Research Prioritization Topic Brief: Comparative effectiveness of alternative interventions to address antimicrobial resistance in hospitals

PCORI Scientific Program Area:
Improving Healthcare Systems

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October 7, 2015

This report was prepared by NORC at the University of Chicago with consultation from Improving Healthcare Systems staff within the Patient-Centered Outcomes Research Institute (PCORI). All statements, findings and conclusions in this publication are solely those of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI) or its Board of Governors.

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Executive Summary

Comparative Research Question. What is the comparative effectiveness of alternative interventions to address antimicrobial resistance in hospitals, including informatics technology, point-of-care prescribing and patient-outcome monitoring, or use of educational materials, and reminder systems, in improving hospital lengths of stay and mortality?

Brief Overview of the Topic. The National Institutes of Health define antimicrobial drug resistance as microbes (bacteria, viruses, fungi, and parasites) evolving to survive in the presence of drugs that previously killed or limited the growth of the microbe (NIAID, 2009). While a certain amount of resistance is expected with appropriate use of medications, misuse and over-use of antimicrobials in healthcare accelerates resistance (WHO, 2015). Recent systematic reviews suggest several promising types of hospital antimicrobial stewardship programs (ASPs) that have been shown to modify prescribing behaviors, yet stronger evidence is needed to test whether such programs directly lead to improvements in patient outcomes (e.g., hospital length of stay, survival).

Patient-Centeredness. Research that compares hospital-based interventions to address antimicrobial resistance is relevant to patient outcomes including patient health status and health care utilization, since the effectiveness of a prescribed treatment regimen is compromised by antimicrobial resistance and lack of adherence to guidelines by health-care providers. Comparative effectiveness research is also relevant to clinicians, public health professionals, and the public at large, because antimicrobial resistance is a threat to many treatments and procedures common in modern medicine, specifically in the hospital setting. Addressing existing gaps in the literature may inform hospital-based ASPs that ultimately improve patient outcomes.

Impact on Health and Populations. According to the Centers for Disease Control and Prevention (CDC), in the United States, at least 2 million people acquire and 23,000 people die from antibiotic-resistant infections each year (CDC, 2013). The CDC estimates the annual economic cost of antibiotic resistance to be as high as $55 billion, accounting for avoidable healthcare costs and lost productivity (e.g., lost wages, extended hospital stays, and premature deaths). For instance, the CDC notes that inappropriate prescribing practices put “patients at risk for a Clostridium difficile infection, deadly diarrhea that causes at least 250,000 infections and 14,000 deaths each year in hospitalized patients” (CDC Vitalsigns, 2014).

Assessment of Current Options. Several recent systematic reviews underscore the effectiveness of ASPs in realizing appropriate antibiotic use in hospitals. A 2013 Cochrane review comprising 89 studies found that a variety of ASP interventions improved antibiotic prescribing; 21 studies indicated a decreased number of infections in hospital as a result of the ASPs (Davey, et al., 2013). A 2011 systematic review of ASPs in critical care noted, “All studies of restriction and pre-approval policies reported a statistically significant reduction in the use of target antibiotics,” but cautioned “a compensatory increase, by ~200% - 300%” in other antibiotic use (Kaki, et al., 2011). There is a lack of high quality research on the impact of ASPs on patient-centered outcomes (e.g., hospital length-of-stay, mortality). Citing the extensive use of uncontrolled, interrupted time series designs in hospital ASP studies, there is a need to improve study...
designs and conduct comparative (i.e., head-to-head) studies of different types of ASPs. Furthermore, many studies are of short duration (one year or less); longer-duration, prospective studies are needed.

**Likelihood of Implementation in Practice.** The White House’s 2014 *National Strategy for Combating Antibiotic Resistant Bacteria* denotes the high priority of this topic for health care. Federal health agencies, states (e.g., California) and other influential stakeholders, such as the Infectious Diseases Society of America (IDSA) have promulgated guidance on the topic. The majority of US hospitals have considered implementing an ASP (Doron, et al., 2013), and even hospitals without ASPs have incorporated some kind of antimicrobial stewardship technique to optimize antibiotic use. AHRQ recently published a “toolkit” to inform the implementation of hospital antimicrobial stewardship programs. All these factors suggest that health care providers will buy-in to implement this guidance in practice, although certain barriers must be overcome (e.g., physician lack of attendance at trainings, physician compliance, and physician buy-in).

**Durability of Information.** The threat of antimicrobial resistance will likely remain stable or grow in the near future – in the U.S. as well as overseas. While the effectiveness of many of the interventions discussed in this brief are likely to remain stable in the near future (e.g., educational materials), interventions that rely on health information technology, such as computer-assisted decision support and clinical practice guidelines may continue to evolve and produce new information that will serve the field.
Topic: Comparative effectiveness of alternative interventions to address antimicrobial resistance in hospitals

Overall Comparative Research Question. What is the comparative effectiveness of alternative interventions to address antimicrobial resistance in hospitals, including informatics technology, point-of-care prescribing and patient-outcome monitoring, or use of educational materials, and reminder systems, in improving hospital lengths of stay and mortality?

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2. Introduction:
According to the Centers for Disease Control and Prevention (CDC), 20-50% of all antibiotics prescribed in U.S. acute care hospitals are either unnecessary or inappropriate, which contributes to “one of the most serious and growing threats to public health”: antimicrobial resistance (CDC, 2014). The National Institutes of Health define antimicrobial drug resistance as microbes (bacteria, viruses, fungi, and parasites) evolving to survive in the presence of drugs that previously killed or limited the growth of the microbe (NIAID, 2009). While a certain amount of resistance is expected with appropriate use of medications, misuse and over-use of antimicrobials in healthcare accelerates resistance (WHO, 2015). As more strains of bacteria become resistant to more antibiotics, treatment choices are limited, less effective, and more expensive. In addition, common medical procedures that rely on antibiotics, such as transplants, surgery, or chemotherapy, could become impossible (The White House, 2014). In the U.S. at least 2 million people acquire and 23,000 people die from antibiotic-resistant infections each year (CDC, 2013), and a growing number of hospital and other healthcare setting-associated infections are caused by bacteria that are resistant to multiple antibiotics (CDC, 2014).

Antimicrobial resistance has drawn national attention in recent years. In 2014, the White House released a National Strategy for Combating Antibiotic Resistant Bacteria, indicating resistance presents a serious threat to both public health and our country’s economy security (The White House, 2014). Also in 2014, the CDC released the publication Core Elements of Hospital Antibiotic Stewardship Programs, which details important characteristics of successful hospital antibiotic stewardship programs (ASPs) (CDC, 2014), complementing similar guidelines published by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America (Dellit, Owens, McGowan, Gerding, & Weinstein, 2007). The Agency for Healthcare Research and Quality (AHRQ) published a pragmatic Toolkit for Reduction of Clostridium difficile Through Antimicrobial Stewardship for hospital staff (Boston University School of Public Health, Montefiore Medical Center, Greater New York Hospital Association (GNYHA)/United Hospital Fund (UHF), Agency for Healthcare Research and Quality, Centers for Disease Control and Prevention, 2014).

This topic brief reviews the effectiveness of interventions that target antimicrobial resistance through prescribing in hospital settings. Appropriate prescribing reflects the following decision and
implementation protocol components: an antimicrobial is needed to treat a condition, the optimal antimicrobial is chosen and administered correctly, and patients are monitored to ensure they are responding appropriately. The aforementioned Cochrane Review classified interventions to improve prescribing into three categories: persuasive, restrictive, and structural (Filice, et al., 2013; Davey, et al., 2013). Persuasive interventions focus on provider education and knowledge, and may include educational materials, reminders, and audit and feedback. Restrictive interventions limit the prescribing freedom of providers for select antibiotics, and may include order forms, expert approval, removal of restricted antimicrobials, and substitution. Structural interventions change normal prescribing procedures, including transitioning from paper to Electronic Health Records (EHRs), rapid laboratory testing, computerized decision support systems, and quality monitoring mechanisms. Patient behavior and lack of adherence to a prescribed regimen can accelerate antimicrobial resistance; however, interventions to address patient behavior have not been a major focus in inpatient settings.

According to Filice, et al. (2013), an antimicrobial stewardship program (ASP) is a focused effort by a healthcare organization to optimize antimicrobial use for the purposes of improving patient outcomes through appropriate selection, dosing, route, and duration of antimicrobial therapy. The CDC states that the core elements of hospital antibiotic stewardship programs are leadership commitment, accountability, drug expertise, action, tracking, reporting, and education (CDC, 2014). ASPs may include a combination of persuasive, restrictive, and/or structural interventions depending on the circumstances and preferences of the organization.

This topic brief focuses on interventions designed to improve antibiotic prescribing in order to address the development of antimicrobial resistance in patients. This complements research on topics related to transmission, such as hospital hand hygiene programs to reduce the incidence of hospital-acquired infections (e.g., CDC’s Guideline for Hand Hygiene in Health-Care Settings, NIH Collaboratory’s work on hand hygiene). In terms of transmission-focused interventions, a systematic review of the World Health Organization’s 2005 “Clean Care is Safer Care” (WHO-5) campaign and similar interventions to improve hand hygiene among healthcare workers in hospital settings found, “Promotion of hand hygiene with WHO-5 is effective at increasing compliance in healthcare workers” (Luangasanatip, et al., 2015). Of the 41 studies reviewed, 19 reported on clinical outcomes; all 19 found that improvements in hand hygiene were associated with reductions in one or more measures of hospital-acquired infection and/or resistance rates. Combinations of interventions and continuous interventions were more effective than single interventions in promoting and sustaining good hand hygiene practices (Luangasanatip, et al., 2015) (Huis, et al., 2012) (Cherry, Brown, Bethell, Neal, & Shaw, 2012). However, while preventing transmission is essential to addressing antimicrobial resistance and is a topic that has garnered significant attention in the literature, it is not the focus of this topic brief.

3. Patient-Centeredness:
Patient outcomes are affected when antimicrobial resistance and incorrect prescribing undermine the effectiveness of a prescribed treatment regimen. Research that compares interventions to address antimicrobial resistance is relevant to patient outcomes, including patient health status (e.g., delay in administration of effective therapy, toxicity level of therapy, activity level at discharge), health care utilization (e.g., length of stay, readmissions, health care costs), and loss of functional time, ability to
work, and excess mortality (Palmer, et al., 2011). In addition, prescribers must be cognizant of more than what treatment is most appropriate for an individual patient, but also how their choice of medication may affect future patients and members of the community. Antimicrobial resistance is also relevant to clinicians, delivery systems, public health professionals, and the public at large, because antimicrobial resistance is a threat to many treatments and procedures common in modern medicine.

4. Impact/Burden of the Condition:
Overall, according to the CDC, in the U.S. at least 2 million people acquire and 23,000 people die from antibiotic-resistant infections each year (CDC, 2013). Antibiotic-resistant infections are a considerable cost to society in terms of avoidable healthcare costs (e.g., prolonged treatments, extended hospital stays, additional doctor visits and medications) and other costs to society. In sum, the CDC estimates the annual economic cost of antibiotic resistance to be as high as $20 billion in excess direct healthcare costs and $35 billion in lost productivity (e.g., lost wages, extended hospital stays, and premature deaths.)

The CDC assessed different antibiotic resistance threats based on seven factors including clinical impact, economic impact, and a 10-year projection of incidence that identified three bacteria considered to be an “urgent” threat (Clostridium difficile, Carbapenem-resistant Enterobacteriaceae, and Drug-resistant Neisseria gonorrhoeae), 11 bacteria as a “serious” threat, and three as “concerning” (CDC, 2013). The CDC labeled Clostridium Difficile an urgent threat, since it typically occurs in hospitalized patients who received antibiotics (CDC, 2013). This bacterium causes 250,000 illnesses, 14,000 deaths, and one billion dollars in excess medical costs per year. The number of deaths related to Clostridium Difficile has increased 400% between 2000 and 2007 as a stronger strain of the bacterium has emerged. Methicillin-resistant Staphylococcus aureus (MRSA) causes a range of illnesses, from skin infections to pneumonia, and was ranked as a “serious” threat. Staph bacteria including MRSA are a leading cause of healthcare-associated infections and in 2011 was responsible for an estimated 80,461 serious infections and 11,285 related deaths.

While antibiotic resistance has been the primary focus of health organizations’ efforts (e.g., work by CDC), other forms of antimicrobial resistance (including drug resistant viruses, fungi, and parasites) also represent a growing concern. Candida, a fungus that is the fourth most common cause of healthcare-associated bloodstream infections and which tends to occur in the sickest patients, is identified as one of the 11 bacteria posing a serious threat. Of the 46,000 Candida infections per year in the U.S., 3,400 are resistant to the first line anti-fungal treatment agent (Fluconazole), which leads to an estimated 220 deaths annually. Antiviral resistance is also a growing concern. In the US in 2007, HIV drug-resistant surveillance at 11 surveillance sites found 17% of newly diagnosed HIV infections were drug-resistant and, of these, 2.2% were resistant to two or more classes of drug (CDC, 2011). Resistance to influenza antiviral agents has complicated treatment and prevention of influenza.

Antimicrobial resistance is a global public health threat, as microbes can easily cross international borders. In 2014 the World Health Organization noted, “Without urgent action we are heading for a post-antibiotic era in which common infections and minor injuries can once again kill” (WHO, 2014).
5. Evidence Gaps:
Five major systematic reviews of antimicrobial stewardship programs (ASPs) in hospitals have been published in the past 5 years:

- Impact of antimicrobial stewardship in critical care: a systematic review (Kaki, et al., 2011);
- Cochrane review: Interventions to improve antibiotic prescribing practices for hospital inpatients (Davey, et al., 2013);
- Antimicrobial stewardship programs in inpatient settings: A systematic review (Filice, et al., 2013);
- Antibiotic stewardship programs in intensive care units: Why, how, and where are they leading us (Zhang & Singh, 2015); and
- Time for action—Improving the design and reporting of behavior change interventions for antimicrobial stewardship in hospitals: Early findings from a systematic review (Davey, Peden, Charani, Marwick, & Michie, 2015).

These systematic reviews summarize the effectiveness of ASPs that have been rigorously evaluated—and identify large evidence gaps related to hospital-based interventions to address antimicrobial resistance. We highlight below key themes:

Overall effectiveness of ASPs in hospitals
A 2013 Cochrane review comprising 89 studies found that overall ASP interventions improved antibiotic prescribing, and 21 studies that indicated a decrease in the number of infections in hospital as a result of the ASP. The evidence clearly demonstrates that ASPs can improve prescribing of antibiotics to patients in hospitals (Davey, et al., 2013). Nearly all studies in a separate Department of Veterans Affairs systematic review of ASPs in inpatient settings also demonstrated an effect that favored the stewardship intervention, specifically related to prescribing, microbial (e.g., resistance in hospitals), or cost outcomes. However, this review noted that the quality of this evidence is low. Furthermore, few of the reviewed RCTs measured patient readmissions, Clostridium difficile infection incidence, length of stay, or mortality (Filice, et al., 2013).

The effectiveness of “restrictive interventions” (e.g., requiring prior authorization for prescriptions by infectious disease specialists) versus “persuasive interventions” (e.g., providing educational resources) emerged as a major theme in the literature on the effectiveness of ASPs. The Cochrane review indicated that restrictive interventions had a larger effect than persuasive interventions in hospital settings for the first six months, but both types of interventions were equally effective after six months. The review found that restrictive interventions may be very useful when the need is urgent, but persuasive interventions may be a better route to engender clinician support for ASPs (Davey, et al., 2013). Another systematic review of ASPs in critical care also noted that restrictive interventions may be effective but can lead to certain unintended consequences. For example, the review noted, “All studies of restriction and pre-approval policies reported a statistically significant reduction in the use of target antibiotics. However, all studies of restriction policies demonstrated a compensatory increase, by ~200% - 300%, in the use of other [pharmaceutical] agents [e.g., efepime, aminoglycosides/macrolides,
piperacillin/tazobactam] with a similar spectrum of use” (Kaki, et al., 2011). However, there is a dearth of head-to-head studies comparing the effectiveness of restrictive hospital interventions with persuasive interventions – or studies examining possible synergistic effects of restrictive and persuasive interventions (Davey, et al., 2013) on a range of key outcomes.

The effect of computer-assisted decision support on the effectiveness of ASPs was another issue explored in these systematic reviews of ASPs. Computer-assisted decision support can be incorporated into persuasive as well as restrictive interventions. The systematic review focused on critical care provided evidence for the usefulness of computer-assisted decision support in ASPs: “Studies of computer-assisted decision support, formal reassessment and the impact of an infectious diseases consultant all demonstrated decreases in antibiotic use among several classes of antibiotics without a pronounced compensatory increase in other agents with a similar spectrum.” One study found that antibiotic management support programs resulted in fewer susceptibility-mismatch alerts (e.g., alerting physicians when the antibiotic therapy they have chosen is inappropriate) and excessive drug-dosage alerts (Kaki, et al., 2011). The Department of Veteran’s Affairs systematic review included only four relevant studies directly related to the implementation of computer decision support systems in ASPs, all with high or medium risk of bias (Filice, et al., 2013). Further research (with improved study designs) on the usability and workflow integration of computer-assisted decision support to promote better adoption and use in hospitals is needed before any claims of effectiveness in ASPs can be made.

A study at St. Luke’s Episcopal Center found that a well-designed ASP can be implemented by tailoring therapy to individualized patient needs. This study utilized real-time data to facilitate optimal antimicrobial therapy individualized to the patient. Furthermore, by identifying individual patient factors (e.g., genetics), the risk of adverse drug reactions was reduced (Palmer, et al., 2011). We found no systematic reviews of ASP programs that tailored therapy to individualized patients. Therefore, further research is needed to identify the optimum design of ASPs that tailors therapy to individualized patients.

Measuring patient outcomes as a primary indicator of the effectiveness of ASPs was also frequently discussed and analyzed in the key systematic reviews. The systematic review of critical care ASPs found, overall, that ASPs did not lead to negative patient outcomes: “Many studies documented no significant difference in the length of stay, none documented an increased length of stay in association with implementation of antimicrobial stewardship and, intriguingly, six studies documented a decrease in the length of stay associated with stewardship.” (The concern is that restrictive interventions could harm vulnerable patients in critical care units if restrictive ASPs result in withholding treatment for this population) (Kaki, et al., 2011). However, despite the strong evidence for improvements in process indicators, more studies with longer follow-up may be needed to fully assess the effect of ASPs on clinical or patient-centered outcomes (e.g., mortality) (Davey, et al., 2013) (Filice, et al., 2013).

Effectiveness of structural interventions focused on rapid reporting of laboratory results
The 2013 Cochrane review focused on three structural hospital ASP RCTs that utilized rapid reporting of laboratory results (e.g., rapid polymerase chain reaction (PCR) to detect bacteremia). The introduction of tests of inflammatory markers demonstrated a reduction in the use of antibiotics for patients with
low risk of infection. Notably, these interventions were able to reduce the number of patients who were treated with antibiotics in hospital, while rapid microbiology tests or PCR tests for viruses had little impact on antibiotic use (Davey, et al., 2013).

Studies of Point of Care Testing (POCT), which allows for informed prescribing within just a few hours of presentation, were also reviewed. However, the systematic review noted the need for stronger evidence on the effectiveness of POCT as part of ASPs, specifically calling for “risk assessment” on the use of an electronic decision support system to determine which patients would benefit from a POCT (e.g., “…PCR of blood to increase detection of bacteraemia over conventional blood culture systems…”) (Davey, et al., 2013).

Antibiotic prescribing behavior interventions in hospitals

Interventions that focus on antibiotic prescribing were positively associated with a decrease in incidence of Clostridium difficile, resistant gram-negative bacteria, Methicillin-resistant Staphylococcus Aureus (MRSA), and Vancomycin-Resistant Enterococcus (VRE). However, the strength of evidence was weak. Only six interventions (29%) in the 2013 Cochrane systematic review provided reliable data about changes in antibiotic prescribing. The findings indicated there was “…not enough data to estimate the likely impact of change in prescribing on microbial outcomes.” Furthermore, five studies of antibiotic prescribing-focused interventions found no statistically significant differences in infection-related hospital readmissions between the intervention and control groups (Davey, et al., 2013).

The Department of Veterans Affairs systematic review corroborates the Cochrane review’s finding regarding the weak strength of evidence in these studies. Although the studies have shown potential that ASPs can lead to improvements in antimicrobial prescribing practices and costs as well as in patient outcomes, implementing these ASPs without further research may be inadvisable, given the low strength of evidence of these studies. The Department of Veterans Affairs systematic review found that improvements in antimicrobial prescribing practices were often not sustained in the long-term. These findings were based on only a few studies, with only one prescribing outcome captured per study (Filice, et al., 2013).

Safety, adverse events, unintended consequences related to ASP interventions in hospitals

While anecdotal evidence exists, no studies have rigorously studied the potential deleterious impacts of ASP interventions (Davey, et al., 2013). Future studies are still needed to examine the risks of restrictive interventions on clinical outcomes.

Understanding how restricting physicians’ clinical freedom may affect patient safety is also a concern regarding inpatient ASPs (Davey, et al., 2013). One review noted: “Restricting the use of certain antibiotic classes is associated with a compensatory increase in unrestricted antibiotics…” within ICU settings (Kaki, et al., 2011). Others reviews detailed the potential risk of a “balloon squeezing effect” (e.g., decreasing use of one antimicrobial results in increased use of another, as a compensatory mechanism, often with a corresponding resistance) when restricting providers in ASPs (Kaki, et al., 2011) (Zhang & Singh, 2015).
Implementation, sustainability, and scalability

The Department of Veteran’s Affairs review called for more studies on the implementation, sustainability, scalability or specific components of interventions that are effective, given the paucity of current evidence on this topic. Most of the reviewed studies were short (one year or less), which made it difficult to make determinations about the sustainability of ASPs. Only four studies addressed implementation barriers – these included low provider attendance at educational sessions and physicians’ lack of agreement with prescribing guidelines. No studies in the review commented on scalability of ASPs (Filice, et al., 2013). Overall, the limited information provided on the long-term overall effectiveness of ASPs may make it difficult for hospitals to invest without a clear understanding of the impact of ASPs beyond the first year of implementation; the challenges they may encounter; and whether the results from these interventions are sustained.

Physician compliance and physician buy-in were additional issues examined in the reviews. One RCT indicated the hospital ASP was ended prematurely due to poor clinician adherence to the algorithm, and recommended further study to examine clinician compliance and noncompliance, especially related to antibiotic start and stop decisions (Zhang & Singh, 2015).

Gaps/Recommendations for Future Research Designs on ASPs

The systematic reviews identified major issues around the study designs of the incorporated literature. Few studies of ASP effectiveness were randomized controlled trials. Thus, researchers have limited ability to control for confounding variables, such as secular trends (Filice, et al., 2013). The preponderance of literature comprises uncontrolled before-after studies; there has been inadequate implementation of interrupted time series (ITS) and/or controlled before-after (CBA) studies (Davey, et al., 2013).

Future studies will also need to strengthen the evaluation design for single hospital and/or single unit (e.g., ICU unit) ASP interventions, because of “selection bias and confounding.” Stepped wedge trials, i.e., staggering the intervention, could be a useful design in this respect if rolling out an ASP in a single hospital (Kaki, et al., 2011). The 2013 Cochrane review described how “improving the quality of ITS [interrupted time series] evaluations in single hospitals will lay the foundation for cluster-randomized trials with embedded time series” (Davey, et al., 2013).

Future research is also needed to determine which specific ASP intervention components (e.g., use of infectious disease physicians, microbiology laboratories, trainee education and certification) are effective. For example, while protocols for switching patients with community-acquired pneumonia from intravenous (IV) to oral therapy resulted in shorter hospital length of stay, details on the development of criteria for switching therapies, or who was responsible for administering the protocols, have not been described (Filice, et al., 2013). Understanding the specific implementation conditions for

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1 These topics were noted as key evidence gaps in the systematic reviews, but we note that issues related to cost/resources are out of PCORI’s scope.

PCORI Topic Brief: Comparative effectiveness of alternative interventions to address antimicrobial resistance in hospitals

10
each of these components and what components will work best together is essential for replicating and tailoring ASPs for different hospitals with diverse sets of resources and needs.

**Clinical Practice Guidelines**

Several clinical practice guidelines (CPGs) for antimicrobial stewardship have been developed in the U.S. and overseas to assist hospitals in the implementation process:

- **Infectious Diseases Society of America (IDSA), Developing an Institutional Program to Enhance Antimicrobial Stewardship (Dellit, Owens, McGowan, Gerding, & Weinstein, 2007)**
- **Australian Commission on Safety and Quality in Health Care, Antimicrobial stewardship in Australian hospitals (2011)**

Among these CPGs, the IDSA utilized the Infectious Diseases Society of America-United States Public Health Service grading system to determine the most appropriate and effective recommendations to include in the clinical guidelines. The system is based on two major categories: the strength of the evidence and the quality of evidence supporting it (literature, expert opinions, etc.). According to IDSA, “Each recommendation is rated on the basis of the strength of the recommendation and the quality of evidence supporting it....” IDSA made 46 recommendations based on a grade of “A” (good strength of evidence) and 18 recommendations based on a grade of “B” (moderate strength of evidence); it rejected any recommendation that received a grade of “C” (poor strength of evidence).

The IDSA made several recommendations for future research (Dellit, Owens, McGowan, Gerding, & Weinstein, 2007):

- “The long-term impact of formulary restriction and preauthorization requirements on antimicrobial use and resistance.”
- “Evaluation of ‘bundled’ approaches that incorporate many or all of the most effective strategies.”
- “The incremental role of antimicrobial stewardship combined with infection control practices, such as hand hygiene and isolation, designed to prevent secondary spread of resistant organisms.”
- “Development and validation of automated surveillance strategies for nosocomial infections and real-time monitoring of resistance trends.”

**6. Ongoing Research**

A search of clinicaltrials.gov on August 27, 2015, using the search term “antimicrobial stewardship” identified 8 ongoing studies defined as “recruiting” or “not yet recruiting.” Upon reviewing these 8 studies, we excluded 2 studies that did not pertain to ASPs, 2 studies focused exclusively on drug dosing...
or drug timing, and 2 studies that focused on improving laboratory tests for antibiotic stewardship (these did not rise to the level of a systems intervention).

Below, we summarize the two remaining studies, which comprise observational studies or RCTs of persuasive and structural ASP interventions.

- **Impact of a Regional Antimicrobial Stewardship on the Length of Stay of Patients Admitted to Hospital With Pneumonia**
  
  - This ongoing observational study (target duration of 60 days) with an estimated enrollment study of 2,000 participants evaluates the effectiveness of an ASP to reduce the length of stay of patients admitted to hospital with a diagnosis of pneumonia. The program will use a prospective audit and feedback intervention to identify patients with pneumonia, review patient charts, and make recommendations to their attending physicians about antibiotic management to reduce treatment variation from guidelines. Primary outcome measures will include the length of hospital stay, while secondary measures will include days of antibiotic therapy, mortality, and readmission.

- **Antimicrobial Stewardship in Pediatric Surgery**
  
  - This observational study (n=100) will assess whether an ASP focused on pediatric general surgery will decrease the use of unwarranted antibiotics. This study will also use an audit and feedback intervention with twice weekly meeting with Infectious Disease and Pediatric Surgery team members to audit antibiotics prescribed and make suggestions for discontinuation.

While these studies provide valuable information on the effectiveness of individual antimicrobial stewardship programs in various hospital settings, they do not directly compare active ASP interventions. Also, the small number of evaluative studies limits the generalizability of these findings across a wide range of inpatient settings.

7. Likelihood of Implementation of Research Results in Practice

The White House’s 2014 *National Strategy for Combating Antibiotic Resistant Bacteria* denotes the high priority of this topic for health care. Federal health agencies, states (e.g., California) and other influential stakeholders, such as the Infectious Diseases Society of America (IDSA), have promulgated guidance on the topic. For instance, California recently enacted antimicrobial stewardship legislation requiring general acute care hospitals to develop a process for monitoring the use of antibiotics (California Department of Public Health, 2015). Also, as described earlier, AHRQ recently published a “toolkit” to inform the implementation of hospital antimicrobial stewardship programs (Boston University School of Public Health, Montefiore Medical Center, Greater New York Hospital Association (GNYHA)/United Hospital Fund (UHF), Agency for Healthcare Research and Quality, Centers for Disease Control and Prevention, 2014). The majority of US hospitals have considered implementing an ASP (Doron, et al., 2013), and even hospitals without ASPs have incorporated some kind of antimicrobial stewardship technique to optimize antibiotic use. All these factors suggest that hospitals will implement this guidance in practice.
8. Durability of Information:
The topic of antimicrobial resistance will likely remain salient or become even more urgent in the years ahead – in the U.S. as well as overseas. Thus, subsequent studies of hospital ASPs will strengthen the field’s evidence base and inform future interventions. Stronger studies, including RCTs, will provide the rigorous data needed to inform durable practice guidelines both feasible and acceptable to clinicians and patients. While the effectiveness of many of the interventions discussed in this brief are likely to remain stable in the near future (e.g., educational materials), interventions that rely on health information technology, such as computer-assisted decision support and clinical practice guidelines may continue to evolve and produce new information that will serve the field.

9. Potential Research Questions:
The various systematic reviews profiled in this topic brief suggest a need for future research along the following domains of ASP-related research:

**Effectiveness and Comparative Effectiveness**

- What is the comparativeness effectiveness of different combinations of “restrictive” interventions versus “persuasive” interventions in the context of ASPs in hospitals?
- What is the comparative effectiveness of ASPs combined with infection control practices, such as hand hygiene and isolation, compared with hand hygiene and isolation alone?
- What is the comparative effectiveness of different types of clinical decision support programs as part of restrictive and persuasive ASPs in hospitals?
- What is the comparative effectiveness of implementing ASPs tailored to individualized patient needs compared to uniform therapy guidelines? What are the challenges, resource and workflow considerations for ASP implementation in specific inpatient settings, including but not limited to the ED?
- What is the relative impact of different approaches to mitigating practice barriers (e.g., resources, training, etc.) to the implementation of ASPs?

10. Conclusions:
There is evidence from recent systematic reviews that ASPs in hospitals can be effective at addressing antimicrobial resistance in hospitals (e.g., by modifying clinicians’ antibiotic prescribing behaviors). However, several challenges remain in producing a robust evidence base for the field. Study design improvements are needed: Many ASP studies have relied on interrupted time series (some uncontrolled) designs of single hospitals and/or single hospital units (e.g., ICUs), thus there is a need to strengthen these single hospital/unit study designs, going forward to address methodological weaknesses. There is also a need to conduct more RCTs on ASPs overall to strengthen the evidence base. Longer-duration studies on ASPs are also needed, given that many of the current studies are short (i.e., one year or less). Finally, further research is needed on potential adverse events and unintended consequences of ASPs in hospitals.

**PCORI Topic Brief: Comparative effectiveness of alternative interventions to address antimicrobial resistance in hospitals**

13
References for Topic: Comparative effectiveness of alternative interventions to address antimicrobial resistance in hospitals


PCORI Topic Brief: Comparative effectiveness of alternative interventions to address antimicrobial resistance in hospitals


Appendix

Methods

Literature search:
Between August and October 2015, we conducted a targeted literature review to identify evidence-based research around the effectiveness of alternative service combinations to reduce antimicrobial resistance in hospitals and other healthcare settings. We utilized scholarly databases and other web-based tools including PubMed, Google Scholar, Cochrane Database of Systematic Reviews, MEDLINE, ScienceDirect, and more to access targeted sources including peer-reviewed literature, systematic reviews, meta-analyses, research reports published by the federal government, and other grey literature on this topic. We also searched certain websites likely to contain relevant material (e.g., government agencies and relevant professional associations and societies) to access information such as clinical practice guidelines and key recommendations.

We used specific search terms to identify the most relevant literature. Search terms for this topic include, but not limited to: “antimicrobial resistance”; “antibiotic resistance”; “antibiotic-resistant infections”; “antibiotic-resistance bacteria”; “antimicrobial stewardship”; “antimicrobial prescribing”; “hospital acquired infections”; “Clostridium difficile” AND “alternative service combinations”; “computer-assisted decision support”; “clinical decision support”; “point-of-care prescribing”; “patient-outcome monitoring”; “educational materials”; “reminder systems.” To help ensure the information in this brief will remain current for several years we limited to majority of our search to literature published in the past five years (i.e., 2010-2015). We also restricted our literature search to hospital and inpatient settings to provide a more targeted brief.

Clinical trials:
In August 2015, we conducted a search on clinicaltrials.gov for open clinical trials related to the topic. We used the broad search term “antimicrobial stewardship” to ensure we identified all relevant trials. The search yielded only eight ongoing studies defined as “recruiting” or “not yet recruiting.” We excluded studies outside of the U.S. and any studies listed as completed. After carefully reviewing each of the eight studies, we excluded two studies that did not pertain to antimicrobial stewardship programs. The final six studies were outlined in the topic brief to provide an overview of ongoing research in the area of antimicrobial resistance in hospitals.

Expert Feedback:
PCORI staff attempted to meet with experts at AHRQ and CDC to obtain their feedback on the brief and relevant CER questions and was unable to do by the time this draft was due to the SOC. PCORI staff plan to distribute the draft brief to subject matter experts at AHRQ and CDC for feedback on the relevant CER questions prior to the Advisory Panel Meeting in November.