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Project Title: **What is the Optimal Antimicrobial Stewardship Strategy: Pre-Prescription Authorization or Post-Prescription Review and Feedback?**

I. Overall Goal and Objectives: Although antimicrobial stewardship programs (ASP) have been successful in improving antimicrobial prescribing and reducing antimicrobial use, the best method for modifying antimicrobial prescription habits of healthcare workers has not been established. Specifically, there have been no head-to-head comparisons of the two most common approaches to stewardship interventions: pre-prescription authorization (PPA), where the prescriber must obtain permission and advice from the stewardship program prior to release of the first dose of antimicrobials, and post-prescription review and feedback (PPRF), where the provider can choose any empiric antimicrobial regimen but the stewardship team reviews the selected antimicrobials 48-72 hours after they were started and provides advice to the prescriber at that time. The **overall goal** of this proposal is to determine which of these two approaches has the greatest impact on appropriate antimicrobial prescribing and clinical outcomes. This goal will be reached via the following **key objectives**:

1) To assess the impact of pre-prescription authorization (PPA) compared to post-prescription review and feedback (PPRF) on antimicrobial use as measured by (a) overall antimicrobial use; (b) appropriate antimicrobial use both when antimicrobials are started and at 48-72 hours; and (c) excess days of therapy.

2) To assess the impact of PPA compared to PPRF on the clinical outcomes as measured by (a) length of hospitalization, (b) rates of *Clostridium difficile* infection, (c) antimicrobial-associated adverse events and (d) emergence of antimicrobial resistance at the patient level.

Differences in antimicrobial use and clinical outcomes between the two antimicrobial stewardship approaches will be measured via a crossover study involving four medical units at The Johns Hopkins Hospital. Two medical teams will be assigned to receive PPA without PPRF and two medical teams will be assigned to receive PPRF without PPA over a four month period. After a one month wash-out period, the teams will switch and receive the opposite intervention. **We hypothesize that while PPA may improve the use of empiric antimicrobial therapy, PPRF will have a greater impact on reduction in overall antimicrobial use and adverse clinical outcomes and increase appropriate antimicrobial use and duration of therapy.** The **expected impact** of this proposal is to provide the first-ever comparison of these two approaches in the same institution and study population. These results will help to guide hospitals and other healthcare institutions in choosing the optimal strategy for performing antimicrobial stewardship. The **primary stakeholders** targeted for this intervention are both antimicrobial stewardship programs, which will gain important information regarding the strengths and weakness of different approaches to stewardship interventions, as well as patients, who will benefit from having their antimicrobial therapy optimized.

II. Evidence of Need for Improvement: In the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America's "Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship" published in 2007, PPA and PPRF are both listed at A-II recommendations as approaches for reducing antimicrobial use in the healthcare setting; however, no recommendation is provided regarding which approach is preferred for reducing antimicrobial use or resistance.[1] An update to these guidelines entitled "IDSA/SHEA

Clinical Practice Guidelines on Antimicrobial Stewardship," is underway that is co-chaired by the principal investigator of this proposal (Sara Cosgrove).[2] Despite an intervening 5 year period since the publication of the previous guideline, the writing committee for the updated guideline has identified a persistent lack of data comparing the impact of PPA and PPRF on antimicrobial use and clinical outcomes.

Both approaches have potential pros and cons (Table 1). PPA facilitates early intervention to ensure that patients who need antimicrobials get the most appropriate agents when they are at the most vulnerable to adverse outcomes from infection; patients have appropriate cultures collected before antimicrobials are initiated; and patients who do not need antimicrobials are not exposed to them as even a day of antimicrobial therapy can alter the gut microbiota and lead to adverse events.[3] However, PPA impacts only the agents that are restricted, allowing prescribers to use unrestricted agents freely; has minimal impact on prescribers decisions about narrowing the spectrum of therapy or duration of therapy after more clinical data are available; and requires someone to be "on-call" to answer requests in real time, which can be resource-intensive. In contrast, PPRF allows for greater flexibility in when review of antimicrobial use and feedback to prescribers occurs and may be easier to incorporate into daily workflow. PPRF allows for a more evidence-based discussion with prescribers including microbiological and clinical data that has evolved since antimicrobials were started. However, uptake of PPRF is generally optional as once antimicrobials have been initiated, stewardship teams generally do not have the authority to discontinue or alter therapy. Additionally, PPRF does not address the large burden of empiric antimicrobials that are started unnecessarily.[4]

Table 1: Primary Approaches to Stewardship Interventions

Approach	Pros	Cons
Pre-prescription authorization (PPA)	• Ensures that patients get the most appropriate empiric therapy which may have greatest impact on outcome • Reduces unnecessary antimicrobial starts and initial antimicrobial exposure	• Impacts use of restricted agents only • Addresses empiric use more than downstream use • Resource intensive in real time • May lead to delays in initiation of therapy
Post-prescription review and feedback (PPRF)	• More clinical and microbiology data available to enhance recommendations • Greater flexibility in timing of intervention	• Compliance with recommendations is optional • No impact on initial antimicrobial exposure in patients who did not require antimicrobials

Information of the comparative effectiveness of different approaches to stewardship is important for several reasons. First, it informs physicians and pharmacists who are implementing antimicrobial stewardship programs what approaches may accomplish the goals of their particular program. Second, as the development of quality metrics regarding appropriate antimicrobial use moves forward, it informs what measures are developed and provides data to support the benefit of these measures.[5, 6]

Our investigative team has a well-established track record of performing both PPA and PPRF. The Johns Hopkins Hospital Antimicrobial Stewardship Program (JHH ASP) (www.hopkinsmedicine.org/amp) was created in 2001 with the mission of ensuring that patients treated with antimicrobial agents receive optimal therapy. The program is headed by

Dr. Cosgrove and by an infectious diseases-trained pharmacist, Dr. Edina Avdic, a co-investigator on the proposal. Dr. Pranita Tamma, another co-investigator, directs the JHH Pediatric ASP. The program's daily activities include oversight of the pre-prescription authorization system in which a phone conversation is required for approval of most broad-spectrum agents (Box 1). Antimicrobial use in days of therapy/1000 patient days is tracked annually by agent and by unit to evaluate the success of the program and areas for investigation.

The program publishes the Johns Hopkins Hospital Antibiotic Guidelines that are updated annually based on new national and local guidelines, changes and additions to the hospital's antimicrobial formulary, and evaluation of the hospital's antibiogram. All physicians, nurse practitioners, and physician assistants who provide direct patient care receive hard copies of the Guidelines annually in July and they are available on the web site above. These guidelines contain sections that address empiric and pathogen-directed therapy as well as duration for the vast majority of clinical syndromes that would be seen on the medicine service.

Box 1: Study Antimicrobials
Restricted Antibiotics at JHH
Amikacin
Ampicillin/sulbactam
Aztreonam
Cefepime
Ceftaroline
Ceftazidime
Ciprofloxacin
Colistin
Daptomycin
Fosfomycin
Linezolid
Meropenem
Moxifloxacin
Piperacillin/tazobactam
Tigecycline
Vancomycin (IV and PO)
Selected Unrestricted Antibiotics at JHH
Cefazolin
Ceftriaxone
Clindamycin
Ertapenem
Gentamicin
Metronidazole
Oxacillin
Tobramycin
TMP/SMX

Dr. Cosgrove and the investigative team have implemented several research interventions to assess the utility of PPRF both at Johns Hopkins and at other institutions.[7-9] Dr. Cosgrove led a multicenter population level intervention trial funded by the Centers for Disease Control and Prevention (CDC) assessing the impact of PPRF on medicine and surgery units at five academic medical centers. Patients on broad spectrum antimicrobials for at least 48 hours were identified prospectively and appropriateness of their antimicrobial therapy was systematically evaluated using standardized definitions for inappropriate use. Three hundred and ninety of 1429 (27.3%) study antimicrobial courses were assessed as unjustified and recommendations to modify or stop therapy were accepted for 260 (66.7%) courses. Broad spectrum antimicrobial days per 1000 patient days decreased significantly during the intervention period at two sites, increased at two sites and stayed the same at one site. The sites that had decreases had existing antimicrobial stewardship programs, suggesting institutional support and endorsement of stewardship may facilitate the success of PPRF programs that target numerous antimicrobial classes.

The research team had led other CDC-funded studies to assess and improve antimicrobial use for pneumonia. An intervention on the JHH medicine services consisting of education and prospective feedback to providers regarding antibiotic choice and duration of therapy for community-acquired pneumonia led to a decrease in antimicrobial days from a median of 10 to 7 days ($p<0.001$).[7] Most recently, after our baseline data suggested that approximately 77% of adult ICU patients at JHH were receiving unnecessary antibiotic therapy for ventilator-associated pneumonia based on assessment by a multidisciplinary adjudication committee, we implemented an intervention consisting of an orderset with automatic stop orders, education

regarding use of a scoring system to guide therapy for pneumonia (i.e., the clinical pulmonary infection score), and feedback regarding antimicrobial decisions to providers to improve antibiotic use. This intervention is ongoing.[10]

In summary, work done by the investigators both as part of the daily activities of the JHH ASP and as part of research investigations establishes their ability to implement the research proposed in this grant. They have the skills to perform PPA and PPRF, access to data to allow identification of patients on broad-spectrum antimicrobial agents and to assess days of antimicrobial therapy by unit and service, and a strong track record of successfully implementing stewardship intervention projects.

III. Study Design and Analytic Methods

III-a. Implementation Plan: As noted in the previous section this proposal **builds upon the existing work, projects and programs** of the JHH ASP. Currently, prescribers at JHH are required to obtain PPA for most antimicrobials by a member of the JHH ASP via a telephone conversation. The JHH ASP currently is not performing PPRF on the medical service. We will conduct a crossover study to assess the impact of PPA compared to PPRF on process measures (a) overall study antimicrobial use, (b) appropriate empiric and definitive antimicrobial therapy, and (c) excess antimicrobial days and outcomes measures (a) duration of hospitalization, (b) rates of *C. difficile* infection, (c) antimicrobial-associated adverse events, and (d) emergence of antimicrobial resistance at the patient level on four internal medicine services over a nine month period. The origins of these interventions and the rationale for the initiative have been described in Section II. **We hypothesize that while PPA may improve the use of empiric antimicrobial therapy, PPRF will have a greater impact on reduction in overall antimicrobial use and adverse clinical outcomes and increase appropriate antimicrobial use and duration of therapy.**

III-a.1. Study Population and Setting: The Johns Hopkins Hospital is a 1059-bed tertiary care hospital in Baltimore, Maryland. The medicine service at JHH is comprised of a hospitalist service, a private service, and four "firms" or teams of housestaff who admit patients to their own non-ICU medicine floor. The intervention will occur on the four firm teams. Each firm has ten interns and ten residents who rotate on that specific service every 2-4 weeks. The attending for the service known as the "assistant chief of service" is constant throughout the year. This structure gives the unique advantage of having the same physicians on each firm during the entire period of the proposed study, limiting potential bias with regard to different practice patterns affecting antimicrobial decisions by the prescribing physicians. Patient populations between firms are similar with regards to demographic characteristics and medical conditions (Table 2). Patients will be included in the study if 1) they reside on the study units and belong to a firm attending, 2) they are started on study antimicrobials listed in Box 1 during the study period, and 3) they are 18 years of age or older. If a patient is started on an antimicrobial while on a non-study unit and transferred to a study unit, the patient will be included

Table 2: Study Unit Demographics

	#Beds	#Admissions	Median Age	% Female	% Black
Unit 1	18	655	56	56%	65%
Unit 2	24	851	54	53%	59%
Unit 3	24	742	55	57%	54%
Unit 4	20	843	58	50%	62%

in the study. If a patient receives a study agent but has been transferred to a non-study unit or discharged at the time of the intervention call, that patient will not be included in the study.

III-a.2. Methods: This is a crossover study of PPA versus PPRF of antimicrobials prescribed by the internal medicine housestaff at JHH over a nine month period (Table 3). Two firms will be assigned to continue obtaining PPA of antimicrobials from a member of the JHH ASP for months

Table 3: Crossover Study Design

Firms	Month 1-4	Month 5	Month 6-9
1 and 3	PPA (standard practice)	PPA (standard practice)	PPRF
2 and 4	PPRF	PPA (standard practice)	PPA (standard practice)

1-4, usually obtained by a phone call with an approved authorizer. The other two firms will be allowed to prescribe antimicrobials without obtaining PPA; however, PPRF for all study antimicrobials that are continued for at least 48-72 hours will be performed by a member of the JHH ASP, also generally via telephone. The intern will be the primary prescriber contacted for both arms. Month 5 will be a wash out period where all firms revert to standard practice of PPA. At month 6, the firms will switch interventions for the subsequent 4 months. Performing the study over a 9 month period will allow completion of the study in the same academic year, ensuring that the same housestaff on each firm are involved in both periods of the study. Antimicrobials prescribed as the result of an infectious disease consult will not be intervened upon or included.

III-a.3. Implementation Plan

a. Medicine services: The JHH ASP has a strong relationship with the medicine housestaff and the housestaff program director, Sanjay Desai, MD. Dr. Cosgrove was both a member of the housestaff and an assistant chief of service and has maintained strong ties with the housestaff program as firm faculty. In our experience, engaging thought-leaders such as Dr. Desai and the assistant chiefs of service in intervention studies has improved study engagement and participation. Dr. Desai, the assistant chiefs of service, and the housestaff have an established track record in developing and executing research projects that involve the entire housestaff.[11] In addition, the JHH ASP has had prior success in engaging housestaff in projects regarding improvement in antimicrobial use.[7, 12] None of the four assistant chiefs of service have specialty training in infectious diseases; such training would have the potential to create bias in antimicrobial selection practices on the firm to which that person practices. At the start of each of the three study periods, our investigative team will meet with the medicine housestaff services to review the study methods and goals. We will have additional meetings when the housestaff rotate each month to ensure smooth transitions from month to month.

b. *Pharmacy services*: The hospital pharmacy that dispenses to the medicine service routinely enforces the standing prior authorization policy at The Johns Hopkins Hospital and will continue to do so except for the periods that the firms are in the PPRF arm of the study. Mechanisms are in place for the medicine pharmacy to identify patients whose antimicrobials do not require PPA during the PPRF period. At the start of each of the three study periods, meetings will be held with the medicine pharmacy to review the study method including which firms/attendings

will not require pre-authorization for antimicrobials during that period. We will have additional meetings monthly to address issues that arise.

III-a.4. Sample Size Calculation: Days of therapy by agent type/1000 patient days from August 2012-February 2013 are shown in Table 4; each floor has ample numbers of antimicrobial starts and days as 48% of patients were started on antimicrobials during their hospitalization.

Table 4: Days of Antibiotic Therapy/1000 Patient Days from August 2012-February 2013

	Carbapenems[a]	Cephalosporins[b]	Quinolones[c]	Vancomycin	Total Rate[d]	Total ABX Days[d]
Unit 1	30	144	41	216	446	1508
Unit 2	46	109	59	402	486	2320
Unit 3[e]	63	131	49	574	589	2814
Unit 4	26	139	38	273	414	1551

[a]Imipenem, meropenem, ertapenem; [b]Cefepime, ceftriaxone; [c]Moxifloxacin, ciprofloxacin

[d]Antibiotics above plus aztreonam, piperacillin/tazobactam, po vancomycin, metronidazole, cefazolin, clindamycin

[e]Antibiotic use higher because adult cystic fibrosis patients admitted to this floor; they are not part of study population

Evaluating data from Table 4, including 14 commonly used antibiotics and projecting through an 8th month (the duration of the study minus the washout period), there would be 9,364 antibiotic days over an eight month period with a mean of 484.3 days of antibiotic therapy per 1,000 patient days across the four units. During this period an estimated 3,532 patients would be admitted with 1,695 receiving antibiotic therapy. As we will evaluate all antibiotic use during the proposed study, and not just the 14 commonly used antibiotics included in the sample size calculations, the calculations in Table 5 are a conservative estimate.

Table 5: Sample Size Calculations

N (antibiotic days)	1,571	699	393
Detectable difference	10%	15%	20%
Power	0.80	0.80	0.80
α	0.05	0.05	0.05

III-a.5. Feasibility of Replicating the Intervention in Other Settings: The primary goals of the proposed study are to compare the strengths and weaknesses of PPA and PPRF with regard to impact on appropriate antimicrobial use as well as to assess clinical outcomes associated with each approach. As both approaches are considered reasonable methods for performing stewardship interventions, reproducing either at another site that is initiating or has an existing antimicrobial stewardship program is likely feasible and depends on the resources present at those sites. The results of our study will be most generalizable to non-ICU settings in other teaching hospitals given that we will be working with housestaff closely in this intervention. They are also likely to be generalizable to community hospitals with hospitalist programs as hospitalists are usually available to engage in discussions about their patients' antimicrobial therapy. It is less generalizable to ICU settings where it is common practice to administer broad spectrum therapy empirically and consequently less opportunity to modify antimicrobial therapy using a PPA approach.

III-b. Evaluation Design and Analytic Methods:

III-b.1. Data Collection

a. *Patient data* include 1) demographics, 2) admission diagnoses, 3) comorbidities, 4) modified APACHE II score at the time of initiation of antimicrobial therapy, 5) indication for antimicrobial

therapy as defined by the treating team, 6) duration of hospitalization after antimicrobial were started, 7) evidence of *C. difficile* infection after antimicrobials were started, and 8) evidence of adverse events related to antimicrobial therapy, and 9) evidence of emergence of antimicrobial resistance after antimicrobials were initiated.

b. Antimicrobial data include 1) the names and duration of study antimicrobials and other antimicrobials prescribed and 2) the appropriateness of the antimicrobial use as determined by review by the ASP using standardized definitions from prior investigations (Table 6).[9]

Table 6: Reasons for Inappropriate Therapy

	Empiric selection	**Definitive selection**
Therapy needs modification	More appropriate choice based on JHH Antibiotic Guidelines	• Organism not susceptible to selected agent • Narrower choice based on clinical or microbiological data • Overlapping spectrum of activity • Unnecessary IV therapy
Therapy needs to be stopped	No evidence of infection	• No evidence of infection • Unnecessary prophylaxis

c. Data sources: Patients started on study antimicrobial will be identified using alerts developed in our clinical surveillance software system (TheraDoc, Hospira, Inc., Lake Forest, Il). Other variables will be obtained via chart review. Collected data and adjudicated outcomes will be entered into data extraction forms and then double entered in a Microsoft Access database.

d. Timing of data collection: Patient data will be collected as patients are entered into the study. For patients in the PPRF arm, the assessment and recording of whether antimicrobial selection is appropriate at 48-72 hours will be determined in real time so that immediate feedback can occur to the teams. Cases will be identified at first at 48 hours. If an intervention can occur at that time then the investigator will make it. If the investigator needs to wait another day for more clinical information, or missed the 48 hour time point because it occurred on a weekend, the intervention will occur at 72 hours. At the time the assessment occurs, the investigators will also determine the appropriateness of the empiric antimicrobial choice for its appropriateness as *empiric therapy before any additional clinical or microbiological information was known*. For patients in the PPA arm, the assessment of the appropriateness of the empiric antimicrobial choice, the changes (if any) made at 48-72 hours, and the duration of therapy will be made retrospectively, after the study period ends. This will occur for two reasons: 1) to avoid having the study team detect possible improvements to antimicrobial regimens in the PPA arm when such intervention should not happen according to the study design and could lead to bias to the null and 2) to lessen the large data collection burden during the nine month study period. Patients can enter the study multiple times if they are started subsequently on a new agent of interest that was not recommended as part of the study intervention

III-b.2. Process Measure Measurement

a. Antimicrobial use: This is the **primary outcome measure** for this investigation. Administration of any agent in Box 1 on a given days will represent a day of therapy for that agent. In instances when antimicrobials are expected to have prolonged activity allowing for infrequent dosing, such as vancomycin, we will also count days of expected activity. Antimicrobial use will be

normalized to days of therapy/1,000 patient days and days of therapy/admission. Patient days will be patient days of patients in the study population.
b. *Appropriate antimicrobial use*: Appropriateness of antimicrobial choices will be assessed at two time points, initiation of empiric therapy and at 48-72 hours after initiation, in both the PPA and PPRF arms of the study using the approach described above in Section III-b.1. Basic classifications of inappropriate antimicrobial use are listed in Table 6. Appropriate durations of therapy will be determined based on published recommendations which are available in the JHH Antibiotic Guidelines. We will express these results both as proportions of patients who received appropriate therapy as well as calculate excess antimicrobial days.

III-b.3. Outcome Measures Measurement

a. Length of hospital stay: Length of stay will be counted from the time antimicrobials are started until the patient is discharged.
b. C. difficile infection: Patients in the study population will be evaluated for development of *C. difficile* infection (positive PCR and ≥3 unformed stools within 24 hours or ileus) during their hospital stay.
c. Antimicrobial-associated adverse events: Adverse events associated with antimicrobials will be categorized as severe allergic reaction (hives, anaphylaxis), nephrotoxicity, hepatotoxicity, myelosuppression, neurological/psychiatric, and dermatological (rash, itching).
d. Antimicrobial resistance at the patient level: Patients in the study population will be evaluated for development of incident infection or colonization with resistant pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococcus species (VRE), or multi-drug resistant Gram negative organism (MDRGN). An MDRGN will be defined as a positive culture growing an organism resistant to at least one agent in at least three of the following classes: (1) aminoglycosides, (2) antipseudomonal penicillins, (3) antipseudomonal penicillin β-lactamase inhibitors, (4) third-generation cephalosporins, (5) aztreonam, or (6) carbapenems, and incident infection or colonization with Candida species within 30 days of initiation of study antimicrobials.[13]

Given the relatively short intervention periods in this study, we will create a combined endpoint called “adverse clinical event” to increase power to detect adverse clinical events associated with antimicrobial use. This will be the combination of *C. difficile* infections, adverse events, and emergence of antimicrobial resistance as defined above.

III-b.4. Statistical Analysis: Student’s t-test and Chi-square tests will be used to compare baseline characteristics for continuous and categorical variables, respectively. Linear regression, after assessing for the need for log-transformation for non-normally distributed data, will be conducted on continuous outcomes (days of overall therapy, days of excess therapy, and duration of hospital stay), adjusting for potential confounders, including seasonal variations in antibiotic prescription if detected. Covariates with p-values <0.20 in the univariable analyses will be included in the multivariable model. The impact of the two stewardship strategies on differences in incidence of CDIs or MDROs will be assessed using Poisson regression modelling to calculate incidence rate ratio (IRR) and 95% confidence intervals (CIs). For all tests, two-sided P-values of <0.05 will be considered statistically

significant. Data will be analysed with Stata version 12.0 software (Stata Corporation, College Station, TX, USA).

III-b.5. Controlling for Bias: A cluster randomized study is not feasible for this project given resources available; therefore, we have maximized the study design as much as possible to limit threats to internal validity. This includes having a cross-over design where each unit serves as a control for itself and also has a control during the same period.[14] An alternative to this study design would be to randomize each event to receive either PPA or PPRF; however, this approach has both logistic and bias-related difficulties. First, in many cases, empiric antimicrobials need to be selected quickly and it is not feasible to wait to determine whether a phone call will need to be placed for authorization before starting antimicrobials. Second, if antimicrobial events are randomized, the same prescribers could be making decisions about patients who are randomized to PPA or PPRF at the same time which has the potential to cause prescribers to pay more attention to antimicrobial decisions they make and may lead to bias towards the null.

Although data are conflicting as to whether seasonality may impact bacterial infections and subsequent antibiotic use, both study periods will include months with similar average temperatures which should account for any seasonal variation that may occur with antimicrobial prescription.[15-18] Additional bias could arise if housestaff "learn" to perform their own PPRF; this is more likely to be seen in the group assigned to PPA in the second intervention period. Based on our experience with other investigations, we believe that the different types and complexities of PPRF recommendations are not easy for housestaff to learn, mitigating this bias. Indeed, in our multicenter PPRF study, antimicrobial use reverted to normal during the post-intervention period. Other approaches to mitigating bias have been discussed in Sections III-a.1., III-a.3., and III-b.1.*d*.

III-b.6. Expected Impact of the Project: The results of this project will **add considerable knowledge to the field** regarding the relative advantages and disadvantages of the two primary approaches to antimicrobial stewardship, PPA and PPRF. The results of this study will inform future guidelines, inform stewardship programs as they make decisions about where to invest valuable resources and inform regulators who are developing quality measures or other requirement related to antimicrobial stewardship.

III-b.7. Dissemination Plan: We will present our results of our investigation at ID Week (hosted by the Infectious Diseases Society of America, Society for Healthcare Epidemiology of America, and other national infectious diseases groups) and produce at least one publication regarding our results. We will post the data collection tools we develop to evaluate antimicrobial use both at the time of prescription and after 48-72 hours on the JHH ASP website (www.hopkinsmedicine.org/amp). This will allow other institutions that are interested in developing an ASP to access these materials easily.

III-c. Detailed Work Plan and Deliverables Schedule: The first three months of the two year study period will be used to prepare for implementation of the intervention. These tasks include IRB submission and approval, development of data collection tools, and development of an Access database. The last two weeks of this period will also include meeting with the medicine housestaff as a whole and the medicine teams (including the clinical specialty

Appendix: References

1. Dellit TH, Owens RC, McGowan JE, Jr., 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. *Clin Infect Dis.* 2007;44(2):159-177.

2. Infectious Diseases Society of America Antimicrobial Agent Use Practice Guidelines. http://www.idsociety.org/Antimicrobial_Agents/#Antimicrobial%20Stewardship. Accessed 4/8/2013.

3. Rangel SJ, Fung M, Graham DA, Ma L, Nelson CP, Sandora TJ. Recent trends in the use of antibiotic prophylaxis in pediatric surgery. *J Pediatr Surg.* 2011;46(2):366-371.

4. Camins BC, King MD, Wells JB, et al. Impact of an antimicrobial utilization program on antimicrobial use at a large teaching hospital: a randomized controlled trial. *Infect Control Hosp Epidemiol.* 2009;30(10):931-938.

5. CMS. Patient Safety Initiative FY 2013 Pilot Phase - Revised Draft Surveyor Worksheets https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/Downloads/Survey-and-Cert-Letter-13-03.pdf. Accessed 4/8/2013.

6. 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). *Infect Control Hosp Epidemiol.* 2012;33(4):322-327.

7. Avdic E, Cushinotto LA, Hughes AH, et al. Impact of an antimicrobial stewardship intervention on shortening the duration of therapy for community-acquired pneumonia. *Clin Infect Dis.* 2012;54(11):1581-1587.

8. Cosgrove SE, Patel A, Song X, et al. Impact of different methods of feedback to clinicians after postprescription antimicrobial review based on the Centers For Disease Control and Prevention's 12 Steps to Prevent Antimicrobial Resistance Among Hospitalized Adults. *Infect Control Hosp Epidemiol.* 2007;28(6):641-646.

9. Cosgrove SE, Seo SK, Bolon MK, et al. Evaluation of postprescription review and feedback as a method of promoting rational antimicrobial use: a multicenter intervention. *Infect Control Hosp Epidemiol.* 2012;33(4):374-380.

10. Nussenblatt V, Advic E, Berenholtz S, et al. The inappropriate diagnosis and treatment of ventilator associated pneumonia is common in medical and surgical intensive care units. Abstract presented at: IDWeek 2012; San Diego, CA.

11. Desai SV, Feldman L, Brown L, et al. Effect of the 2011 vs 2003 duty hour regulation-compliant models on sleep duration, trainee education, and continuity of patient care among internal medicine house staff: a randomized trial. *JAMA Intern Med.* 2013:1-7.

12. Redding W, E A, Carroll K, Cosgrove S. Gut check: an antimicrobial stewardship intervention to improve clinician ordering and prescribing behaviors surrounding *Clostridium difficile* testing with PCR. Abstract presented at ID Week 2012; San Diego, CA.

13. Magiorakos AP, Srinivasan A, Carey RB, 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.* 2011;18(3):268-281.
14. Harris AD, Bradham DD, Baumgarten M, Zuckerman IH, Fink JC, Perencevich EN. The use and interpretation of quasi-experimental studies in infectious diseases. *Clin Infect Dis.* 2004;38(11):1586-1591.
15. Fukuta Y, Clarke LG, Shields RK, Wagener MM, Pasculle AW, Doi Y. Lack of seasonality in the occurrence of multidrug-resistant Acinectobacter baumannii complex. *Infect Control Hosp Epidemiol.* 2012;33(10):1051-1052.
16. Leekha S, Diekema DJ, Perencevich EN. Seasonality of staphylococcal infections. *Clin Microbiol Infect.* 2012;18(10):927-933.
17. Patrick DM, Marra F, Hutchinson J, Monnet DL, Ng H, Bowie WR. Per capita antibiotic consumption: how does a North American jurisdiction compare with Europe? *Clin Infect Dis.* Jul 1 2004;39(1):11-17.
18. Richet H. Seasonality in Gram-negative and healthcare-associated infections. *Clin Microbiol Infect.* 2012;18(10):934-940.
19. Tamma PD, Cosgrove SE. Duration of antibiotic therapy for community-acquired pneumonia in children. *Clin Infect Dis.* 2012;54(6):883-884; author reply 885.
20. Tamma PD, Cosgrove SE. Antimicrobial stewardship. *Infect Dis Clin North Am.* 2011;25(1):245-260.
21. Tamma PD, Cosgrove SE, Maragakis LL. Combination therapy for treatment of infections with gram-negative bacteria. *Clin Microbiol Rev.* 2012;25(3):450-470.
22. Tamma PD, Turnbull AE, Milstone AM, et al. Clinical outcomes of seasonal influenza and pandemic influenza A (H1N1) in pediatric inpatients. *BMC Pediatr.*2010*;*10:72.
23. Tamma PD, Turnbull AE, Milstone AM, Hsu AJ, Carroll KC, Cosgrove SE. Does the piperacillin minimum inhibitory concentration for Pseudomonas aeruginosa influence clinical outcomes of children with pseudomonal bacteremia? *Clin Infect Dis.* 2012;55(6):799-806.
24. Tamma PD, Turnbull AE, Milstone AM, Lehmann CU, Sydnor ER, Cosgrove SE. Ventilator-associated tracheitis in children: does antibiotic duration matter? *Clin Infect Dis.* 2011;52(11):1324-1331.
25. Tamma PD, Wu H, Gerber JS, et al. Outcomes of children with enterobacteriaceae bacteremia with reduced susceptibility to ceftriaxone: do the revised breakpoints translate to improved patient outcomes? *Pediatr Infect Dis J.* Mar 6.