Implementation of Antimicrobial Stewardship Interventions in Children's Hospitals Using Benchmarking

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Overuse and misuse of antibiotics is widespread in pediatrics. Over 60% of hospitalized children receive antimicrobial therapy and as much as one-third is inappropriate.[1,2] Collectively, this contributes to avoidable adverse events, promotes the expansion of antimicrobial resistant infections, and results in unnecessary costs.

Antimicrobial stewardship programs (ASP) have been developed to help promote the appropriate use of antimicrobials. **Antimicrobial use benchmarking** is a complimentary strategy that may be used to support ASPs by highlighting antimicrobial overuse and directing practice change and improvement. **Benchmarking** is a process whereby hospitals compare their antimicrobial use to similar institutions via a process of audit and feedback. Although audit and feedback has been used successfully to promote practice improvement in many areas of medicine, including for the use of antimicrobials, it has typically been performed at the level of the individual provider rather than the hospital.

Hospital-level benchmarking is a promising strategy for antimicrobial stewardship and is recommended by the Infectious Diseases Society of America.[3] The IDSA, however, has not developed specific guidelines for the use of antimicrobial benchmarking. Further, no studies have examined whether use of benchmarking data via audit and feedback facilitates both the implementation and evaluation of ASP interventions. **We have developed a standardized approach to benchmarking antimicrobial use in pediatrics, allowing for comparison of both composite and indication-specific antimicrobial use across centers.** In this proposal **we will study this novel approach** in implementing and improving ASPs in children's hospitals.

Goals and Objectives

Overall Goal

The overarching goal of this proposal is to improve the use of antimicrobials for hospitalized children by utilizing benchmarking as an audit-and-feedback strategy. This will be accomplished through the following 2 objectives:

Objectives

1) **To establish a sustainable, pediatric collaborative devoted to best practices for antimicrobial stewardship through 1) the generation and refinement of standardized metrics for benchmarking antimicrobial use, 2) data sharing, and 3) the development of common clinical guidelines for antimicrobial use.**

Quality improvement (QI) collaboratives are effective in improving outcomes in healthcare and include a track record of success in pediatrics.[4,5] Seven hospitals at different stages of ASP development have agreed to participate in this collaborative: Children's Hospital of Omaha (CHO), Robert & Ann Lurie Children's Hospital of Chicago (LCH), Cincinnati Children's Hospital Medical Center (CCHMC), The Children's Hospital of Philadelphia (CHOP), Children's Mercy Hospitals & Clinics (CMHC) in Kansas City, MO, Primary Children's Medical Center (PCMC) in Salt Lake City, UT and Seattle Children's Hospital (SCH). All are members of The Children's Hospital Association (CHA) which has demonstrated success in improving outcomes through hospital

collaboratives, including the CHA collaborative on reducing central line associated blood stream infections has resulted in a significant reduction in these infections and a cost savings of now over $100 million,[4] and the nephrology collaborative on reducing peritoneal dialysis related peritonitis, which led to a 29% reduction in the annualized peritonitis rate.[6] This collaborative will utilize the Institute of Healthcare Improvement (IHI) Models for Improvement methodology to help in establishing and implementing stewardship strategies at these hospitals. This QI model will provide a mechanism to scale the interventions to other institutions in the future.

2) **To evaluate the impact of using benchmarking data for guiding stewardship activities to improve antimicrobial use for hospitalized children. Benchmarking data will be developed, shared and then integrated into action plans for targeted stewardship interventions within 7 freestanding children's hospitals in the United States.**

A central challenge for starting and continuously improving an ASP is determining the highest priority areas to target with stewardship interventions. Many programs have implemented general stewardship strategies that 1) apply to the entire population of hospitalized patients and 2) are regulated based upon a perceived threshold for antimicrobial use deemed appropriate by the prescribing culture within a given institution. These fundamental antimicrobial prescribing strategies, however, might not effectively target areas where antimicrobial use is most problematic. For example, targeted interventions might focus on overuse of a particular drug class (e.g. carbapenems) or unnecessarily prolonged use for specific patient populations (e.g. neonates) when such prescribing patterns are identified through examination of detailed, comparative data. **As a result of failing to objectively identify and reflexively target the areas of highest priority, ASP interventions may be inefficient and/or underperforming.** The hospitals in this proposal will be provided benchmarking data that will aid them in developing such targeted stewardship interventions.

Evidence of Need for Improvement

Preliminary Data

Most hospitalized children will receive an antimicrobial and a substantial percentage of this antimicrobial exposure may be inappropriate. The implementation and refinement of ASPs has resulted in significant successes in ensuring appropriate antimicrobial use in pediatric patients. Two hospitals, CHOP (led by Dr. Gerber) and CMHC (led by Dr. Newland) have had formal ASPs for over 5 years and have published data on the effectiveness of their programs. CHOP reported that using a prior-authorization structure, the ASP improved appropriate antimicrobial use while limiting costs.[7] At CMHC, implementation of a prospective audit-and-feedback program has led to an average monthly decline of 7% in overall antimicrobial days of therapy (DOT) per 1000 patient-days over a 2-year period. A substantial portion of this reduction was due to stopping unnecessary therapy.[8] Neither institution, however, utilizes standardized antimicrobial benchmarking data to direct and improve stewardship practices.[9]

In order to continue to improve the outcomes associated with these programs as well as to provide guidance to other hospitals about high-impact targets for stewardship activities, Dr.s Newland, Gerber and Hersh have recently completed a study that identified the clinical services and patient diagnoses that are associated with greatest antimicrobial use in a large population

of over 500,000 hospitalized children.[10] We found that among clinical services, surgical patients account for over 40% of the overall days of antimicrobial therapy. This is significant because these patients account for only 28% of total hospital days and surgical patients have been shown to have the highest rate of inappropriate antibiotic use.[11] Additional analyses revealed that more than 10% of antimicrobial days were accounted for by only 4 conditions (among a total of 316): pneumonia, cystic fibrosis, appendectomy and skin and soft tissue infections (SSTI).[10] Collectively this information provides actionable insight to direct stewardship activities towards high priority clinical areas in pediatrics.

While these data are helpful to understand antimicrobial use for hospitalized children from a global perspective, there is substantial variability in antimicrobial use at the level of the individual institution.[2] The approach of defining "achievable benchmarks" holds promise in many clinical contexts.[12,13] As part of a multimodal intervention, the addition of feedback with achievable benchmarks has been shown to improve care beyond routine physician-specific feedback for influenza vaccine, foot examination, long-term glucose control, and lipid monitoring.[14] This principle has been applied to antibiotic prescribing with some success,[15-17] but has not been implemented comprehensively on a large scale nor at the level of an individual hospital. For ASPs the use of benchmarking data can facilitate more refined identification of target areas for stewardship that can be customized to the specific needs of each institution.

We have recently developed a method to benchmark antimicrobial use across hospitals that is adapted from an approach applied for adult patients.[18] This approach evaluates antimicrobial use using the metric of DOT per 1000 patient days via calculation of an observed (O) DOT for an individual institution relative to the expected (E) DOT based on aggregate data from comparator institutions. These data can be summarized as the ratio of O/E. For example, an O/E of 1.0 indicates that a hospital's antimicrobial use is equal on average to the comparison group, while a ratio of 1.1 indicates that use is 10% greater than comparator hospitals. **Importantly, the mechanism by which we categorize the DOT allows for adjusting the antimicrobial use by both the distribution of clinical conditions and disease severity for patients in each institution as a mechanism for case-mix adjustment.** Benchmark data can be used to compare antimicrobial utilization for an institution overall or for targeted clinical areas such as within orthopedics or oncology. These comparisons can assist hospitals in identifying clinical areas where utilization substantially exceeds that of comparable hospitals and to measure practice improvement over time such as after implementation of stewardship interventions. We have utilized a similar process to develop benchmarking data for the children's hospitals in this proposal.

The Institute of Medicine suggests that quality improvement is driven by the use of performance measures to drive practice change within the healthcare system. These performance measures can help motivate a system to improve and put in interventions that lead to better care for the patients. The Veterans Hospital Administration (VHA) has been a model in utilizing hospital-based performance measures to drive patient-level quality improvement or to provide feedback to the individual hospitals. Data from VHA demonstrated that patients in their hospitals received better care than those cared for in the community setting.[19] Benchmarking antimicrobial use data is an ideal performance measure that can be used to motivate quality-improvement efforts for appropriate prescribing

Data Source

The seven hospitals involved in this proposal are members of CHA and contribute administrative and billing data to the Pediatric Health Information Systems (PHIS) database. Forty-two freestanding children's hospitals, a geographically diverse group representing 17 of 20 major metropolitan areas of the US, submit data to PHIS (Figure 1). This database accounts for 85% of freestanding pediatric acute care hospital admissions and includes over 15% of all pediatric admissions that occur annually in the United States. This dataset has been utilized in previous work both describing antimicrobial use across centers as well as to determine the impact of ASP implementation on antimicrobial use. [2,8,20]

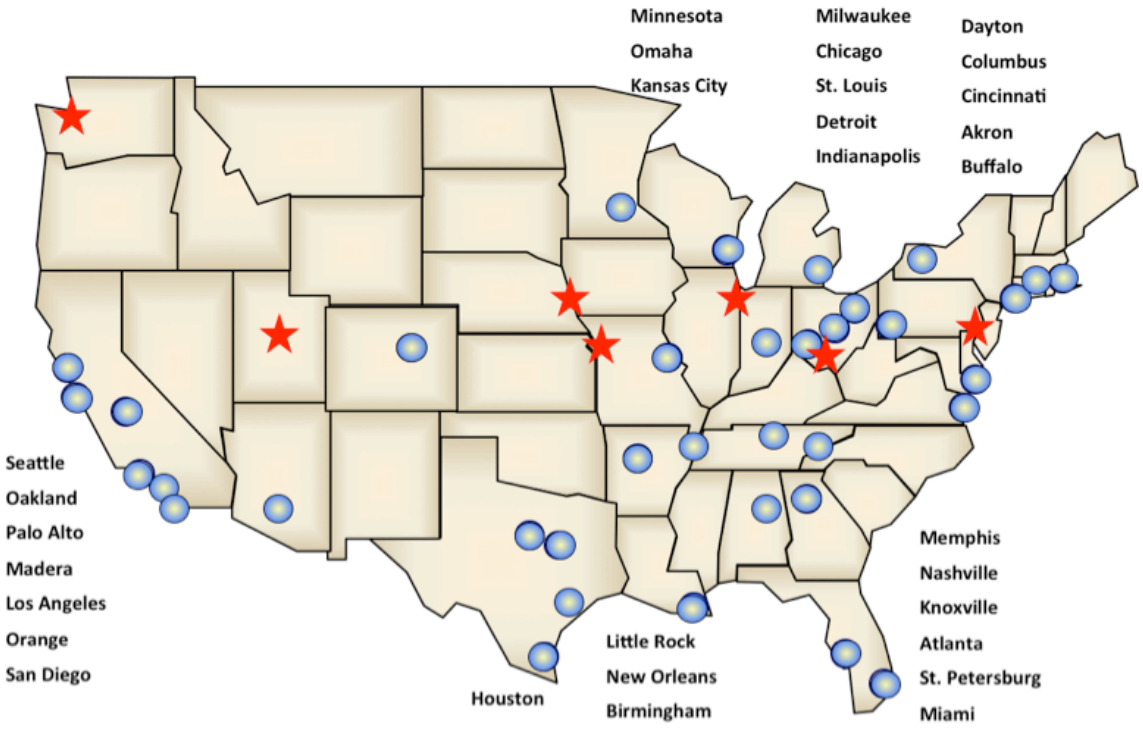

Figure 1. Children's Hospitals that contribute data to PHIS. The red stars represent hospitals participating in this proposal; blue circles represent the remainder of PHIS hospitals, which represent targets for future expansion.

Baseline Data

A major strength of this proposal is that we are using antimicrobial use data to identify high-priority target areas where stewardship interventions may be most needed for hospitalized children. The recent IDSA guidelines recognized the lack of data-driven approaches to stewardship as well as a specific deficiency in pediatric data, calling for research to occur in this area and this population.[3]

Figure 2 displays the O/E ratios for the 7 hospitals in the proposal based on data from 2011. These data demonstrate the substantial variability in baseline antimicrobial use across these institutions. Additionally, Figure 2 highlights the fact that even those institutions with established ASPs, have substantial opportunities for improvement, given that 3 of 4 (blue dots) have O/E ratios exceeding 1.0. These data reflect antimicrobial use in aggregate among the 42 hospitals contributing to PHIS, accounting and adjusting for case-mix differences within each hospital.

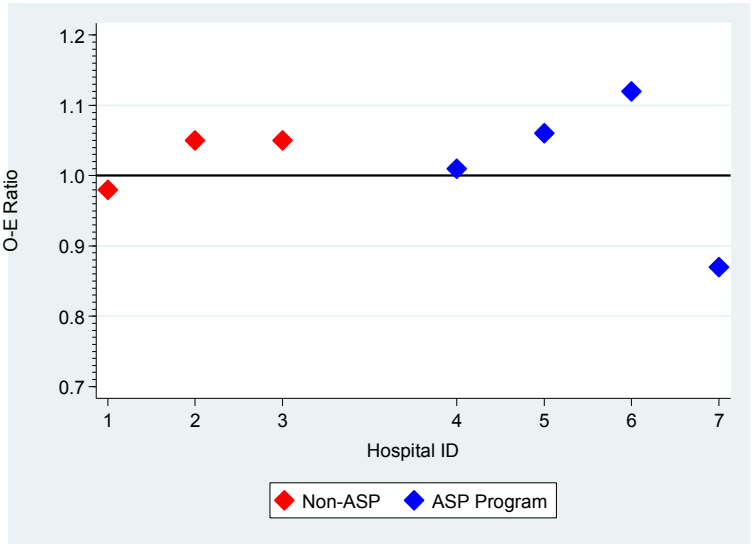

Figure 2. Overall O/E ratios for the 7 hospitals in the proposal utilizing 2011 antimicrobial use data.

Within each individual hospital, further evaluation using O/E ratios for more specific target areas, which could be at the level of a specific antimicrobial and/or the clinical service line. For

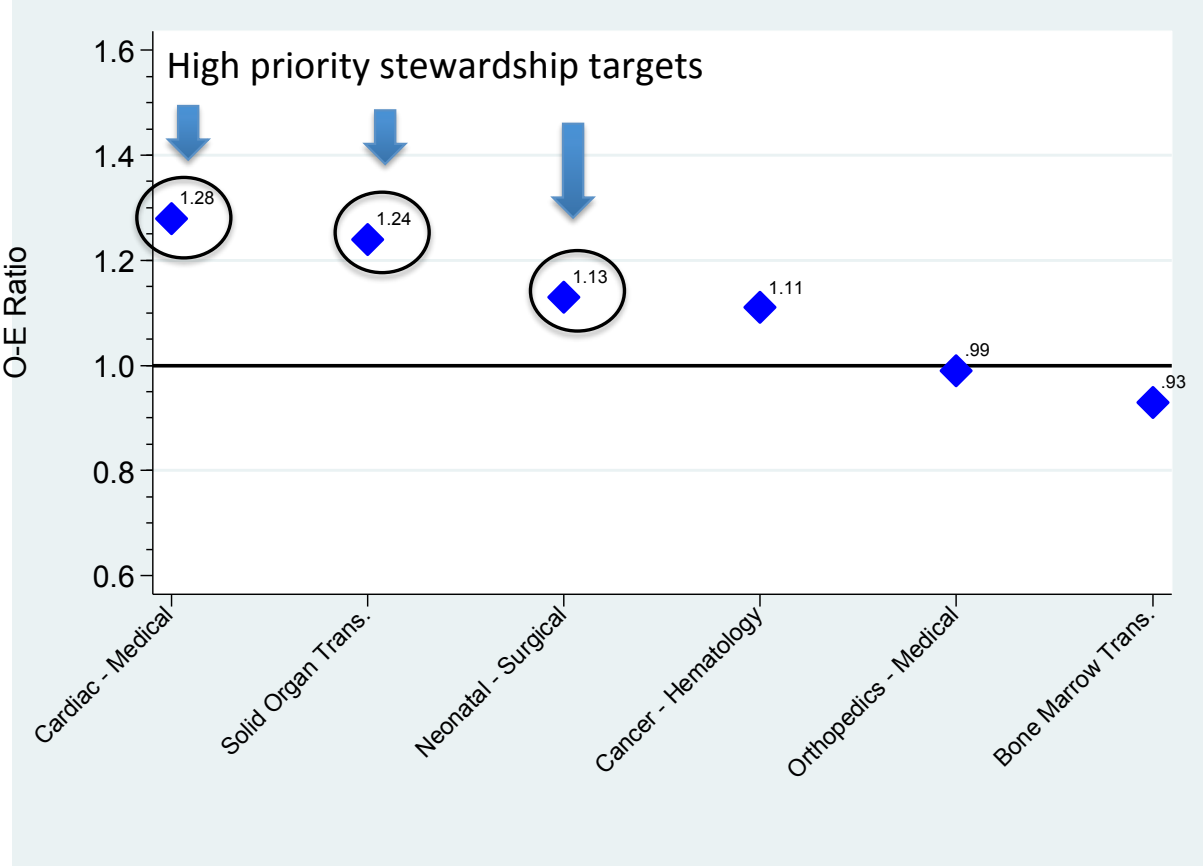

Figure 3. Service line specific O/E ratios for hospital number 3 according to 2011 antimicrobial use data.

example, Figure 3 plots the O/E ratios of specific service lines for hospital 3. Utilizing this information, stewardship efforts for this center would likely benefit from a prioritization on developing strategies to impact cardiac care, solid organ transplant and neonatal surgical care, all of which have O/E ratios that substantially exceed 1.0, which indicates higher use for these clinical areas than comparator hospitals. Utilizing these benchmark data gives the hospital the best opportunity to identify areas with the greatest need, make targeted interventions, and assess the impact of these interventions.

Study Design and Analytic Methods

Implementation Plan

Study Population

Seven children's hospitals from the CHA network are included in this proposal. These hospitals are tertiary care children's hospitals within major metropolitan areas across the US. (Figure 1) The patient population served by these centers include a diverse mix of race, ethnicity, and payor (up to 50% Medicaid in some of the hospitals).

The hospitals in this proposal feature ASPs in various stages of development, ranging from newly forming to well established. Although all relatively large, freestanding children's hospitals, there is a mix of hospital resources and stage of ASP development and maturity allowing us to test interventions across a variety of settings, which enhances the generalizability of this approach. Additionally, since these hospitals have been providing data to PHIS for over 2 years prior to the implementation of this proposal, sufficient data will be available to perform time-series analyses of the impact of the benchmarking intervention for each individual hospital. Each of these hospitals has committed to participation in both objectives of this proposal.

Interventions

Objective 1: Establishment of a QI Collaborative

The quality improvement collaborative will be formed immediately after notification of the award. The models of improvement utilized by IHI will be the foundation for improving antimicrobial use by the collaborative and hospitals. The overall collaborative as well as each hospital will develop an aim statement and driver diagram to guide their improvement. It will be expected that "plan, do, study, act" cycles will be performed and documented.

An important feature of a collaborative is the constant sharing of data and best practices. The hospitals involved will be expected to participate in monthly meetings. These meetings will be structured to review institution-specific data and overall collaborative antimicrobial use. Additionally, each hospital will be expected to share both their successes and current barriers to the identification and implementation of stewardship efforts. Other topics that will be addressed will include barriers to implementing guidelines, addressing difficult clinicians, and demonstrating the economic benefits of ASPs all of which have been identified as crucial to implementation and sustainability of ASPs. Finally, we will establish a collaborative website that will further enhance our sharing of information among hospitals. This website will serve as a central repository for the tools used in developing and implementing the hospitals' stewardship strategies.

Objective 2: Development, Sharing and Integration of Benchmarking Data into Action Plans

Initially, an antimicrobial use report with benchmarking data will be developed for each hospital. These reports will contain the overall antimicrobial use in DOT per 1000 patient days and benchmarking data. The benchmarking data will be the overall O/E ratio, the O/E ratio based on clinical service lines, and O/E ratios based on specific antimicrobials. Institutions will be instructed on how to interpret their reports and will have the opportunity to provide feedback on the content and layout of the report. If necessary, modifications of these aspects of the report will be made. This incorporation of hospital feedback is important to establish "buy-in" from participating centers and to maximize the effectiveness of the benchmarking data.

Each institution will then meet with the PI and Co-Is on this proposal to create an action plan based upon their data. For example, one hospital's benchmark data may demonstrate high O/E ratios for surgical patients. The ASP team, in conjunction with the PI and Co-Is, will review these data and subsequently evaluate antibiotic use in these areas in more clinical detail. If this investigation revealed unnecessarily prolonged antibiotic courses for patients following appendectomy, a responsive action plan might include the development of a clinical guideline to standardize antimicrobial use based on the established evidence-base, supplemented by prospective-audit and feedback specific to clinicians prescribing to surgical patients. Since the PI and co-Is have been instrumental in the development of guidelines at their respective institutions (Drs. Newland, Gerber, and Hersh), as well as specifically on surgical antimicrobial use (Drs. Newland and Gerber), their resources will be shared with ASP teams to aid in the implementation of this strategy. While clinical guidelines and prospective-audit and feedback are two of the many stewardship strategies described in the national guideline, others will be specifically tailored to the situation, considering the scope of the problem, institutional resources, and past experiences. For example, if an institution is identified as a relatively high user of meropenem based on its O/E ratio for oncology patients, an action plan could include education on and local adaptation of the most recent IDSA fever and neutropenia guidelines (which discourage routine carbapenem use). This might include development of a specific guideline for appropriate carbapenem use for the oncology service.

After developing and implementing their action plans, hospitals will receive their overall antimicrobial use data and benchmark data quarterly. These data will be evaluated to determine if additional interventions or refinements are needed. Furthermore, members of the leadership team will discuss and provide feedback on potential additional strategies and ideas regarding their current work.

Replication and Spread

The approach for benchmarking (objective 2) is designed as a standardized approach to improving antimicrobial use in hospitalized children that is not specific to the participating centers. The expansion of this approach to additional hospitals is not only possible but also expected, and will be facilitated through the development of a sustainable antimicrobial stewardship collaborative (objective 1). Since these hospitals are a part of a larger group of hospitals that submit data to PHIS, this initiative can be rapidly scaled up across the entire network by utilizing the same audit and feedback approach.

Evaluation Design and Analytic Methods

The data to be evaluated on a quarterly basis will be each hospitals' monthly DOT per 1000 patient-days. 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. The denominator, 1000 patient-days, includes all hospital days for patients admitted during the study period. Additionally, we will evaluate the O/E for antimicrobial use overall and across clinical service lines. In these two areas we will analyze the overall hospital antimicrobial use rates as well as use in targeted areas.

Data Source/Collection

The hospitals in this proposal submit data to the PHIS database quarterly. This is comprised of administrative and billing data and is submitted on all discharged patients. The database contains detailed information for each patient hospitalization, including demographics, diagnoses, medications, procedures, and laboratory tests. The database undergoes routine validation and reliability checks to ensure is regularly validated to ensure accuracy. Antimicrobial use reports from PHIS have been developed and utilized that provide the DOT rates.

We will have two outcomes to assess the effectiveness of benchmark-driven ASP interventions. The primary analysis will be in antimicrobial use, assessed by monthly O/E and the traditional metric, DOT per 1000 patient days. Secondary outcomes will include measures of antimicrobial resistance, including participating hospitals' composite antibiograms as well as assessments of resistance within specific organisms. Antibiograms will be obtained annually starting in 2010 through the end of the study period. Additionally, we will obtain the total number of Extended Spectrum Beta lactamase (ESBL) producing *E. coli and Klebsiella pneumoniae*, Carbapenem Resistant *Enterobacteriaciae* (CRE), methicillin resistant *S. aureus* (MRSA) and vancomycin resistant enterococcus (VRE) annually starting in 2010 and extending through the end of the study period. Finally, we will obtain the *C. difficile* rates per 100 discharges from each hospital starting in 2010 extending through the study period.

Data Analysis

An interrupted time series design with a control group[21] will be applied using ARIMAX intervention analysis (AutoRegressive, Integrated, and Moving Averages with Independent variables-X).[22] Because O/E and DOT are reported monthly, ARIMA modeling will be performed to control for autocorrelations, variance nonstationarity, seasonality, and trends.[22,23] Separate time series analyses for O/E and DOT will be performed for all seven hospitals combined and then for each individual hospital. Additionally, these analyses will be 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 (APR-DRG) severity levels. These analyses will also be performed using the combined O/E and DOT at the other PHIS hospitals.

A crucial aspect for the primary analysis will be the impact of the interventions on the observed-to-expected ratios. After obtaining the rates of use, the O/E ratios will be calculated. Expected antibacterial drug use will be derived similar to the method described by Polk using 4

years of PHIS inpatient data encompassing the study period.[18] In order to describe disease specific (as well as severity of illness specific) durations of antimicrobial therapy commonly employed across hospitals within the PHIS database (the "expected" use values), data will be stratified by each APR-DRG and severity of illness (SOI) score, as well as by antibacterial agent, and route of administration. For the expected duration of use values, we will use the Winsorized mean for DOT/1000 patient days which reduces bias due to outliers.

In the analysis of the secondary outcomes we are primarily interested in comparing the rates/prevalence of drug resistant organisms and *C. difficile* at two time points – the time of intervention and the completion of the study. In order to provide stable estimates, each time period will represent 3 months of pooled data. Rates will be compared using either a paired t-test or incidence rate ratio, depending on the distribution of the data. Proportions will be compared using chi-square statistics.

The strengths of this study design and analysis plan are substantial. First, the study institutions are members of CHA, the organization that maintains the PHIS administrative database, which enables the efficient abstraction of antimicrobial use data. The lead investigators on this application—Drs. Newland, Gerber, and Hersh—have extensive experience working with these data and with biostatisticians that are proficient in managing and analyzing these data. This dataset will facilitate our analysis using interrupted time series because the data can be aggregated on a monthly basis and a large amount of pre-intervention data are available. Additionally, we can compare antimicrobial use in the study hospitals to a large group of concurrent controls, which include the 34 other hospitals in the PHIS database. **Collectively these features will enable, to our knowledge, the first investigation of use of benchmarking data as an audit-and-feedback intervention to improve antimicrobial use in children's hospitals.** This will provide important new knowledge to the limited evidence-base in the area of pediatric antimicrobial stewardship.

The study design has certain limitations. The proposal is focused on freestanding children's hospitals. Although this setting accounts for a substantial proportion of acute pediatric care, the generalizability of our findings about benchmarking may not be generalizable to other types of hospitals providing care for children, especially those that do not have the resources for comprehensive ASPs. Second, because each study site is unique, our study may not be able to account for certain local contextual factors that may either facilitate or serve as barriers to the benchmarking intervention. To some extent, the creation of the QI collaborative will mitigate this challenge because the experiences at each individual site will be shared and updated with the larger group.

Expected Results

We expect these interventions to lead to a significant improvement that might vary across institutions with different resources and experience with improvement initiatives. Previous data from a pediatric ASP demonstrated an 18% average monthly decrease in targeted antimicrobial use.[8] Therefore, for hospitals with new ASPs and the center with a recently initiated program, we expect an overall decrease in antimicrobial use based on DOT per 1000 patient days of at least 10-20%. For hospitals in which some stewardship strategies are already underway, we expect at least a 5-10% decline in the O/E ratios. For established, mature ASPs, we believe that a minimum of a 5-10% decrease in both DOT per 1000 patient days and O/E

should be observed for the targeted areas in which interventions are implemented. Given the relative novelty of benchmarking data, the motivation of clinicians who have agreed to participate, and the documented effect of the impact of antimicrobial overuse on the emergence of antimicrobial resistance, we feel that these estimates are both conservative and clinically significant.

Dissemination of Project Outcomes

The outcomes of this project will be disseminated in many different forums. First, abstracts will be submitted to the Infectious Diseases Society of America annual meeting on both the aggregate results as well as individual hospital results. We will also present the results at the annual Pediatric Antimicrobial Stewardship Conference, organized by Dr. Newland. Manuscripts will also be prepared and published in national peer-reviewed journals. Finally, the ASP collaborative is designed to become a sustainable forum for antimicrobial stewardship. We expect that the initial investment of resources into the formation of this collaborative and the tools developed through its work will provide a template for ongoing initiatives in the field of pediatric antimicrobial stewardship.

Work Plan

Following notification of the award at the end of June, a kick-off webinar will be scheduled outlining the deliverables and expected implementation plan. All sites will be expected to obtain IRB approval by the end of August 2013. Following IRB approval each institution will receive their benchmark data. The site investigators will have the opportunity to review the data as well as request additional data to be gathered in areas that the investigator might believe an ASP intervention could be beneficial. During September of 2013, the PI, co-Is and each site investigator will conduct a webinar to develop an antimicrobial stewardship action plan that will describe the target area and the stewardship intervention.

Following this meeting the site PIs will take the necessary steps to implement the intervention and determine the additional data that will be collected during the intervention by January 1, 2014 including the antibiogram data, multi-drug resistant organisms rate, and *C. difficile* rate. Following the implementation, quarterly benchmarking data will be reported to each hospital for review.

During the development of the ASP interventions, quality improvement (QI) science education will be provided to the participants during the first 2 monthly webinars. This education will aid the groups in developing a specific aim, identifying their stewardship interventions and determining what additional data they will need to collect. Following the QI webinars, education on implementation science will be provided in the webinars scheduled for September through December 2013. Following these, the monthly webinars will be focused on reviewing the antimicrobial data, sharing lessons learned, and troubleshooting barriers to performing the stewardship interventions. These reviews may result in additional interventions or changing the interventions if determined to not be beneficial or too difficult to implement. At the completion of the study period, time series analysis will be conducted to determine if the overall use declines, O/E ratio improved, and if specific areas that were targeted improved in their use.

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