP implementation (β_2); and an interaction term multiplying the quarter value by zero during quarters prior to ASP implementation and by one during and after the quarter of ASP implementation (β_3). This interaction term indicated the difference in the percent change in nonsusceptibility per quarter post-ASP implementation compared to pre-ASP implementation, i.e., the slope post-implementation minus the slope pre-implementation. For

each antibiotic class, model 2 included DOT per 10,000 patient days (β_1); a binary changepoint variable with a value of zero for quarters before ASP implementation and a value of one during and after the quarter of ASP implementation (β_2); calendar year quarter as it was defined in model 1 (β_3); and an interaction term between the changepoint variable for ASP implementation and the quarter variable (β_4). The changepoint variable indicated the change in DOT per 10,000 patient days at the quarter of ASP implementation, while the interaction term indicated the difference in the change in DOT per 10,000 patient days per quarter post-ASP implementation compared to pre-ASP implementation. The model for DOT included a changepoint variable because antibiotic prescribing might be expected to change immediately with ASP implementation, as well as long term, while the model for antibiotic susceptibility did not include a changepoint variable because a delay would occur between changing prescribing behavior and changing hospital microbe ecology. The hospitals were analyzed separately, given differences in patient population between children's and general acute care hospitals.

Statistical significance was determined at the $P < 0.05$ level with a t-test. Analyses were conducted using Stata IC 13.1.

RESULTS

Antibiotic susceptibility

The number of susceptibility test records varied by organism-antibiotic combination (Table 2). At the children's hospital, 69 to 110 susceptible tests for MRSA, 2 to 15 tests for clindamycin-nonsusceptible *S. pneumoniae* and erythromycin-nonsusceptible *S. pneumoniae*, and 173 to 243 tests for MDR *P. aeruginosa* were included per quarter. At the general acute care hospital, 55 to 96 susceptibility tests for MRSA, 1 to 10 susceptibility tests for clindamycin-

nonsusceptible *S. pneumoniae*, 1 to 9 tests for erythromycin-nonsusceptible *S. pneumoniae*, and 175 to 315 tests for MDR *P. aeruginosa* were included per quarter.

Table 2. Total number of susceptibility test results (n) and difference in the percent change of nonsusceptible isolates per quarter after ASP implementation compared to pre-ASP implementation with 95% confidence intervals (CI) for MRSA, clindamycin-nonsusceptible *S. pneumoniae*, erythromycin-nonsusceptible *S. pneumoniae*, and MDR *P. aeruginosa* at a children's hospital and a general acute care hospital.

Outcome	Children's hospital		General acute care hospital	
	n	Difference in % change per quarter (95% CI)	n	Difference in % change per quarter (95% CI)
MRSA ^a	1,940	0.19 (-0.84, 1.24)	3,634	-0.54 (-1.02, -0.07)
Clindamycin-nonsusceptible <i>S. pneumoniae</i> ^b	201	0.56 (-2.02, 3.14)	163	1.78 (-0.32, 3.88)
Erythromycin-nonsusceptible <i>S. pneumoniae</i> ^b	202	-0.02 (-5.50, 5.45)	161	2.27 (-0.92, 5.47)
MDR <i>P. aeruginosa</i> ^a	4,644	-0.45 (-0.80, -0.10)	12,797	0.01 (-0.16, 0.17)

^aFrom July 2010 – December 2015 at the children's hospital and January 2003 – December 2015 at the general acute care hospital.

^bFrom July 2010 – December 2015 at the children's hospital and January 2003 – December 2012 at the general acute care hospital.

ASP implementation was associated with a statistically significant decrease in the percent change of *P. aeruginosa* isolates that were MDR per quarter after ASP implementation compared to pre-ASP implementation at the children's hospital (Figure 4), but not at the general acute care hospital (Table 2). *S. aureus* isolates that were MRSA decreased significantly per quarter after ASP implementation compared to pre-ASP implementation at the general acute care hospital (Figure 5), but not at the children's hospital (Table 2). ASP implementation was not associated with statistically significant changes in the percent of *S. pneumoniae* isolates nonsusceptible to clindamycin or to erythromycin at either hospital.

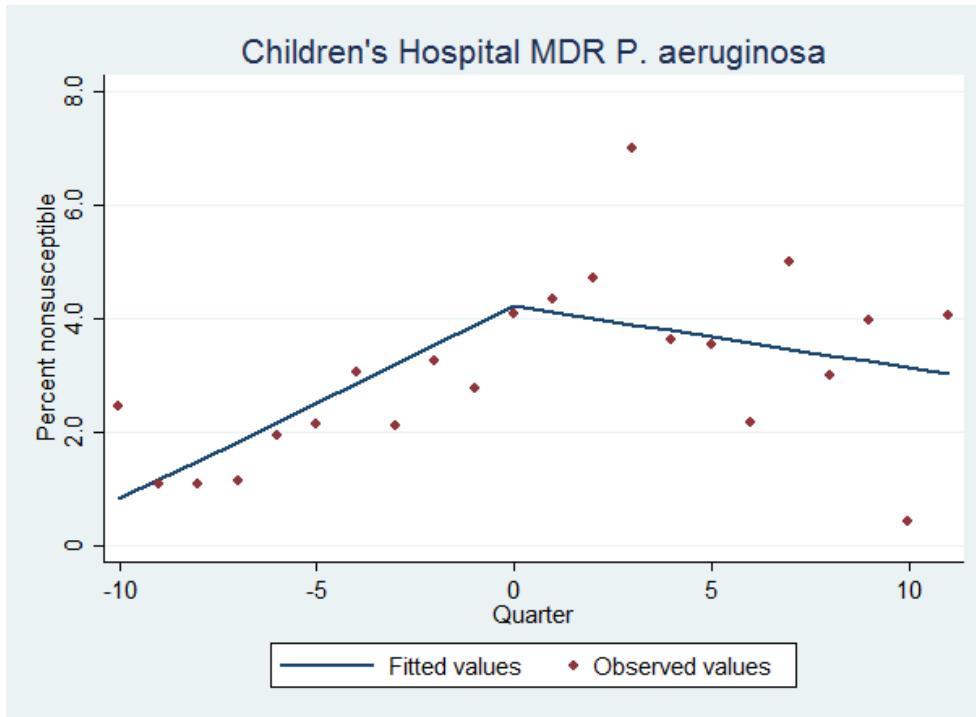


Figure 4. Percent of *P. aeruginosa* isolates that were MDR (nonsusceptible to at least one antibiotic in at least three antimicrobial categories) over time at a children's hospital. ASP implementation took place at quarter zero.

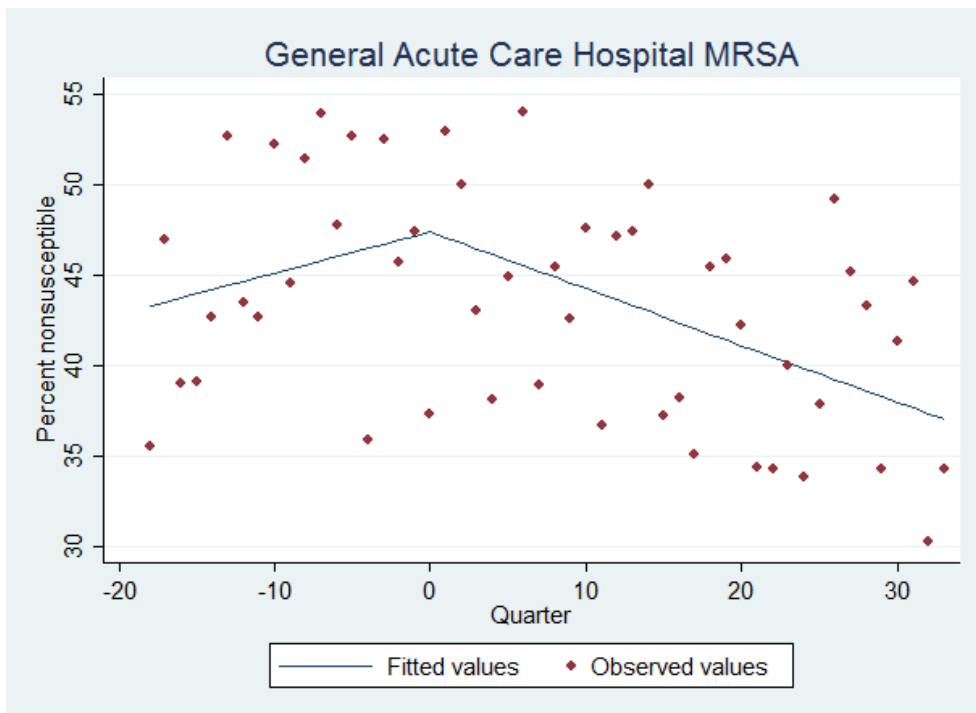


Figure 5. Percent of *S. aureus* isolates that were MRSA (nonsusceptible to oxacillin) over time at a general acute care hospital. ASP implementation took place at quarter zero

Antibiotic DOT

DOT and the number of pharmacy record observations varied by antibiotic and antibiotic class at each hospital, with antibiotic class DOT per 10,000 patient days totaled across all quarters ranging from 5.3 for lipopeptides to 2,549.0 for cephalosporins at the children's hospital and from 43.3 for nitrofurans to 2,040.9 for cephalosporins at the general acute care hospital (Table 3).

ASP implementation was associated with statistically significant decreases in glycopeptide (vancomycin) DOT and monobactam (aztreonam) DOT at both hospitals: glycopeptide DOT per 10,000 patient days decreased by 108.1 (95% CI: -199.1, -17.0) and monobactam DOT per 10,000 patient days decreased by 12.1 (95% CI: -22.0, -2.2) at the quarter of ASP implementation at the children's hospital, and the change in DOT per quarter post-ASP implementation compared to pre-ASP implementation decreased by 38.3 DOT per 10,000 patient days for glycopeptides (95% CI: -63.8, -12.7) and by 8.5 DOT per 10,000 patient days for monobactams (95% CI: -13.9, -3.0) at the general acute care hospital (Figure 6, Figure 7, Figure 8). While ASP implementation was associated with decreases in the change in β -lactam/ β -lactamase inhibitor combination, fluoroquinolone, macrolide, and oxazolidinone DOT per quarter after ASP implementation compared to pre-ASP implementation at the general acute care hospital, no statistically significant associations were present for these antibiotics at the children's hospital. At the children's hospital, ASP implementation was associated with decreases in carbapenem DOT at the quarter of ASP-implementation and in the change in carbapenem DOT per quarter after ASP implementation compared to pre-ASP implementation, as well as rifampin DOT at the quarter of ASP implementation; however, ASP implementation was not associated with changes in these antibiotics at the general acute care hospital.

Table 3. Number of pharmacy observations and DOT per 10,000 patient days per antibiotic class and antibiotic at a children's hospital from October 2010 to December 2015 and at a general acute care hospital from January 2005 to December 2015.

Antibiotic class	Antibiotic	Children's hospital		General acute care hospital	
		n observations	DOT/10,000 patient days	n observations	DOT/10,000 patient days
Aminoglycoside		2,799	380.4	11,486	145.5
	Amikacin	39	8.4	320	6.9
	Tobramycin	726	159.5	1,798	39.4
	Gentamicin	2,034	212.5	9,368	99.2
β-lactam/β-lactamase inhibitor combination		6,690	790.3	30,992	641.0
	Amoxicillin clavulanate	2,452	204.0	4,932	118.6
	Ampicillin sulbactam	988	113.7	10,960	175.3
	Piperacillin tazobactam	3,250	472.7	15,100	347.1
Carbapenem		1,600	387.0	14,706	447.7
	Ertapenem	23	2.8	3,239	61.1
	Imipenem cilastatin	14	4.0	4,123	168.2
	Meropenem	1,563	380.2	7,344	109.9
Cephalosporin		24,434	2,549.0	148,186	2,040.9
	Cefazolin	11,637	1,002.1	115,075	1,261.5
	Cefepime	1,142	279.2	5,331	140.7
	Cefotaxime	788	79.1	1,050	20.2
	Cefoxitin	1,583	106.6	54	0.7
	Ceftazidime	3,145	505.3	9,679	294.1
	Ceftriaxone	5,923	555.6	16,067	290.9
	Cefuroxime	216	21.0	930	32.8
Fluoroquinolone		1,599	207.2	57,096	1,114.7
	Ciprofloxacin	1,264	161.2	21,070	383.5
	Levofloxacin	276	36.5	32,393	647.8
	Moxifloxacin	59	9.5	3,633	83.4
Folate pathway inhibitor		10,784	830.1	20,281	550.1
	Sulfamethoxazole trimethoprim	10,699	820.8	20,268	549.6
	Trimethoprim	85	9.3	13	0.5
Glycopeptide		4,439	578.7	67,830	1,250.1
	Vancomycin	4,439	578.7	67,830	1,250.1

Lincosamide		4,631	525.7	18,557	244.0
	Clindamycin	4,631	525.7	18,557	244.0
Lipopeptide		21	5.3	1,860	51.4
	Daptomycin	21	5.3	1,860	51.4
Macrolide		3,496	267.2	11,291	227.1
	Azithromycin	2,968	189.5	9,726	180.7
	Clarithromycin	82	11.4	322	13.5
	Erythromycin	446	66.4	1,243	32.9
Monobactam		36	9.3	1,753	55.8
	Aztreonam	36	9.3	1,753	55.8
Nitrofurans		376	42.7	1,540	43.3
	Nitrofurantoin	376	42.7	1,540	43.3
Oxazolidinone		356	62.7	2,325	71.2
	Linezolid	356	62.7	2,325	71.2
Penicillin		5,666	641.2	12,745	244.0
	Amoxicillin	2,651	249.4	1,846	53.1
	Ampicillin	2,210	240.9	3,999	74.1
	Nafcillin	252	55.5	611	26.1
	Penicillin G	151	26.3	5,635	69.9
	Penicillin V	402	69.1	654	20.8
Rifampin		344	74.8	1,564	45.2
	Rifampin	344	74.8	1,564	45.2
Tetracycline		346	66.7	3,342	76.6
	Doxycycline	150	20.3	2,617	54.5
	Minocycline	196	46.4	725	22.1
Total (by either antibiotic or antibiotic class)		67,617	7,418.4	405,554	7,248.6

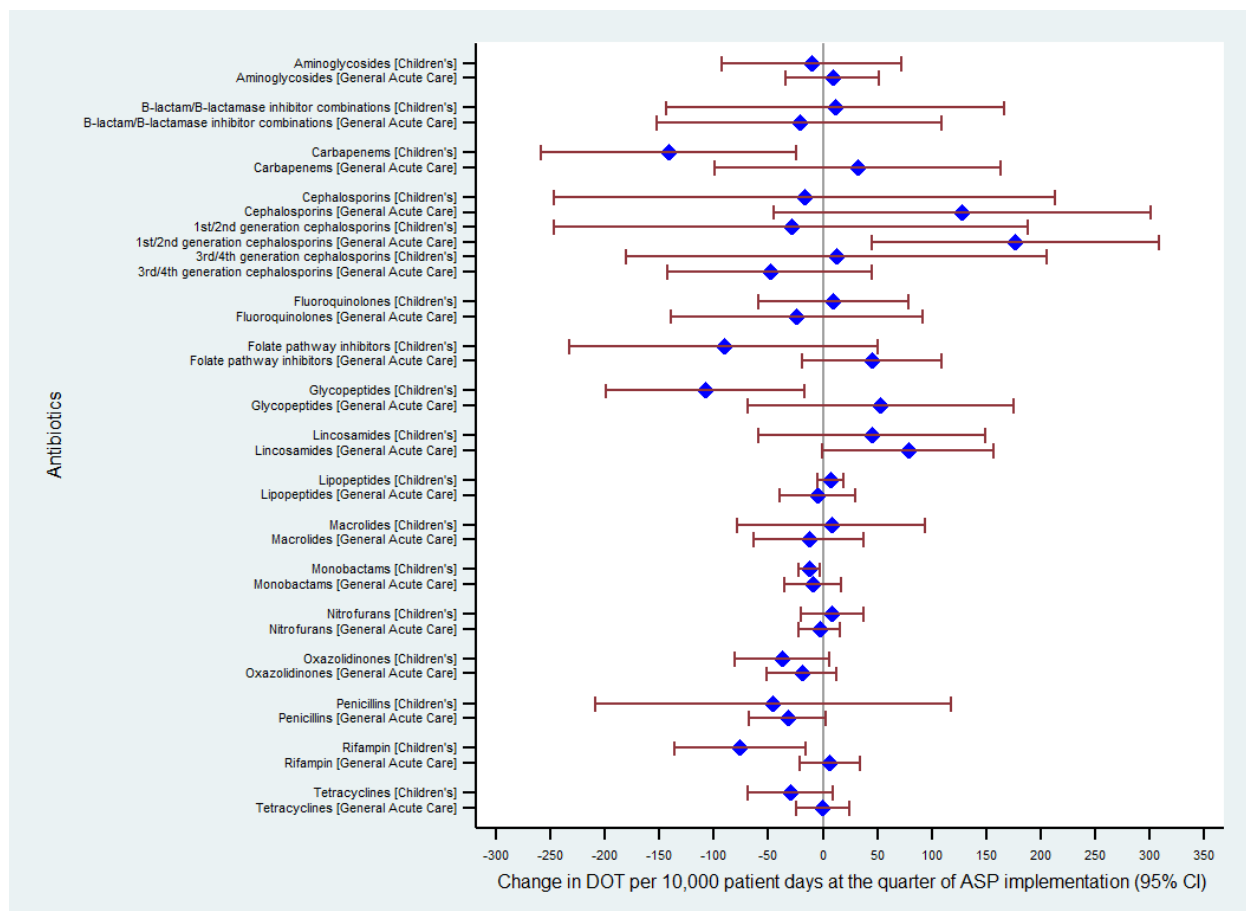


Figure 6. Forest plot of the change in DOT per 10,000 patient days at the quarter of ASP implementation with 95% CI for antibiotic classes at a children's hospital from October 2010 to December 2015 (ASP implemented January 2013) and at a general acute care hospital from April 2005 to December 2015 (ASP implemented August 2007).

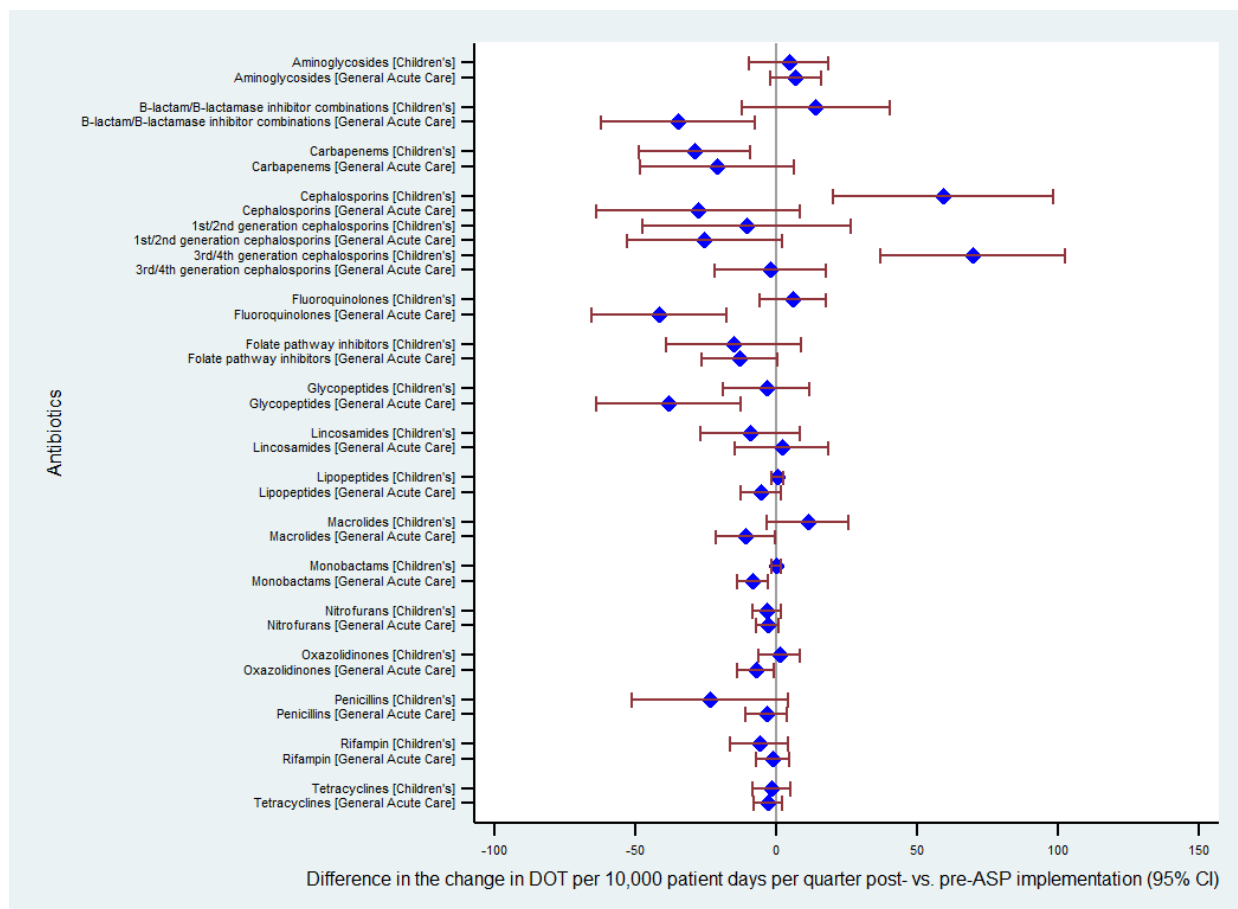


Figure 7. Forest plot of differences in the change in DOT per 10,000 patient days per quarter after ASP implementation compared to pre-ASP implementation with 95% CI for antibiotic classes at a children's hospital from October 2010 to December 2015 (ASP implemented January 2013) and at a general acute care hospital from April 2005 to December 2015 (ASP implemented August 2007).

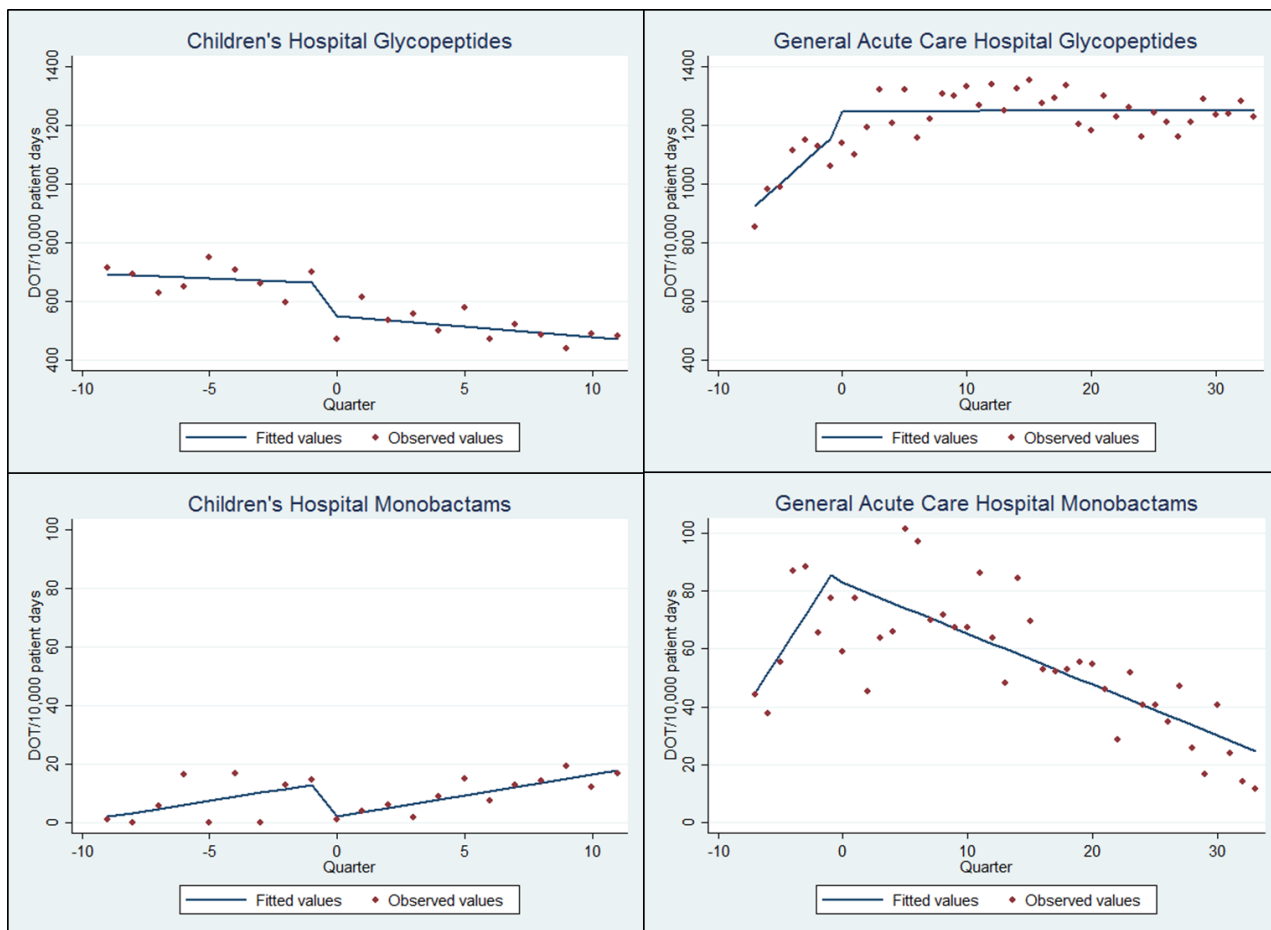


Figure 8. DOT per 10,000 patient days over time for glycopeptides and monobactams at a children's and a general acute care hospital. ASP implementation occurred at quarter zero.

ASP implementation was associated with an increase in cephalosporin DOT per quarter after ASP implementation at the children's hospital, with an even larger increase for third and fourth generation cephalosporins specifically. In contrast, no statistically significant association was present for cephalosporins overall at the general acute care hospital, while a statistically significant increase was present for first and second generation cephalosporins specifically at the quarter of ASP implementation.

No statistically significant association was found between ASP implementation and aminoglycoside, folate pathway inhibitor, lincosamide, lipopeptide, nitrofurans, penicillin, or tetracycline DOT per 10,000 patient days at either hospital.

DISCUSSION

ASP implementation was found to be associated with decreases in the percent of *P. aeruginosa* that was MDR at the children's hospital and the percent of *S. aureus* that was MRSA at the general acute care hospital, without any significant impact for clindamycin-resistant or erythromycin-resistant *S. pneumoniae*. The ASP implementation was found to either decrease antibiotic DOT or have no impact for all studied antibiotic classes except cephalosporins, for which increases were observed.

The linear regression model indicates that 0.8 percent of *P. aeruginosa* isolates at the children's hospital were MDR 2.5 years prior to ASP implementation and that, if the pre-ASP trend of increasing MDR isolates per quarter had continued without ASP intervention, 8% of *P. aeruginosa* isolates would have been MDR after 5.5 years instead of the 3% MDR with ASP intervention. ASP implementation was thus associated with a 62% reduction in MDR *P. aeruginosa* three years after ASP implementation compared to the pre-ASP trendline at the children's hospital.

P. aeruginosa can develop resistance to multiple classes of antibiotics through acquisition of resistance genes or through mutations, including during the course of treating a single infection.¹⁵ The decrease in the percent of *P. aeruginosa* isolates that were MDR at the children's hospital was accompanied by decreases in DOT for carbapenems and monobactams, two of the antimicrobial categories which are included in the MDR *P. aeruginosa* definition. However, an increase in DOT was observed for the third and fourth generation cephalosporins, another of the antimicrobial categories included in the MDR *P. aeruginosa* definition, and either no change was observed or the category was unmeasured for DOT of the other antimicrobial

categories included in the definition of MDR *P. aeruginosa*. Thus, evidence is mixed for whether the decrease in the percent of *P. aeruginosa* that was MDR at the children's hospital was due to ASP implementation via changes in antibiotic prescribing.

For *S. aureus* isolates at the general acute care hospital, the linear regression model indicates that 43.3% of *S. aureus* isolates were MRSA 4.5 years prior to ASP implementation and that, if the pre-ASP trend of increasing MRSA isolates per quarter had continued without ASP intervention, 54.9% of *S. aureus* isolates would have been MRSA after 13 years instead of the 37% MRSA with ASP intervention. Thus, ASP intervention was associated with a 32.6% reduction in MRSA 8.5 years after ASP implementation compared to the pre-ASP trendline at the general acute care hospital.

Methicillin-resistance in *S. aureus* is caused by the *mecA* gene which codes for penicillin binding protein 2a that is not responsive to β -lactams.¹⁶ It is debated whether MRSA cases are the result of clonal spread of a few ancestral strains that acquired *mecA*, increasing relative to methicillin susceptible *S. aureus* (MSSA) due to selective pressure, or whether the *mecA* gene is still acquired by MSSA through horizontal gene transfer.^{17, 18} Reversion of infections from MSSA to MRSA and from MRSA to MSSA has been documented, though it is unclear if this is due to antibiotic exposure.^{19, 20} Nafcillin and oxacillin are the preferred antibiotic choice for most MSSA infections, while vancomycin and daptomycin are the preferred antibiotic choice for most MRSA infections.²¹ Nafcillin is prescribed at the general acute care hospital, but oxacillin is not. The decrease in the percent of *S. aureus* nonsusceptible to methicillin at the general acute care hospital without a concomitant decrease in penicillins (which includes nafcillin) DOT suggests that the decrease in MRSA is not due to changes in antibiotic prescribing. The decrease in

MRSA could be due to other factors such as infection prevention and control (e.g., contact precautions) or community infection rates.

While changes in DOT per quarter after ASP implementation (either plateauing or decreasing) suggest a lasting impact of ASPs, changes in DOT at the quarter of ASP implementation may be a reflection of the Hawthorne Effect,²² with physicians changing their behavior short-term because they are newly being observed but then returning to their previous practices. These changes in level of DOT at the quarter of ASP implementation were seen in carbapenems (for which there was also a sustained change), glycopeptides, monobactams, and rifampin at the children's hospital and only in first or second generation cephalosporins at the general acute care hospital. However, prospective audit and feedback, once implemented, is a regular component of the ASPs that should not vary over time.

This study was subject to several limitations. First, this observational study does not include a control group for antibiotic prescribing, so we cannot rule out the possibility of an underlying secular trend over and above the time scale that we explicitly modeled. However, by including two hospitals with different time periods of analysis, we can mitigate this limitation.

In addition, the administrative nature of the outcome data raises limitations. The measure of antibiotic DOT varied between the two hospitals because of differences in data availability, with administered DOT at the children's hospital and prescribed DOT at the general acute care hospital. It is possible that antibiotics were prescribed at the general acute care hospital but not administered. DOT were calculated from start date and stop date, start date and the combination of frequency and number of doses, and start date and discharge date at the general acute care hospital. It is possible that the administrative data contained some data entry errors, which could lead to misclassification of the outcome, and using discharge date could bias toward longer DOT.

However, records were winsorized at 17 DOT, which should limit this bias. Because MRN was the only unique identifier, dropping records without MRN at the general acute care hospital had the potential to bias the results by changing the study sample. However, MRN was expected to be missing completely at random, i.e., records with MRN missing were assumed to be a random sample of the study population.

This ecological study compares institutions rather than individuals, raising the possibilities of unaccounted for factors impacting the outcomes and of hospital-level associations not necessarily translating to individual associations. ASP implementation is a bundled exposure with multiple components which could limit comparability of the sites and causal interpretation, but a central component of implementation – prospective audit and feedback – is identified in the implementation quarter at both hospitals. Finally, a range of outcomes were assessed, raising the possibility that multiple testing led to finding chance associations. However, all outcomes were pre-specified and all results presented. As this study is unique in assessing the broad impact of ASPs rather than the effect on a narrow set of outcomes, it was necessary to include many outcomes.

This study suggests that ASPs may have a beneficial impact on decreasing antibiotic prescribing and may be beneficial for decreasing MDR *P. aeruginosa* within children's hospitals and MRSA within general acute care hospitals. However, the generally limited impact overall suggests that additional strategies may be needed to produce stronger and more durable reductions in antibiotic prescribing, and other factors may have large influences on antibiotic resistance.

BIBLIOGRAPHY

1. Centers for Disease Prevention and Control. Antibiotic resistant threats in the United States, 2013. In: U.S. Department of Health and Human Services, editor.
2. Davies J, Davies D. Origins and evolution of antibiotic resistance. *Microbiology and molecular biology reviews* : MMBR. 2010; 74:417-33.
3. Okeke IN, Edelman R. Dissemination of Antibiotic-Resistant Bacteria across Geographic Borders. *Clinical Infectious Diseases*. 2001; 33:364-9.
4. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). *Infection control and hospital epidemiology*. 2012; 33:322-7.
5. Centers for Disease Prevention and Control. Core elements of antibiotic stewardship programs. In: U.S. Department of Health and Human Services, editor. Atlanta, GA2014.
6. Dellit TH, Owens RC, McGowan JE, Jr., Gerding DN, Weinstein RA, Burke JP, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clinical infectious diseases* : an official publication of the Infectious Diseases Society of America. 2007; 44:159-77.
7. Karanika S, Paudel S, Grigoras C, Kalbasi A, Mylonakis E. Systematic Review and Meta-analysis of Clinical and Economic Outcomes from the Implementation of Hospital-Based Antimicrobial Stewardship Programs. *Antimicrob Agents Chemother*. 2016; 60:4840-52.
8. Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *The Cochrane database of systematic reviews*. 2013:Cd003543.
9. Schuts EC, Hulscher ME, Mouton JW, Verduin CM, Stuart JW, Overdiek HW, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. *The Lancet Infectious diseases*. 2016; 16:847-56.
10. Baur D, Gladstone BP, Burkert F, Carrara E, Foschi F, Dobele S, et al. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infection: a systematic review and meta-analysis. *The Lancet Infectious diseases*. 2017.
11. Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. *The Journal of infectious diseases*. 2008; 197:1079-81.
12. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. *Clinical infectious diseases* : an official publication of the Infectious Diseases Society of America. 2009; 48:1-12.
13. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect*. 2012; 18:268-81.
14. Ruppert D. Trimming and Winsorization. *Encyclopedia of Statistical Sciences*: John Wiley & Sons, Inc.; 2004.

15. Lister PD, Wolter DJ, Hanson ND. Antibacterial-Resistant *Pseudomonas aeruginosa*: Clinical Impact and Complex Regulation of Chromosomally Encoded Resistance Mechanisms. *Clinical Microbiology Reviews*. 2009; 22:582-610.
16. Chambers HF. Methicillin resistance in staphylococci: molecular and biochemical basis and clinical implications. *Clinical Microbiology Reviews*. 1997; 10:781-91.
17. Kreiswirth B, Kornblum J, Arbeit RD, Eisner W, Maslow JN, McGeer A, et al. Evidence for a clonal origin of methicillin resistance in *Staphylococcus aureus*. *Science (New York, NY)*. 1993; 259:227-30.
18. Wielders CLC, Fluit AC, Brisse S, Verhoef J, Schmitz FJ. *mecA* Gene Is Widely Disseminated in *Staphylococcus aureus* Population. *Journal of clinical microbiology*. 2002; 40:3970-5.
19. Patel AB, Hill E, Simpson EL, Hanifin JM. Reversion of methicillin-resistant *staphylococcus aureus* skin infections to methicillin-susceptible isolates. *JAMA Dermatology*. 2013; 149:1167-71.
20. Proulx MK, Palace SG, Gandra S, Torres B, Weir S, Stiles T, et al. Reversion From Methicillin Susceptibility to Methicillin Resistance in *Staphylococcus aureus* During Treatment of Bacteremia. *The Journal of infectious diseases*. 2016; 213:1041-8.
21. Auwaerter PG. *Staphylococcus aureus*. *Johns Hopkins Medicine*; [updated May 12 2016; cited 2017 August 14]; Available from: https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540518/all/Staphylococcus_aureus.
22. Chen LF, Vander Weg MW, Hofmann DA, Reisinger HS. The Hawthorne Effect in Infection Prevention and Epidemiology. *Infection control and hospital epidemiology*. 2015; 36:1444-50.